Clinical Trial Protocol

A Randomised, Open-Label, Active-Comparator, Multi-Center Trial Comparing a Once-Weekly and Once-Monthly Long-Acting Subcutaneous Injectable Depot of Buprenorphine (CAM2038) to Buprenorphine Standard of Care in Adult Outpatients with Opioid Dependence

The Depot Evaluation - Buprenorphine Utilisation Trial (DEBUT)

Trial Code:	HS-17-585
Development Phase:	Therapeutic Use
Investigational Medicinal Product:	CAM2038 50 mg/mL q1w (buprenorphine FluidCrystal® once-weekly subcutaneous injection depot) CAM2038 356 mg/mL q4w (buprenorphine FluidCrystal® once-monthly subcutaneous injection depot)
Indication:	Opioid dependence
Protocol Version and Date:	4.0 20 November 2018
Protocol Amendments Included:	Amendments 1 and 2
Sponsor	Camurus AB Ideon Science Park Sölvegatan 41 SE-223 70 Lund, Sweden
Contract Research Organisation – Local Sponsor	PAREXEL International Pty Ltd. 15 Talavera Road Suite B, Level 6 Macquarie Park, Australia NSW 2113
Co-Ordinating Investigator:	Nicholas Lintzeris, MBBS, FAChAM, PhD

This trial will be conducted in compliance with the Clinical Trial Protocol, applicable regulations and with the principles of Good Clinical Practice

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ABBREVIATIONS

Abbreviations

AD-SUS	Alcohol & Drug adapted Adult Service Use Schedule
AE	Adverse Event
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical
ATOP	Australian Treatment Outcomes Profile
BPN	Buprenorphine
CDF	Cumulative distribution function
CI	Confidence interval
CNS	Central nervous system
COWS	Clinical Opiate Withdrawal Scale
CRF	Case Report Form
CRO	Contract Research Organisation
CYP	Cytochrome P450
DASS-21	Depression, Anxiety and Stress Scales 21
DSM-5	Diagnostic and Statistical Manual of Mental Disorders – 5th Edition
ECG	Electrocardiogram
eCRF	Electronic CRF
ePRO	Electronic PRO
EQ-5D	EuroQol five dimensions health questionnaire
FAS	Full Analysis Set
FC	FluidCrystal®
G	Gauge
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HEOs	Health economic outcomes
HIV	Human immunodeficiency virus
HRU	Healthcare resource utilisation
IB	Investigator's Brochure
ICD-10	International Statistical Classification of Diseases and Related Health Problems – 10th Edition
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

IEC	Independent Ethics Committee
IMP	Investigational medicinal product
ITT	Intention-to-treat
IWRS	Interactive Web-based Randomisation System
MAOI	monoamine oxidase inhibitors
MAT	Medication assisted treatment
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
NX	Naloxone
OSTQOL	The Opioid Substitution Treatment Quality of Life Scale
PGIC	Patient's Global Impression of Change
PP	Per protocol
PRO	Patient Reported Outcomes
QALY	quality-adjusted life year
QoL	Quality of life
SAE	Serious Adverse Event
SAP	Statistical Analysis plan
SC	Subcutaneous
SF-36	Short Form 36
SL	Sublingual
SURE	Substance Use Recover Evaluator
TBQ	Treatment Burden Questionnaire
TLFB	Timeline follow back
TSQM	Treatment Satisfaction Questionnaire for Medication
UDS	Urine drug screen
VAS	Visual analogue scale
WPAI:GH	Work Productivity and Activity Impairment Questionnaire: General Health

1 PROTOCOL SYNOPSIS

Name of Sponsor
Camurus AB

Trial Title
A Randomised, Open-Label, Active-Comparator, Multi-Center Trial Comparing a Once-Weekly and Once-Monthly Long-Acting Subcutaneous Injectable Depot of Buprenorphine (CAM2038) to Buprenorphine Standard of Care in Adult Outpatients with Opioid Dependence

Sponsor Protocol No
HS-17-585

Phase
Therapeutic Use

Coordinating Investigator
Prof. Nicholas Lintzeris, MBBS, FAChAM, PhD, Australia

Trial Sites
The trial will be conducted at approximately 6-10 sites in Australia.

Objectives and Endpoints

Primary Objective	*Primary Endpoint*
To compare patient satisfaction with CAM2038 to buprenorphine (BPN) standard of care in adult outpatients with opioid dependence	Treatment Satisfaction Questionnaire for Medication (TSQM) global satisfaction score
Secondary Objectives	*Secondary Endpoints*
To assess patient satisfaction with treatment	TSQM effectiveness score TSQM side effects score TSQM convenience score Patient satisfaction visual analogue scale (VAS)
To assess treatment effects on illicit, non-prescribed and unsanctioned prescribed use of opioids	Illicit opioid drug use measured by urine drug screen (UDS) and self-reports of illicit opioid drug use by timeline follow-back method (TLFB)
To assess treatment effects on illicit drug use other than opioids	Illicit drug use measured by UDS and self-reports of drug use by Australian Treatment Outcomes Profile (ATOP)
To assess treatment effects on retention in treatment	Retention in treatment
To assess treatment effects on adherence to medication	Trial drug adherence measured by dispensing records (for CAM2038) and self-reports of drug accountability (for BPN standard of care)
To assess treatment effects on quality of life and patient functioning	Substance Use Recover Evaluator (SURE) EuroQol five dimensions health questionnaire (EQ-5D) Opioid Substitution Treatment Quality of Life Scale (OSTQOL) Patient Global Impression of Change (PGIC)

To assess the effect on treatment related behaviours and perception of treatment	Treatment Burden Questionnaire (TBQ) Opioid Related Behaviours In Treatment (ORBIT) scale
To assess treatment effects of measures of general physical, mental and psychosocial functioning	Short Form 36 (SF-36) Depression, Anxiety and Stress Scale 21 (DASS-21)
To assess treatment effects on health economic outcomes (HEOs) including treatment utilization	Work Productivity and Activity Impairment Questionnaire: General Health (WPAI:GH) Estimates of health care resource utilisation (HRU) through modified Alcohol & Drug adapted Adult Service Use Schedule (AD-SUS) questionnaire Estimates of social service utilisation (AD-SUS questionnaire) Estimation of quality-adjusted life years (QALYs)
To assess treatment effects on criminal activity	Criminal offences and incarcerations during the trial (AD-SUS questionnaire)
To assess treatment effects on diversion and misuse of the trial medications	Self-reported diversion and misuse of the trial medications using ORBIT (for BPN standard of care) Self-reported overdoses
To assess treatment effects on opioid withdrawal symptoms	Clinical Opiate Withdrawal Scale (COWS)
To assess treatment effects on opioid cravings	Craving VAS
To assess the safety and tolerability of CAM2038	Adverse events (AEs)

Trial Design and Schedule

This is a prospective, randomised, open-label, active-controlled, multi-center trial comparing treatment effects of CAM2038 with BPN standard of care (for example, sublingual [SL] BPN or BPN/naloxone [BPN/NX]) in adult outpatients with opioid dependence.

Opioid dependent patients who are either currently receiving medication assisted treatment (MAT) with SL BPN or BPN/NX, or patients who are actively seeking BPN standard of care treatment but who have not yet begun a treatment regimen, may be eligible for the trial. Patients currently on MAT with methadone may be included after conversion to BPN standard of care according to local practice for at least 1 week before randomisation.

Patients who have previously received treatment with CAM2038 or another BPN injection depot product are eligible for the trial if they have not been treated with these products for the past 90 days before Screening. Patients should be willing to remain on BPN treatment for the duration of the trial.

Patients will be randomised in a 1:1 ratio to either CAM2038 or BPN standard of care MAT. Stratification by new to treatment will be applied (i.e. by patients who have not received MAT within 30 days before Screening).

The trial will consist of a Screening Period of up to 4 weeks duration, a Treatment Period of 24 weeks duration, and a Follow-up Period of 2 weeks duration.

CAM2038 will be administered by either weekly (CAM2038 q1w) or monthly (CAM2038 q4w) subcutaneous (SC) injections. Patients receiving CAM2038 can be switched between the weekly and monthly products at any time during the entire trial at the discretion of the treating Investigator. The BPN standard of care will be administered as prescribed product according to the local standard of practice and may be dispensed at local clinics or community pharmacies as per usual practice.

Patients in the CAM2038 arm will be allowed to receive supplemental treatment during the trial with SC injections of CAM2038 q1w 8 mg at the discretion of the treating clinical investigator up to a maximum of 32 mg per week or 160 mg per month. Dose adjustments (up or down titrations) in both arms after monitoring of the patient's clinical response to the treatment will also be allowed at any time during the trial. Documentation of titration and accountability will be done at each visit where trial treatment is administered/dispensed and at the Week 24/premature discontinuation visits. Switching between CAM2038 and BPN standard of care during the trial will not be allowed.

Mandatory scheduled clinic site visits where the Investigator performs safety assessments and where independent researchers performs efficacy assessments (UDS and Patient Reported Outcomes [PROs]) will take place on Day 1 (Baseline/Randomisation), and at Week 4 (Day 28 ± 7), Week 8 (Day 56 ± 7), Week 12 (Day 84 ± 7), Week 16 (Day 112 ± 7), Week 20 (Day 140 ± 7) and Week 24 (Day 168 ± 7). Depending on the treatment the patient is receiving (weekly or monthly CAM2038, or BPN standard of care), dosing may occur at the same time as a mandatory scheduled clinic visit, or at separate visits. Additional clinic site visits and review may be scheduled by the Investigator or requested by patients as per standard care. For patients who have not been previously treated with BPN, the randomisation process can take place on Day -3 to Day -1, depending on the time needed to obtain approval from local authorities to start treatment with BPN products. The randomisation can be performed provided that patients are eligible for inclusion based on assessments performed at the Screening Visit, including the safety laboratory tests. The randomisation can be performed without the patient being present at the clinic. When the patient visits the clinic for the Day 1 (baseline) visit, the approval for starting treatment must be available prior to administration of trial treatment. Efficacy and safety assessments must be performed prior to dose administration.

Patients who miss a scheduled dosing visit by more than 7 days while receiving CAM2038 q1w or BPN standard of care, or by more than 30 days while receiving CAM2038 q4w, will be considered as discontinued from trial treatment. Patients who discontinue trial treatment are still eligible to continue in the trial and may be treated according to clinical practice, outside the trial setting, at the discretion of the Investigator.

Investigators will be instructed to provide psychosocial case management and counselling for patients during the trial according to local guidelines and to provide counselling visits independently of the mandatory scheduled visits.

The Follow-up Visit/Contact at Week 26 is the last protocol specified contact with the patient.

Trial Treatments

Test Products

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

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

Comparator

BPN standard of care (for example, SL BPN or BPN/NX) for MAT of opioid dependence at licensed doses

Trial Population

Opioid dependent adult male or female outpatients ≥18 years of age

Number of Patients (Planned)

Approximately 120 patients will be randomised 1:1 to CAM2038 or BPN standard of care (60 in each arm)

Planned Trial Period (Estimated):

First patient first visit: approximately Q3, 2018

Last patient first visit: approximately Q1, 2019

Summary of Main Inclusion Criteria

- Adult male or female patient (≥18 years old)
- Meet the criteria for opioid dependence as defined by either the criteria for moderate to severe opioid use disorder in the Diagnostic and Statistical Manual of Mental Disorders – 5th Edition (DSM-5) OR opioid dependence in the International Statistical Classification of Diseases and Related Health Problems – 10th Edition (ICD-10) according to local practice.
- Appropriate candidate for MAT with a partial opioid agonist as determined by the Investigator and is willing to continue in BPN treatment for the duration of the trial.

Summary of Main Exclusion Criteria

- Any known allergy, hypersensitivity or intolerance to BPN or NX or any related drug, or history of any drug hypersensitivity or intolerance which in the opinion of the Investigator, would compromise the safety of the patient or the trial.
- A contra-indicated serious medical condition, including unstable and severe pain, which in the opinion of the Investigator may prevent the patient from safely participating in trial.
- Clinically significant laboratory abnormalities, which in the opinion of the Investigator may prevent the patient from safely participating in trial.
- History of risk factors of Torsades de Pointes heart arrhythmia (e.g., heart failure, hypokalemia, family history of long QT syndrome) or an electrocardiogram (ECG) demonstrating a clinically significant abnormality, as judged by the Investigator.
- Requires chronic use of agents that are strong inhibitors or inducers of cytochrome P450 3A4 (CYP 3A4) such as some azole antifungals (e.g. ketoconazole), macrolide antibiotics (e.g. clarithromycin), or protease inhibitors (e.g. ritonavir, indinavir, and saquinavir).
- Recent history of significant suicidal ideation or active suicidal behavior, in the opinion of the Investigator.
- Participants with serious untreated psychiatric comorbidity at the discretion of the Investigator.

Efficacy and Safety Variables and Assessments

Assessments of the primary efficacy variable

The primary efficacy variable the TSQM will be administered by independent researchers at Baseline (Day 1), Weeks 4, 12, and 24/Premature Discontinuation.

Assessments of secondary efficacy variables

- Patient satisfaction VAS will be administered by independent researchers at Baseline (Day 1), Weeks 4, 12, and 24/Premature Discontinuation.
- Illicit opioid and non-opioid drug use measured by UDS and self-reports will be collected by independent researchers at all mandatory scheduled visits from Screening to Week 24/Premature Discontinuation.
- Self-reports of drug accountability (collected by the Investigator) at Weeks 4, 8, 12, 16, 20, and 24/Premature Discontinuation.
- SURE, EQ-5D, OSTQOL, PGIC, TBQ, ORBIT, SF-36, DASS-21, WPAI:GH, and AD-SUS will be administered by independent researchers at Baseline (Day 1), Weeks 12 and 24/Premature Discontinuation. PGIC will not be assessed on Day 1.
- Self-reported overdoses of illicit opioids (including BPN) and other illicit drugs will be collected by independent researchers at all mandatory scheduled visits from Baseline (Day 1) to Week 24/Premature Discontinuation.
- COWS and Craving VAS will be administered by the Investigator at Baseline (Day 1), Weeks 4, 12, and 24/Premature Discontinuation.

Assessments of safety variables

AEs will be assessed by the Investigator at all clinic site visits.

Statistical Methods (Data Analysis)

Primary Efficacy Analysis

The Week 24 assessment in TSQM global satisfaction score, is the primary variable and will be analysed over time by a longitudinal data analysis method using Mixed Model Repeated Measures (MMRM) methods. All post-baseline observations will be utilised; missing values will remain as missing, i.e. no attempt will be made to impute missing values, and only observed values will be used in the data analysis. The model will include treatment, post-baseline weeks, treatment by week interaction as fixed effects. The covariance will be assumed to be unstructured. If the estimates do not converge, Statistical Analysis System default covariance structure (Variance Components) may be assumed.

The estimated treatment effects, treatment differences, and the two-sided 95% confidence intervals (CI) of the treatment differences at all post baseline time points will be presented. The primary comparison will be the treatment difference at Week 24.

Secondary Efficacy Analyses

- Retention in treatment will be compared between treatments with a log-rank test.
- For continuous endpoints, the same methodology as for the primary endpoint will be used, where appropriate, with further details provided in the Statistical Analysis Plan.
- For variables based on UDS, the percent weeks will be analysed in an analysis of variance with treatment as factor. The cumulative distribution function of these variables will be compared between treatments with a Wilcoxon test. In addition, the responder rate defined as 75% negative UDS (with and without self-reports) will be calculated and compared with a 95% CI for the difference. This will also include a description of the relative risk with the associated 95 % CI.
- Health-economic endpoints will be summarised using descriptive statistics.

Safety Analyses

AEs will be summarised using descriptive statistics.

Analysis Sets

All efficacy variables will be assessed using the Full Analysis Set (FAS) and all safety evaluations will be performed using the safety analysis set. The FAS comprises all randomised patients who were administered at least one dose of trial treatment and for which data for the endpoints to be analysed are available. The safety analysis set comprises all randomised and treated patients and is analysed according to the actual treatment received.

Sample Size Determination

All endpoints will be analysed using descriptive statistics, including 95% CIs. As the primary outcome measure (TSQM) has not previously been used in this type of trial with these substances, the residual standard deviation from an analysis using an MMRM method in a trial studying the treatment of multiple sclerosis was used. With a sample size of 60 patients per treatment arm, the 95% CI for the treatment difference would then extend approximately 9.3 units from the estimated difference in either direction. This precision is judged as sufficient for the current trial.

2 INTRODUCTION

2.1 Background

2.1.1 Opioid Dependence

Opioid dependence is a neurobehavioral disorder characterised by repeated, compulsive seeking, and use of an opioid despite adverse social, psychological, and/or physical consequences (ICD-10). Dependence on opioids constitutes a huge global burden to patients suffering from the disease, their families and the wider society (1).

Opioid dependence is a chronic and relapsing-remitting brain disorder that requires long-term treatment (2). It is estimated that 33 million people misused opioids globally in 2014 and of these, 17 million people misused opiates (heroin, morphine or opium) (1). Worldwide there were an estimated 207,400 drug-related deaths in 2015, one third of which were due to overdoses. Illicit opioids were responsible for a majority of these deaths, with more than 33,000 deaths reported only in the US in 2015 (1, 3). There were 1,489 accidental deaths from overdose reported in Australia in 2015, and opioids are responsible for most overdose deaths (4). In several countries, there is a trend of increasing overdose deaths from methadone and potent synthetic opioids, like fentanyl, as shown by recent statistics (4-8). This may also be related to poor adherence to current daily medication assisted treatment (MAT), with methadone and buprenorphine (BPN), the two most commonly used medications for treatment of the disease with continued on-top use of illicit opioids, as well as to diversion and misuse of these medications.

The number of patients receiving opioid pharmacotherapy treatment in Australia almost doubled between 1998 and 2015 (9). Over 48,000 Australians received pharmacotherapy treatment for their opioid dependence on a specific single day in June 2015.

Currently, methadone, BPN sublingual (SL) tablets and BPN/naloxone (BPN/NX) SL tablets or SL film are the medications registered in Australia for long-term maintenance treatment for patients with opioid dependence.

Buprenorphine is a partial mu opioid receptor agonist, and together with appropriate counselling and psychotherapy, has been shown to be effective in the treatment of opioid dependence. BPN produces dose-dependent reduction in opioid withdrawal and attenuates the euphorigenic effects of exogenously administered opioids, two critical mechanisms that reduce illicit opioid use and decrease risk of relapse (10, 11). Over time, MAT with BPN therefore leads to a reduction in mortality compared to no MAT in patients with opioid dependence (12). As a partial receptor agonist, BPN has as a good safety profile with less risk for respiratory depression and overdose and it also appears to have less cardiac toxicity compared to methadone (12). Naloxone has been added to some formulations of BPN in order to try to reduce parenteral misuse of the product.

Daily SL administration of BPN or BPN/NX however is associated with a risk for low compliance and suboptimal dosing and thereby non-sufficient opioid receptor blockade, leading to a risk of overdoses with illicit opioids during treatment (13, 14). For methadone, the risk for fatal overdoses appears to be particularly high during the first induction phase of treatment (15). A second issue with both SL BPN and BPN/NX and methadone is the risk of diversion, abuse and misuse, which, in addition to an increased risk of overdoses with the diverted and misused medications, paradoxically also often lead to underdosing of the patients due to fear among physicians of diversion of their prescribed medication (16). Administration of SL BPN, SL BPN/NX and methadone is therefore supervised in many countries and treatment settings and this has been shown to be a potential barrier to entering and adhering to treatment and also

stigmatizing for the patients (17, 18). Finally, there is a risk of accidental paediatric exposure and fatalities to SL BPN, SL BPN/NX and methadone if the medication is prescribed to outpatients and stored in their homes (19). There is a clear unmet medical need for treatment options addressing these issues with MAT of opioid dependence with SL BPN and methadone.

In addition to the medical issues with MAT with SL BPN and methadone, there is also a need to address the burden of these treatments to society from a health economic point of view. There is a low treatment retention and adherence in MAT with SL BPN, SL BPN/NX and methadone, with continued illicit use of opioids. The long-term treatment outcomes in MAT are reflective of the severity of opioid dependence as a chronic relapsing disease (20). Although SL BPN, SL BPN/NX and methadone are cost-effective compared to no pharmacological intervention there is a need for further studies of the impact on both healthcare and societal economic outcomes of MAT (21, 22). There is also a need to study these outcomes in relation to the quality of life (QoL) gained with MAT over time and the impact of continued use of illicit opioids (23). A low adherence to MAT with SL BPN, SL BPN/NX and methadone is also contributing to the low work productivity and continued criminal activity in this patient population leading to a high societal cost of treatment (24, 25). Finally, the economic cost of diversion and misuse of SL BPN, SL BPN/NX and methadone is considerable (26).

2.1.2 CAM2038

CAM2038 is a long-acting BPN formulation being developed for the treatment of opioid dependence disorders and chronic pain. CAM2038 has been designed to deliver prolonged therapeutic doses of BPN, in the range of currently approved daily BPN products. CAM2038 uses a unique, low viscosity, lipid-based FluidCrystal® injection depot technology containing dissolved BPN and is subcutaneously (SC) administered by healthcare professionals at weekly (CAM2038 once weekly [q1w]) or monthly (CAM2038 once monthly [q4w]) intervals. The CAM02038 products are available in multiple fixed doses, and the weekly and monthly durations of CAM2038 are intended to allow for flexible and individualised therapy across treatment phases of opioid dependence, from initiation and stabilization to maintenance treatment.

The principle behind the proprietary FluidCrystal injection depot technology is a liquid-to-gel phase transition, occurring immediately as the lipid-based FluidCrystal system is exposed to *in vivo* conditions of SC tissue. The phase transition proceeds from the outside towards the center of the injected FluidCrystal by absorption of minute quantities of water. Thus, injection of CAM2038 q1w and q4w into SC tissue results in an immediate and spontaneous formation of controlled BPN release matrix providing long-acting release in vivo with a minimum initial burst release. The dual nature of the FluidCrystal system, i.e., a true liquid drug product in vitro before injection and stable gel in vivo after injection, enables a ready-to-use drug product in a prefilled syringe. CAM2038 q1w and q4w are designed for convenient and safe SC injection using a pre-filled syringe including a needle safety device and with no need for mixing or temperature adjustment prior to administration. In addition, the injection volumes for CAM2038 q1w and q4w are relatively low (from 0.15 to 0.6 mL volume depending on dose and product) and can be administered using a fine gauge needle (23 G). Overall, these ready-to-use, long-acting CAM2038 depots have been designed with a focus of enabling easy administration, dosing flexibility, and importantly, minimizing risks of misuse, diversion and poor patient compliance.

The clinical development program with CAM2038 for the treatment of opioid dependence comprises 7 completed clinical trials, whereof 2 are in healthy volunteers and 5 in patients with opioid dependence. In the trials in patients with opioid dependence in the clinical development program, 531 patients were exposed to CAM2038 q1w at doses of 8 to 32 mg, corresponding to

127.5 subject-exposure years, and 346 patients were exposed to CAM2038 q4w at doses of 64 to 160 mg, corresponding to 142.5 subject-exposure years. As some patients in the trials could receive both q1w and q4w, the total number of patients exposed to CAM2038 is 594, corresponding to 264.3 subject-exposure years and a total of 8513 injections.

As CAM2038 q1w and q4w were considered to have acceptable safety profiles in the completed trials, using the same doses in this trial is justified.

2.2 Rationale for Conducting the Trial

This trial is intended to study CAM2038 in treatment of adult outpatients with opioid dependence in a real-life setting. The current standard of care of opioid dependence is daily MAT, which has several issues, such as stigma for the patient, burden on the healthcare system, and poor treatment adherence. As CAM2038 represents a new treatment option for patients, offering potential advantages over BPN standard of care, such as weekly and monthly dosing, and minimal risk of diversion, misuse, and accidental paediatric exposure, it is relevant to study the differences between these two treatment options. Outcomes relevant to study include the treatments' respective impact on patient's satisfaction of treatment and other patient reported outcomes (PROs), as well as understanding the potential health economic impact and resource utilization with CAM2038 treatment.

2.3 Dose Rationale

The CAM02038 products are available in multiple fixed doses, and the weekly and monthly durations of CAM2038 are intended to allow for flexible and individualised therapy across treatment phases of opioid dependence, from initiation and stabilization to maintenance treatment.

The dose range and the flexible dose regimen of CAM2038 to be used in this trial were considered to have acceptable safety profiles for treatment up to 48 weeks in the two Phase 3 trials in the clinical program. The dose range for CAM2038 from 8 mg to 32 mg q1w and 64 mg to 160 mg q4w corresponds to the doses of BPN standard of care approved for MAT of opioid dependence in Australia. Thus, patients currently treated with BPN standard of care can be transitioned directly to an equivalent dose of CAM2038.

Additional information about CAM2038 can be found in the current edition of the Investigator's Brochure (IB).

The comparator treatment, BPN standard of care (for example, SL BPN/NX), will be administered in line with the doses approved for MAT of opioid dependence in Australia.

The treatment duration of 24 weeks is in line with previous prospective randomised controlled clinical trials in this disease.

2.4 Overall Benefit/Risk Aspects

CAM2038 is formulated as a weekly and a monthly depot (CAM2038 q1w and CAM2038 q4w), both containing the active ingredient BPN. CAM2038 has been designed to deliver prolonged therapeutic doses of BPN, in the range of currently approved daily SL BPN products. The CAM2038 products will be available in multiple fixed doses, and the weekly and monthly durations of CAM2038 are intended to allow for flexible and individualised therapy across all treatment phases of opioid dependence; from initiation and stabilisation to longer-term maintenance treatment.

Compared with other standard of care products for MAT of opioid dependence on the market, CAM2038 q1w and q4w have several potential advantages, addressing many of the unmet medical needs:

- Less use of illicit opioids compared to standard treatment: CAM2038 was shown to increase the likelihood of adherence to treatment in terms of urine drug screen (UDS) negative for illicit opioids compared to current standard treatment with SL BPN/NX in a pivotal, double-blind, double-dummy Phase 3 clinical trial. These results were further supported by a long-term Phase 3 safety trial of CAM2038, showing high trial retention and low overall mean percentage of positive UDS across the 48-week trial period.
- Long-acting BPN release and blocking of opioid effects and overdoses: Treatment with CAM2038 has been shown to result in prolonged BPN release across the dosing period, with less fluctuations and more stable BPN exposure levels compared to current standard treatment with SL BPN, as shown in three clinical Phase 1 trials. In addition, CAM2038 was shown to provide a rapid and sustained blockade of the effects of exogenously administered opioids in a clinical Phase 2 trial. The results support protection of patients from illicit opioid use and potentially fewer occurrences of opioid overdoses.
- Minimal risk of diversion, misuse and accidental paediatric exposure: Due to administration by health care professionals and long-acting effects, CAM2038 is expected to reduce the grave public health risks of misuse, abuse and diversion, including accidental paediatric exposure of current MAT.
- Reduced stigma and burden of daily supervised administration of MAT: Use of CAM2038 is expected to reduce the stigma and burden of treatment by eliminating the need for daily dosing with supervised dispensing by the weekly or monthly administration compared to currently available daily treatment options.
- Favourable safety profile: BPN, as a partial opioid mu-receptor agonist, has as a better safety profile than full opioid mu-receptor agonists currently used in MAT, such as methadone, as BPN has a ceiling effect on respiratory depression with potential to protect against opioid overdosing. In the present clinical development programme, no emerging safety issues or important risks have been identified. Tolerability has been overall good and comparable to currently available treatments with SL BPN or BPN/NX.

In the completed trials in the clinical development programme, a total of 729 subjects (of which 549 were patients with opioid dependence) were exposed to CAM2038 for up to 48 weeks. Except for mild to moderate injection site reactions, which are expected with SC injection formulations, the CAM2038 safety profile in these trials was comparable to the well-established safety profile of BPN.

The most commonly reported adverse events (AEs) with CAM2038 in the two Phase 3 trials in the clinical development programme included injection site pain (12.3%), injection site swelling (8.2%), headache (7.7%), injection site erythema (7.5%), and nausea (7.0%). Across all trials, 118 subjects (16.2%) receiving CAM2038 reported a total of 385 injection site AEs. The most commonly reported injection site AEs were injection site pain, injection site erythema and injection site swelling. The local tolerability was good and all injection site AEs were mild or moderate, except for a single transient event of severe injection site pain that resolved within a day.

Across all trials, a total of 17 subjects (2.3%) receiving CAM2038 experienced 20 treatment-emergent serious adverse events (SAEs). Road traffic accident and seizure were reported in 2 subjects each; all other SAEs were reported in 1 subject each. One death occurred during the clinical trials; a subject on CAM2038 was involved in a fatal road traffic accident

deemed unrelated to the trial medication. There was 1 treatment-related SAE (vomiting) occurring within 30 days after the last dose of CAM2038.

The potential risks identified for CAM2038 are described in the current edition of the IB, including a potential risk associated with accidental intravascular injection. The potential risk of accidental intravascular injections is generally applicable for any product intended to be injected SC or intramuscularly. Adherence to injection procedure minimises the risk of intravascular injection. In case of an intravascular administration of CAM2038, the patient should be immediately referred to a hospital and monitored closely for any adverse signs or symptoms by a health care professional.

In conclusion, the safety profile of CAM2038 is comparable to approved treatments with SL BPN, and good local tolerability was demonstrated with findings limited to a transient and mostly mild to moderate cases of injection site AEs such as pain, swelling and erythema.

The safety monitoring practices to be used in this trial are adequate to protect the patients' safety.

Patients in both treatment groups will receive active treatment. In addition, an indirect health benefit to the patients enrolled in this trial is the free medical tests received during the trial.

In summary, the available information suggests that the present clinical trial with CAM2038 and BPN standard care has a favorable benefit/risk profile.

3 TRIAL OBJECTIVES AND ENDPOINTS

The objectives of this trial and the corresponding endpoints are listed in Table 1.

Table 1. Trial Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare patient satisfaction with CAM2038 to BPN standard of care in adult outpatients with opioid dependence	• Treatment Satisfaction Questionnaire for Medication (TSQM) global satisfaction score
Secondary	
• To assess patient satisfaction with treatment	• TSQM effectiveness score • TSQM side effects score • TSQM convenience score • Patient satisfaction visual analogue scale (VAS)
• To assess treatment effects on illicit, non-prescribed and unsanctioned prescribed use of opioids	• Illicit opioid drug use measured by urine drug screen (UDS) and self-reports of illicit opioid drug use by timeline follow-back method (TLFB)
• To assess treatment effects on illicit drug use other than opioids	• Illicit drug use measured by UDS and self-reports of drug use by Australian Treatment Outcomes Profile (ATOP)
• To assess treatment effects on retention in treatment	• Retention in treatment
• To assess treatment effects on adherence to medication	• Trial drug adherence measured by dispensing records (for CAM2038) and self-reports of drug accountability (for BPN standard of care)
• To assess treatment effects on quality of life and patient functioning	• Substance Use Recover Evaluator (SURE) • EuroQol five dimensions health questionnaire (EQ-5D) • Opioid Substitution Treatment Quality of Life Scale (OSTQOL) • Patient Global Impression of Change (PGIC)
• To assess the effect on treatment related behaviours and perception of treatment	• Treatment Burden Questionnaire (TBQ) • Opioid Related Behaviours In Treatment (ORBIT) scale
• To assess treatment effects of measures of general physical, mental and psychosocial functioning	• Short Form 36 (SF-36) • Depression, Anxiety and Stress Scale 21 (DASS-21)
• To assess treatment effects on health economic outcomes (HEOs) including treatment utilization	• Work Productivity and Activity Impairment Questionnaire: General Health (WPAI:GH) • Estimates of health care resource utilization (HRU) through modified Alcohol & Drug adapted Adult Service Use Schedule (AD-SUS) questionnaire • Estimates of social service utilisation (AD-SUS questionnaire) • Estimation of quality-adjusted life years (QALYs)
• To assess treatment effects on criminal activity	• Criminal offences and incarcerations during the trial (AD-SUS questionnaire)

• To assess treatment effects on diversion and misuse of the trial medications	• Self-reported diversion and misuse of the trial medications using ORBIT (for BPN standard of care) • Self-reported overdoses
• To assess treatment effects on opioid withdrawal symptoms	• Clinical Opiate Withdrawal Scale (COWS)
• To assess treatment effects on opioid cravings	• Craving visual analogue scale (Craving VAS)
• To assess the safety and tolerability of CAM2038	• AEs

4 INVESTIGATIONAL PLAN

4.1 Overall Trial Design and Plan

This is a prospective, randomised, open-label, active-controlled, multi-center trial comparing PROs of CAM2038 with BPN standard of care (for example, SL BPN or SL BPN/NX) in adult outpatients with opioid dependence. An overview of the trial design is shown in Figure 1.

Opioid dependent patients who are either currently receiving MAT with SL BPN or BPN/NX, or patients who are actively seeking BPN standard of care treatment but who have not yet begun a treatment regimen, may be eligible for the trial. Patients currently on MAT with methadone may be included after conversion to BPN standard of care according to local practice for at least 1 week before randomisation.

Patients who have previously received treatment with CAM2038 or another BPN injection depot product are eligible for the trial if they have not been treated with these products for the past 90 days before Screening. Patients should be willing to remain on BPN treatment for the duration of the trial.

Patients will be randomised in a 1:1 ratio to either weekly or monthly treatment with CAM2038 or daily BPN standard of care MAT. Stratification by new to treatment will be applied (i.e. by patients who have not received MAT within 30 days before Screening).

The trial will consist of a Screening Period of up to 4 weeks duration, a Treatment Period of 24 weeks duration, and a Follow-up Period of 2 weeks duration.

CAM2038 will be administered by either weekly (CAM2038 q1w) or monthly (CAM2038 q4w) SC injections. Patients receiving CAM2038 can be switched between the weekly and monthly products at any time during the entire trial at the discretion of the treating Investigator. The BPN standard of care will be administered as prescribed product according to the local standard of practice and may be dispensed at local clinics or community pharmacies as per usual practice.

Patients in the CAM2038 arm will be allowed to receive supplemental treatment during the trial with SC injections of CAM2038 q1w 8 mg at the discretion of the treating clinical investigator up to a maximum of 32 mg per week for CAM2038 q1w or 160 mg per month for CAM2038 q4w. Dose adjustments (up or down titrations) in both arms after monitoring of the patient's clinical response to the treatment will also be allowed at any time during the trial. Documentation of titration and accountability will be done at each visit were trial treatment is administered/dispensed and at the Week 24/premature discontinuation visits. Switching between CAM2038 and BPN standard of care during the trial will not be allowed.

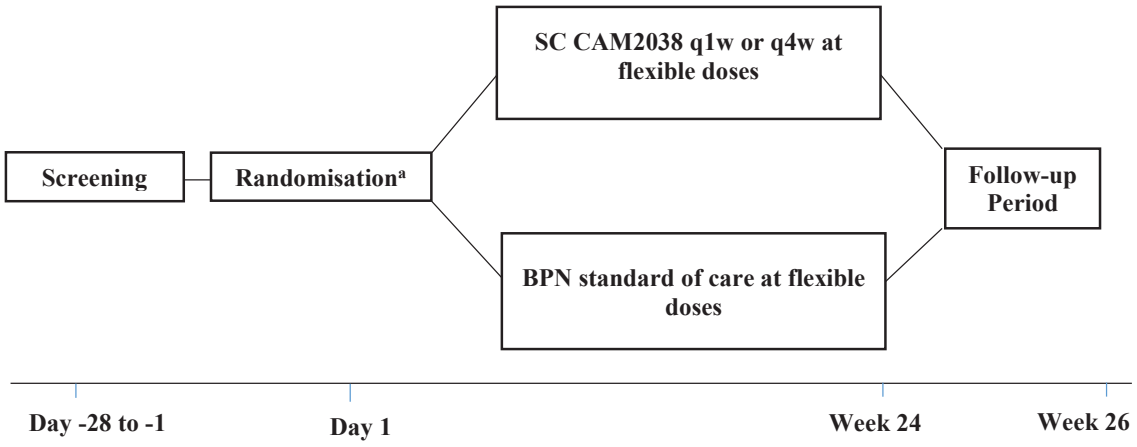
Mandatory scheduled clinic site visits where the Investigator performs safety assessments and where independent researchers administers efficacy assessments (UDS and PROs) will take place on Day 1 (Baseline/Randomisation), and at Week 4 (Day 28 ± 7), Week 8 (Day 56 ± 7), Week 12 (Day 84 ± 7), Week 16 (Day 112 ± 7), Week 20 (Day 140 ± 7) and Week 24 (Day 168 ± 7). Depending on the treatment the patient is receiving (weekly or monthly CAM2038, or BPN standard of care), dosing may occur at the same time as a mandatory scheduled clinic visit, or at separate visits. For patients who have not been previously treated with BPN, the randomisation process can take place on Day -3 to Day -1, depending on the time needed to obtain approval from local authorities to start treatment with BPN products. The randomisation can be performed provided that patients are eligible for inclusion based on assessments performed at the Screening Visit, including the safety laboratory tests. The randomisation can be performed without the patient being present at the clinic. When the patient visits the clinic for the Day 1 (baseline) visit, the approval for starting treatment must be available prior to administration of trial treatment. Efficacy and safety assessments must be performed prior to dose administration.

Patients who miss a scheduled dosing visit by more than 7 days while receiving CAM2038 q1w or BPN standard of care, or by more than 30 days while receiving CAM2038 q4w, will be considered as discontinued from trial treatment. Patients who discontinue trial treatment are still eligible to continue in the trial and may be treated according to clinical practice, outside the trial setting, at the discretion of the Investigator.

Investigators will be instructed to provide psychosocial case management and counselling for patients during the trial according to local guidelines and to provide counselling visits independently of the mandatory scheduled visits.

The Follow-up Visit/Contact at Week 26 is the last protocol specified contact with the patient.

Figure 1. Trial Design



a For patients who have not been previously treated with BPN, the randomisation process can take place on Day -3 to Day -1, depending on the time needed to obtain approval from local authorities to start treatment with BPN products.

4.2 Rationale of Overall Trial Design and Choice of Control Groups

4.2.1 Trial Design

The choice of selection criteria allows for a broad group of potential patients who will be eligible for participation, including patients not currently receiving BPN treatment for their opioid dependence.

The evaluation of efficacy and safety will be performed in an open-label manner, consistent with standard practice for long-term safety follow-up trials. To minimise bias, patients will be randomly allocated to treatment with CAM2038 or BPN standard of care.

BPN standard of care (for example SL BPN or SL BPN/NX) was chosen as a comparator as it represents the standard of care for MAT of opioid dependence and uses the same active ingredient as CAM2038 (BPN) but with a different route of administration and dosing regimen. Given the availability of an effective existing treatment for opioid dependence, the use of a placebo-controlled trial was considered unethical due to the high risk of failure of these patients on placebo treatment, and the potential harms associated with treatment failure.

A treatment duration of 24 weeks was considered appropriate and is in line with previous prospective clinical randomised controlled trials in the disease (27-29).

4.2.2 Selection of Endpoints

The primary endpoint for this trial, Treatment Satisfaction Questionnaire for Medication (TSQM), was chosen as it is a good way to measure satisfaction with treatment, has good psychometric properties, is validated, and has been used in a wide range of patient populations and clinical trials, albeit not in trials of patients with opioid dependence.

The secondary endpoints of the trial assess other treatment effects of CAM2038 including effects on QoL and patient functioning, health economic outcomes (HEOs), criminal offences and incarcerations, diversion and misuse of the trial medications, and consequences of incidents of lapse to illicit opiate use. A number of these outcomes have not been studied in this patient population in a comprehensive clinical trial of this duration before. The outcomes will be studied with a number of evaluation instruments, some which are partially overlapping, including some disease-specific questionnaires such as the Substance Use Recover Evaluator (SURE), Treatment Burden Questionnaire (TBQ), and Opioid Substitution Treatment Quality of Life Scale (OSTQOL) as well as general QoL and HEO questionnaires such as EuroQol five dimensions health questionnaire (EQ-5D), Short Form 36 (SF-36), Work Productivity and Activity Impairment Questionnaire: General Health (WPAI:GH), and the modified Alcohol & Drug adapted Adult Service Use Schedule (AD-SUS) questionnaire. The trial will thereby provide new information about the efficacy of CAM2038 and more broadly the extent to which this product addresses the unmet needs and burdens of currently approved MAT of opioid dependence.

4.3 Follow-up Procedures

All patients will enter a 2-week Follow-up Period. At the end of the period, the Investigator will contact the patient to assess the patient's well-being and any AEs. The follow-up contact can either be a visit to the clinic or a phone call.

4.4 Trial Duration

Planned first patient first visit: approximately Q3, 2018

Planned last patient first visit: approximately Q1, 2019

Expected total duration of the trial: approximately 30 weeks, including Screening and Follow-up Periods.

4.5 Planned Number of Trial Sites and Patients

Approximately 160 patients will be screened at approximately 6-10 trial sites to achieve approximately 120 randomised patients.

5 SELECTION OF TRIAL POPULATION

5.1 Trial Population

5.1.1 Inclusion Criteria

Patients meeting all of the following criteria will be eligible to participate in the clinical trial:

1. Able to provide written informed consent to participate in the trial and able to understand the procedures and trial requirements
2. Willingness and ability to comply with the protocol
3. Adult male or female patient (≥ 18 years old)
4. Meet the criteria for opioid dependence as defined by either the criteria for moderate to severe opioid use disorder in the Diagnostic and Statistical Manual of Mental Disorders – 5th Edition (DSM-5) OR opioid dependence in the International Statistical Classification of Diseases and Related Health Problems – 10th Edition (ICD-10) according to local practice
5. Appropriate candidate for MAT with a partial opioid agonist as determined by the Investigator and is willing to continue in BPN treatment for the duration of the trial
6. Female patients of childbearing potential must be willing to use a highly effective method of contraception during the entire trial (see Section 7.2.10)

5.1.2 Exclusion Criteria

Patients meeting any of the following criteria will not be eligible to participate in the clinical trial:

1. Previous participation in this trial
2. Known mental incapacity or language barriers precluding adequate understanding of the informed consent information and the trial activities
3. Patient is pregnant, lactating, or planning to be pregnant during the trial
4. Unwilling or unable to comply with the requirements of the protocol (e.g. current or pending incarceration) or are in a situation or condition that, in the opinion of the Investigator, may interfere with participation in the trial
5. Participating in any other clinical trial in which medication(s) are being delivered or have used an investigational drug or device within the last 30 days before screening (90 days if treated with a BPN depot product)
6. Any known allergy, hypersensitivity or intolerance to BPN or NX or any related drug, or history of any drug hypersensitivity or intolerance which in the opinion of the Investigator, would compromise the safety of the patient or the trial
7. On the staff, affiliated with, or a family member of the personnel directly involved with this trial.
8. Severe respiratory insufficiency
9. Severe hepatic insufficiency
10. Any other contra-indicated serious medical condition, including unstable and severe pain, which in the opinion of the investigator may prevent the patient from safely participating in trial
11. Clinically significant laboratory abnormalities, which in the opinion of the Investigator may prevent the patient from safely participating in trial
12. History of risk factors of Torsades de Pointes heart arrhythmia (e.g., heart failure, hypokalemia, family history of long QT syndrome) or an electrocardiogram (ECG) demonstrating a clinically significant abnormality, as judged by the Investigator

13. Requires chronic use of agents that are strong inhibitors or inducers of cytochrome P450 3A4 (CYP 3A4) such as some azole antifungals (e.g. ketoconazole), macrolide antibiotics (e.g. clarithromycin), or protease inhibitors (e.g. ritonavir, indinavir, and saquinavir)
14. Recent history of significant suicidal ideation or active suicidal behavior, in the opinion of the Investigator
15. Participants with serious untreated psychiatric comorbidity at the discretion of the Investigator

5.2 Method of Assigning Patients to Treatment Groups

5.2.1 Recruitment

Participant recruitment will occur from patients of participating clinical services, and include patients already enrolled in SL BPN treatment, and patients with opioid dependence seeking to enrol in treatment during the recruitment period of the trial. Recruitment strategies will differ for existing versus new patients.

For new patients presenting to participating services seeking to enter opioid substitution treatment with BPN, clinicians involved in the assessment of the patient (nursing and medical staff) will inform the patient of the trial as part of the routine clinical assessment, and if the patient is interested in participating, they will be provided with the Independent Ethics Committee (IEC)-approved Patient Information and Informed Consent Form (ICF). A trial Investigator will then perform the consenting process and request written informed consent from the participant.

For existing patients of participating services, the approach will involve informing all participants in BPN treatment of the trial through (a) direct communication with case workers and treating medical staff at routine clinical review appointments; and (b) posters informing patients of the trial in participating clinic waiting rooms, and to speak to their case worker or treating doctor for more information. Patients will be briefly informed of the trial by the clinicians and provided with the IEC-approved Patient Information and ICF. If interested in participating in the trial, a trial Investigator will then perform the consenting process and request written informed consent from the participant.

Each site will maintain a screening log of all patients screened.

5.2.2 Randomisation

To minimise bias, eligible patients will be randomised 1:1 to one of the treatment groups (CAM2038 or BPN standard of care), using an interactive web-based randomisation system (IWRS) provided by the contract research organization (CRO). Stratification by new to treatment will be applied. With new to treatment means that the patients should not have received MAT within 30 days before Screening.

5.2.3 Blinding

This is an open-label trial, no blinding will be used.

5.3 Prior and Concomitant Medication/Therapies

All non-trial medications, including prescription, over-the-counter, or herbal therapies, used by the patient will be documented for the 30 days prior to Screening and throughout the trial. The Investigator will determine if the prior/concomitant medication(s) affect the patient's eligibility

to participate or continue to participate in the trial. The following restrictions on concomitant medications will be in place during the trial:

- Opioid receptors are likely to be occupied by BPN, which may reduce the analgesic effects of an opioid. The dissociation of BPN from the receptors may take several days following discontinuation of BPN standard of care treatment, or up to 2 weeks (for CAM2038 q1w) or at least 2 months (for CAM2038 q4w) following the last CAM2038 injection. Therefore, patients requiring analgesic emergency treatment or anesthesia for surgery should ideally be treated with a non-opioid analgesic. Opioids may be used with caution, but as higher doses may be required for analgesic effect, there may be a higher potential for toxicity with opioid administration. The clinical course should carefully be evaluated and be fully documented for patients who have a requirement for any opioid analgesic for >7 days continually or general anesthesia for surgery.
- BPN is metabolised via CYP3A4. Because CYP3A4 inhibitors may increase plasma concentrations of BPN, patients receiving BPN should be monitored and may require dose reduction if combined with potent CYP3A4 inhibitors such as azole antifungals (e.g. ketoconazole), macrolide antibiotics (e.g. erythromycin), and human immunodeficiency virus (HIV) protease inhibitors (e.g. ritonavir, indinavir, and saquinavir).
- Concomitant use of CYP3A4 inducers with BPN may decrease BPN plasma concentrations. It is recommended that patients receiving BPN should be closely monitored if inducers (e.g. phenobarbital, carbamazepine, phenytoin or rifampicin) are co-administered. The dose of either BPN or the CYP3A4 inducer may need to be adjusted accordingly.
- Concomitant use of monoamine oxidase inhibitors (MAOI) may cause exacerbation of the opioids effects, based on experience with morphine. It is recommended that patients receiving BPN and MAOI should be closely monitored.
- Concomitant use of other narcotic anesthetics, benzodiazepines, phenothiazines, other tranquilisers, or other central nervous system (CNS) depressants (including alcohol and sedative/hypnotics) may cause respiratory and CNS depression. Use of these substances should be minimised during treatment with BPN products. Patients should be advised of the danger of concomitant use of sedatives while participating in the trial. Patients should be explicitly advised of the danger of use and abuse of benzodiazepines and alcohol while under treatment with CAM2038 or SL BPN or BPN/NX.

5.4 Withdrawal Criteria

Withdrawal from trial treatment

A patient may be withdrawn from trial treatment at the discretion of the Investigator (if clinically indicated), at the patient's own request, or if the patient becomes pregnant.

Patients who discontinue trial treatment, are still eligible to continue in the trial, and may be treated according to clinical practice, outside the trial setting, at the discretion of the Investigator.

Efforts should be made by the Investigator to continue collection of efficacy and safety assessments at the protocol-defined trial visit intervals, including concomitant medications, and AEs in patients that discontinue trial treatment, unless the patient withdraws his/her consent at the time of early discontinuation. The Investigator should also ask the patient to return for the Follow-up assessments, provided that the patient has not withdrawn consent for those assessments. If a patient refuses to complete early termination procedures and/or Follow-up, this information will be recorded.

Withdrawal from trial

A patient is free to withdraw his/her consent and discontinue participation in the trial at any time for any reason. A patient's participation must therefore be terminated immediately upon his/her request, and the reason(s) for discontinuation appropriately documented.

A patient must be discontinued from the trial for any of the following reasons:

- Safety reasons, including AEs or significant concomitant illness, injury, or urgent surgeries/procedures that would, in the judgment of the Investigator, affect assessments of clinical status to a significant extent
- At the request of the Sponsor, regulatory agency, or Ethics Committee
- Patient is lost to follow-up

A patient may also be discontinued from the trial, at the discretion of the Investigator and/or Sponsor, for any of the following reasons:

- Patient refuses or is unable to adhere to the trial protocol
- Administrative discharge due to non-adherence with site policies (e.g. violence towards other clients or staff)
- Patient who misses two or more consecutive monthly assessment visits

The Investigator must maintain a record of all patients who discontinue from the trial prior to completion; the reason(s) for trial discontinuation will be documented. If a patient chooses to withdraw from the trial, the Investigator should make a reasonable attempt to obtain and record the reason(s) for withdrawal, if possible, although the patient is not obligated to provide such a reason.

Withdrawn patients will not be replaced.

6 TREATMENTS

6.1 Treatments Administered

The treatments to be administered in this trial are summarised in Table 2.

Table 2. Trial Treatments

Treatment name:	CAM2038 50 mg/mL q1w (BPN FluidCrystal® once-weekly subcutaneous injection depot)	CAM2038 356 mg/mL q4w (BPN FluidCrystal® once-monthly subcutaneous injection depot)	BPN standard of care (comparator treatment, as prescribed by the Investigator)
Manufacturer:	Rechon Life Science AB	Rechon Life Science AB	As per Product Information
Dosage formulation:	FluidCrystal injection depot, pre-filled syringe	FluidCrystal injection depot, pre-filled syringe	As per Product Information
Unit dose strength(s)/ Dosage level(s):	8 mg, 16 mg, 24 mg, and 32 mg	64 mg, 96 mg, 128 mg, and 160 mg	As per Product Information
Route of administration:	SC	SC	As per Product Information
Dosing instructions:	Once-weekly injection	Once-monthly injection	As per Product Information
Packaging and labelling	Single dose 1 mL pre-filled syringe with plunger stopper with needle (½-inch, 23 G, 12 mm) and needle shield. Plunger rod supplied separately. The filled syringe is assembled in a safety device for post-injection needle stick prevention. Supplied in boxes (one syringe per box). Each pre-filled syringe and box will be labeled as required per country requirement.	Single dose 1 mL pre-filled syringe with plunger stopper with needle (½-inch, 23 G, 12 mm) and needle shield. Plunger rod supplied separately. The filled syringe is assembled in a safety device for post-injection needle stick prevention. Supplied in boxes (one syringe per box). Each pre-filled syringe and box will be labeled as required per country requirement.	The comparator treatment (BPN standard of care) products will be supplied as is. No trial-specific labelling will be applied.

BPN = buprenorphine, G = gauge, SC = subcutaneous

6.2 Trial Treatment Administration

6.2.1 CAM2038

CAM2038 q1w and q4w SC injections will be administered by a designated healthcare professional(s) at the trial site. Injection sites shall be rotated to avoid injection into the same site. The injection sites may be alternated between the different injection areas i.e., the buttock, thigh, abdomen, or upper arm. Detailed instructions for use, including a pictorial of available

injection areas are provided in the Trial Reference Manual. In addition to the instructions for use, the Sponsor will ensure that the persons performing the injections will be properly trained before initiation of the trial sites.

The recommended starting dose for patients not currently receiving BPN maintenance treatment is 24 mg CAM2038 q1w. An additional 8 mg dose may be administered after a minimum of 24 hours, to a maximum of 32 mg during the first treatment week.

To avoid the risk of precipitated withdrawal, the first CAM2038 administration in patients not currently on SL BPN or BPN/NX should be started when objective and clear signs of mild to moderate withdrawal are evident.

During subsequent treatment weeks dose adjustments in terms of decreases or increases in dose may be performed based on the patient's individual need (up to a maximum dose of 32 mg per week).

Patients treated with SL BPN or SL BPN/NX may be transitioned directly to weekly or monthly CAM2038 starting on the day after the last daily SL treatment dose, according to the recommendations in Table 3.

Table 3. Doses of CAM2038 q1w and q4w for Patients Transitioning from SL BPN or BPN/NX

Weekly Prescription: Daily SL BPN or BNX Dose Category	**Once Weekly CAM2038 q1w SC Injection**
≤6 mg	8 mg (0.16 mL)
8-10 mg	16 mg (0.32 mL)
12-16 mg	24 mg (0.48 mL)
18-24 mg	32 mg (0.64 mL)
Monthly Prescription: Daily SL BPN or BNX Dose Category	**Once Monthly CAM2038 q4w SC Injection**
≤6 mg	No monthly equivalent
8-10 mg	64 mg (0.18 mL)
12-16 mg	96 mg (0.27 mL)
18-24 mg	128 mg (0.36 mL)
26-32 mg	160 mg (0.45 mL)

BPN = buprenorphine; NX = naloxone; q1w = once weekly; q4w = once monthly; SC = subcutaneous; SL = sublingual

CAM2038 should be administered weekly or monthly according to individual patient's needs and clinical judgement and at doses established after initiation or switching. If required, patients randomised to CAM2038 may receive additional 8 mg injections during a dosing period, up to a maximum dose of 160 mg for the monthly injections (CAM2038 q4w), or up to 32 mg for the weekly injections (CAM2038 q1w). There must be at least one day between each supplemental 8 mg injection.

Patients may be switched from weekly to monthly dosing or from monthly to weekly dosing based on the recommendations in Table 4.

Table 4. Recommended dosing when switching between CAM2038 dosing regimens

Weekly dose of CAM2038 (q1w)	**Monthly dose of CAM2038 (q4w)**
16 mg	64 mg
24 mg	96 mg
32 mg	128 mg

To avoid missed doses, the weekly dose may be administered up to 2 days before or after the weekly time point, and the monthly dose may be administered up to 1 week before or after the monthly time point.

If a dose is missed, the next dose should be administered as soon as practically possible.

6.2.2 Comparator Treatment (BPN Standard of Care)

Patients in the comparator treatment arm (BPN standard of care) will receive a daily dose of a BPN containing product for MAT (for example, SL BPN or BPN/NX) based on the Investigator's judgment and in accordance with the product specific labelling. Patients in the BPN standard of care arm will be allowed to receive supplemental treatment with BPN standard of care during the trial at the discretion of the Investigator; the maximum daily dose should not exceed that of the current approved product labelling.

The BPN standard of care will be provided to patients enrolled in the trial according to local practice, and consistent with guidance for MAT of opioid dependence (31).

6.3 Characteristics and Source of Supply, Packaging and Labelling

CAM2038 is provided by the Sponsor and will be handled according to the principles of Good Manufacturing Practice (GMP). The labelling will comply with applicable regulatory requirements.

6.4 Conditions for Storage

Store CAM2038 below 25°C, do not refrigerate or freeze.

BPN is a Schedule 8 drug and CAM2038 must be handled and stored strictly in accordance with restrictions related to controlled drugs. CAM2038 must be kept securely locked with access limited to appropriate trial personnel, according to applicable regulations.

6.5 Blinding / Un-blinding

Not applicable, this is an open-label trial.

6.6 Treatment Compliance

6.6.1 Dispensing and Accountability

Only eligible patients participating in the trial will receive CAM2038. Only authorised site staff may administer CAM2038. Once dispensed, CAM2038 must not be relabelled or reassigned for use by other patients.

The Investigator (or his/her designated personnel) will maintain an Injection Log detailing the dates and quantities of CAM2038 administered to each patient, the location of the injection site, as well as the batch numbers. The monitor will verify the drug accountability during the trial.

Documentation of CAM2038 titration, supplemental dosing, and drug accountability will be done at all clinic visits (beginning with Day 1).

A drug accountability log for the comparator, BPN standard of care, will be maintained at the local clinic or community pharmacy in accordance with local regulations for schedule 8 drugs.

6.6.2 Assessment of Compliance

CAM2038 will be administered by a designated healthcare professional at the trial site. Dosing compliance will be recorded by the Investigator or designee at the trial site.

Patients in the comparator treatment arm (BPN standard of care) will be asked to bring any unused medication to the clinic/pharmacy for an assessment of compliance, in accordance with the local regulation for assessment of compliance for schedule 8 drugs.

Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the electronic Case Report Form (eCRF) for both treatment arms.

6.7 Return and Destruction

All used trial drug (both CAM2038 and comparator treatment) can be destroyed at the trial site or at any other certified site, such as depot, (in accordance with local requirements) after the drug accountability has been finalised and signed off by the Investigator.

All unused trial drug (CAM2038) will be accounted for and must be destroyed in a certified way after approval by the Sponsor (either at trial site or any other certified site, such as depot). All unused comparator treatment will be accounted for and must be destroyed in a certified way (in accordance with local requirements).

7 TRIAL PROCEDURES AND ASSESSMENTS

7.1 Overview

Trial procedures and their timing are summarised in Table 5.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue trial drug.

Adherence to the trial design requirements, including those specified in Table 5, is essential and required for trial conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Table 5. Schedule of Trial Procedures and Assessments

Procedure/ Assessment	Screening	Baseline	Week						Other visits	Premature Discontinuation	Follow -up
	(Day -28 to -1)	Day 1	4	8	12	16	20	24			Week 26
			± 7 days visit window								
Screening/Baseline Procedures and Assessments											
Informed consent	X										
Inclusion/ exclusion criteria	X	X									
Demographic and baseline characteristics	X										
Medical and medication history	X										
Substance use and treatment history	X										
Physical examination	X										
ECGs	X										
Safety labs[1]	X										
Vital signs	X										
Randomization		X[2]									
Efficacy Assessments											
TSQM		X[3]	X		X			X		X	
Patient satisfaction (VAS)		X[3]	X		X			X		X	
UDS for illicit opioids and	X	X	X	X	X	X	X	X		X	

Procedure/ Assessment	Screening	Baseline	Week						Other visits	Premature Discontinuation	Follow -up
	(Day -28 to -1)	Day 1	4	8	12	16	20	24			Week 26
			± 7 days visit window								
other illicit drugs											
Self-report of illicit opioid and other drug use	X	X	X	X	X	X	X	X		X	
Trial treatment adherence		X	X	X	X	X	X	X		X	
SURE		X			X			X		X	
EQ-5D		X			X			X		X	
OSTQOL		X			X			X		X	
PGIC					X			X		X	
TBQ		X[3]			X			X		X	
ORBIT		X			X			X		X	
SF-36		X			X			X		X	
DASS-21		X			X			X		X	
WPAI:GH		X			X			X		X	
AD-SUS		X			X			X		X	
Self-reported overdoses		X	X	X	X	X	X	X		X	
COWS		X	X		X			X		X	
Craving VAS		X	X		X			X		X	
Safety Assessments											
AEs	X[4]	X	X	X	X	X	X	X	X[5]	X	X
Other Assessments and Procedures											
Trial treatment administration & dose titration assessment		X	X	X	X	X	X	X	X[6]		
Documentation of psychosocial counselling		X	X	X	X	X	X	X		X	
Previous and concomitant medication	X	X	X	X	X	X	X	X		X	
Pregnancy test (female patients)	X							X		X	

Abbreviations: AD-SUS = Alcohol & Drug adapted Adult Service Use Schedule, AE = adverse event, BPN = buprenorphine, COWS = Clinical Opiate Withdrawal Scale DASS-21 = Depression, Anxiety and Stress Scale 21, ECG = electrocardiogram, EQ-5D = EuroQol five dimensions health questionnaire, ORBIT = Opioid Related

Behaviours In Treatment, OSTQOL = Opioid Substitution Treatment Quality of Life Scale, PGIC = Patient Global Impression of Change, SF-36 = Short Form 36, SURE = Substance Use Recover Evaluator, TSQM = Treatment Satisfaction Questionnaire for Medication, UDS = urine drug screen, VAS = visual analogue scale
1. Safety labs at screening includes clinical chemistry, hematology, urinalysis, and serological markers (HIV, Hepatitis B and C). Patients who have had negative HIV, hepatitis B and C tests within 3 months prior to Screening do not need to have the serological marker tests repeated at Screening. Patients who previously have had a positive HIV, or hepatitis B or C test do not need to have that specific test repeated for this trial.
2. For patients who have not been previously treated with BPN, the randomisation process can take place on Day -3 to Day -1, depending on the time needed to obtain approval from local authorities to start treatment with BPN products. The randomisation can be performed provided that patients are eligible for inclusion based on assessments performed at the Screening Visit, including the safety laboratory tests. The randomisation can be performed without the patient being present at the clinic. When the patient visits the clinic for the Day 1 (baseline) visit, the approval for starting treatment must be available prior to administration of trial treatment. Efficacy and safety assessments must be performed prior to dose administration.
3. Assessments of the TSQM, Patient satisfaction VAS, and the TBQ at the Baseline Visit is not needed for patients who are new to treatment.
4. Any new event, sign or symptom occurring in the period between Screening and Baseline (Day 1) will be recorded in the same manner as an AE.
5. AEs must be collected if the visit is a dosing visit where CAM2038 q1w or q4w is administered (including supplemental doses) or if the dose of the comparator treatment (BPN standard of care) is adjusted.
6. Trial treatment administration and dose titration assessment can take place at other visits, depending on the treatment the patient is receiving.

7.2 Screening and Baseline Procedures and Assessments

7.2.1 Informed Consent

The nature of the trial and its risks and benefits will be explained to the patient by the Investigator or designated trial personnel. The patient must voluntarily provide written informed consent on an ethics-approved ICF, prior to performing any trial-related procedures. The patient's medical records must document that the consent process has been completed and that written informed consent has been obtained from the patient prior to the initiation of any trial-specific procedures. Documentation that the patient was given adequate time to ask the Investigator (or designee) questions about their participation in the trial and that a signed and dated copy of the ICF was provided to the patient should also be included in the medical records or clinical chart.

7.2.2 Demographics

The following demographics will be recorded: age (birthdate), sex, race, and ethnicity.

7.2.3 Medical History

The complete medical history based on patient interview of 5 years prior to the screening visit and any clinically significant medical history greater than 5 years prior to the screening visit will be collected, these will include histories of acute, chronic, or infectious disease; surgical or oncologic histories; and any reported conditions affecting major body systems. All findings on medical history will be evaluated by the Investigator for clinical significance.

7.2.4 Medication History

All medications (prescription and non-prescription, herbal medications/natural health products, or investigational drugs) taken by the patients during the 30 days prior to Screening will be recorded in the source documentation as medication history.

7.2.5 Substance Use and Treatment History

A complete history of previous and current illicit drug use, substance abuse/dependence, and treatments for any substance use disorders (pharmacologic as well as non-pharmacologic) will be obtained. This will include drugs used, type, frequency and patterns of abuse, routes, doses, drug preferences, concomitant medications information regarding previous MAT of opioid dependence episodes (including lifetime duration of MAT of opioid dependence), number of episodes of methadone and BPN treatment, age when first used heroin, age at first regular heroin use, and age at first MAT of opioid dependence.

7.2.6 Physical Examinations

A physical examination including all major body systems will be performed at Screening. Height, weight and body-mass index (BMI) will be measured/calculated at Screening.

7.2.7 Vital Signs

Vital signs will consist of temperature, blood pressure (systolic and diastolic blood pressure, mmHg), pulse rate (beats per minute), and respiratory rate (breaths/min) collected while sitting, following a rest period of at least 3 minutes. Vital signs should preferably be taken prior to taking ECG and blood samples.

7.2.8 Electrocardiograms (ECGs)

12-Lead ECGs will be performed at Screening after the patient has been resting in a recumbent/supine position for at least 3 minutes. The ECGs will be signed and dated by a medically-qualified individual to confirm review of the ECG and verify whether any abnormalities are clinically significant. ECGs should preferably be taken after vital signs and prior to blood samples for clinical safety laboratory assessments.

7.2.9 Clinical Safety Laboratory Assessments

Clinical safety laboratory assessments (including clinical chemistry, hematology, serological markers [HIV and hepatitis B and C], and urinalysis) will be performed at Screening. Patients who have had negative HIV, hepatitis B and C tests within 3 months prior to Screening do not need to have the serological marker tests repeated at Screening. Patients who previously have had a positive HIV, or hepatitis B or C test do not need to have that specific test repeated for this trial. Clinical safety laboratory assessments will be performed according to local laboratory procedures. Patients' eligibility will be assessed based on the Investigator's clinical judgement of the available clinical safety laboratory assessments prior to randomisation.

The following assessments will be performed:

- Clinical chemistry: Creatinine, glucose, urea, uric acid, bilirubin, albumin, sodium, potassium, calcium, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and gamma glutamyl transferase
- Hematology: Hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red blood cell count, white blood cell count and differential (absolute and percentage), and platelets
- Urinalysis (dipstick): pH, protein, glucose, ketone, bilirubin, urobilinogen, blood, nitrite, leucocytes, and specific gravity
- Serological marker: Anti-HIV-1/2 antibodies, hepatitis B surface antigen, and hepatitis c virus antibodies

For women of childbearing potential, a urine dipstick pregnancy test will be performed at Screening and at Week 24/Premature Discontinuation. The results of the pregnancy test at Screening must be reviewed and confirmed to be negative prior to randomisation to assess the patient's eligibility for the trial.

Blood samples should preferably be taken after the assessment of vital signs and ECG.

7.2.10 Contraceptive Requirements

Women of childbearing potential must agree to use highly-effective method(s) of birth control as defined in the ICF for the duration of participation in the trial and must agree to be tested for pregnancy. Highly-effective method(s) of birth control include:

- Oral, implantable, or injectable contraceptives for 3 consecutive months before Screening, in combination with a condom.
- Intrauterine device (IUD) in combination with a condom.
- Double barrier method (condom or diaphragm)

Male patients must agree to use condoms for the duration of the trial.

7.3 Efficacy Assessments

7.3.1 Treatment Satisfaction Questionnaire for Medication (TSQM)

The TSQM is a measure of the major dimensions of patient's satisfaction with medication. Evidence suggests that the TSQM may also be a good predictor of patients' medication adherence across different types of medication and patient populations (30). The TSQM (version 1.4) comprises 14 items across four domains focusing on effectiveness (3 items), side effects (5 items), convenience (3 items), and global satisfaction (3 items) of the medication. Except for item 4 (presence of side effects; yes or no), all items have five or seven responses, scored from one (least satisfied) to five or seven (most satisfied).

7.3.2 Patients Satisfaction Visual Analogue Scale (VAS)

Patient satisfaction of treatment will be measured by a 100-mm VAS ranging from "not at all" (score = 0) to "extremely" (score = 100) (32).

7.3.3 Urine Drug Screen (UDS) for Illicit Opioids and other Drugs

Urine samples will be analysed for the presence of illicit opioids, and other drugs of abuse. Further details on sampling and analysis will be described in a separate Laboratory Manual.

7.3.4 Self-report of Illicit Opioid Use

Patients will be questioned about use of illicit or prescription opioids using a timeline follow-back (TLFB) type of interview (33).

7.3.5 Self-report of Other Drug Use

Patients will be questioned about use of other drugs using the same questions about substance use as in the Australian Treatment Outcomes Profile (ATOP) instrument (34).

7.3.6 Retention in Treatment

Retention in treatment is calculated as days in treatment since randomization until the last day of medication during the 24 weeks of treatment (plus the respective duration of CAM2038 q1w, CAM2038 q4w or BPN standard of care). Data for retention will be censored at Week 24. The Investigator should confirm a patient's discontinuation date in relation to the last dose in the eCRF.

7.3.7 Trial Drug Adherence

Trial drug adherence will be measured by a drug accountability for CAM2038, and self-reports of drug accountability for the comparator treatment (BPN standard of care).

7.3.8 Substance Use Recover Evaluator (SURE)

The SURE is a psychometrically valid patient-reported outcome measure that measures recovery from drug and alcohol dependence (35). SURE has good face and content validity, acceptability and usability for patients in recovery.

7.3.9 EuroQol Five Dimensions Health Questionnaire (EQ-5D)

EQ-5D is a standardised measure of health status developed by the EuroQol Group in order to provide a generic measure of health for clinical and economic appraisal (36).

The EQ-5D-3L descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, and extreme problems. The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results into a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state.

The EQ VAS records the patient's self-rated health on a vertical VAS where the endpoints are labelled "Best imaginable health state" and "Worst imaginable health state". The VAS can be used as a quantitative measure of health outcome that reflects the patient's own judgement.

7.3.10 Opioid Substitution Treatment Quality of Life Scale (OSTQOL)

The OSTQOL is a 38-item multidimensional PRO designed to capture aspects of QoL in patients on opioid substitution treatment (37). The items capture aspects of personal development, mental distress, social contacts, material wellbeing, opioid substitution treatment, and discrimination. The patient rates each item from 0, "does not apply to me at all" to 4, "applies to me extremely".

7.3.11 Patient Global Impression of Change (PGIC)

The self-report measure Patient Global Impression of Change (PGIC) is a single-item scale, which aims to evaluate all aspects of a patient's health and determine if there has been an improvement or not in the patient's opioid dependence (38). Patients rate their change as (1) very much improved, (2) much improved, (3) minimally improved, (4) no change, (5) minimally worse, (6) much worse, (7) very much worse.

7.3.12 Treatment Burden Questionnaire (TBQ)

The TBQ measures treatment burden without restricting the scope to a single condition or treatment context (39). The English version of the TBQ is composed of 15 items rated on a Likert scale ranging from 0 (not a problem) to 10 (big problem). It assesses the burden associated with taking medicine, self-monitoring, laboratory tests, doctor visits, need for organization, administrative tasks, following advice on diet and physical activity, social impact of the treatment, and financial burden. Item scores can be summed into a global score.

7.3.13 Opioid Related Behaviours In Treatment (ORBIT)

The Opioid Related Behaviours In Treatment (ORBIT) is a 10-item unifactorial scale with good discrimination between groups acceptable test-retest reliability and strong face validity (40). The ORBIT is validated for use in diverse patient groups receiving opioids. Each item is rated from Never (0) to Very Often (4).

7.3.14 Short Form 36 (SF-36)

The SF-36 is a widely used standardized instrument with strong psychometric properties (41). The SF-36 will be used to assess self-perceptions of general health functioning across multiple dimensions (including general, physical and emotional/psychiatric functioning). The SF-36 has shown good internal, consistency, stability, and concurrent validity in outpatients with serious mental illness. Higher scores indicate better quality of life.

7.3.15 Depression, Anxiety and Stress Scale 21 (DASS-21)

The Depression, Anxiety and Stress Scale 21 (DASS-21) is a set of three self-report scales designed to measure the negative emotional states of depression, anxiety and stress (42). Each of the three DASS-21 scales contains 7 items, divided into subscales with similar content. The Depression scale assesses dysphoria, hopelessness, devaluation of life, self-deprecation, lack of interest/involvement, anhedonia, and inertia. The Anxiety scale assesses autonomic arousal, skeletal muscle effects, situational anxiety, and subjective experience of anxious affect. The Stress scale is sensitive to levels of chronic non-specific arousal. It assesses difficulty relaxing, nervous arousal, and being easily upset/agitated, irritable/over-reactive and impatient. Scores for Depression, Anxiety and Stress are calculated by summing the scores for the relevant items. The scales of the DASS-21 have been shown to have high internal consistency and to yield meaningful discriminations in a variety of settings.

7.3.16 Work Productivity and Activity Impairment Questionnaire: General Health (WPAI:GH)

The WPAI is an instrument to measure impairments in both paid work and unpaid work (43). It measures absenteeism, presenteeism as well as the impairments in unpaid activity because of health problem during the past seven days. It has been validated to quantify work impairments for numerous diseases such as asthma, psoriasis, irritable bowel syndrome, ankylosing spondylitis and Crohn's disease. In addition, the WPAI questionnaire has been used to compare work impairments between treatment groups in clinical trials or between subjects with different disease severity levels.

The WPAI:GH consists of 6 questions: 1 = currently employed; 2 = hours missed due to health problems; 3 = hours missed other reasons; 4 = hours actually worked; 5 = degree health affected productivity while working (using a 0 to 10 VAS); 6 = degree health affected productivity in regular unpaid activities (VAS). The recall period for questions 2 to 6 is 7 days. Four main

outcomes can be generated from the WPAI-GH and expressed in percentages by multiplying the following scores by 100, with higher percentages indicating greater work productivity loss and activity impairment: 1) percent work time missed due to health = Q2/(Q2 + Q4) for those who were currently employed; 2) percent impairment while working due to health = Q5/10 for those who were currently employed and actually worked in the past 7 days; 3) percent overall work impairment due to health Q2/(Q2 + Q4) + ((1 - Q2/(Q2 + Q4)) × (Q5/10)) for those who were currently employed; 4) percent activity impairment due to health Q6/10 for all respondents. For those who missed work and did not actually work in the past 7 days, the percent overall work impairment due to health will be equal to the percent work time missed due to health.

7.3.17 Alcohol & Drug Adapted Adult Service Use Schedule (AD-SUS)

Estimates of health care resource utilization (HRU), social service utilisation and criminal offences and incarcerations during the trial will be done through the Alcohol & Drug Adapted Adult Service Use Schedule (AD-SUS) questionnaire (44).

7.3.18 Self-reported Overdoses

Patients will be questioned about overdoses of illicit or prescription opioids and other drugs of abuse.

7.3.19 Clinical Opiate Withdrawal Scale (COWS)

Clinical observations indicative of withdrawal will be assessed using the Clinical Opiate Withdrawal Scale (COWS) (45). This scale consists of 11 common opiate withdrawal signs or symptoms, rated on a numeric scale and based on a timed period of observation of the subject by the rater.

7.3.20 Craving VAS

Opioid craving will be measured by a 100-mm VAS ranging from “not at all” (score = 0) to “extremely” (score = 100) (46).

7.4 Other Assessments

7.4.1 Psychosocial Counselling

Investigators will be instructed to provide psychosocial case management and counselling for patients during trial according to local guidelines and to provide counselling visits independently of the visits for administration of the trial treatments. Documentation of counselling visits will be done by the Investigator at mandatory clinic visits. Psychosocial counselling is any intervention with a patient that is not directly related to medication treatment.

7.4.2 Prior and Concomitant Therapy

All non-trial medications, including prescription, over-the-counter, or herbal therapies, used by the patient will be documented for the 30 days prior to Screening and throughout the trial. The Investigator will determine if the prior/concomitant medication(s) affect the patient’s eligibility to participate or continue to participate in the trial.

7.5 Adverse Events and Serious Adverse Events

7.5.1 Adverse Event Definitions

An **adverse event** (AE; synonym: adverse experience) is defined as any untoward medical occurrence associated with the use of a drug in humans, in a patient or clinical trial subject administered a trial treatment and which does not necessarily have a causal relationship with this treatment (i.e., whether or not considered drug-related). An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a trial treatment, whether or not considered related to the trial treatment. Patients will be instructed to contact the Investigator at any time after enrollment if any symptoms develop.

Adverse reaction: All untoward and unintended responses to a trial treatment assessed as related to any dose administered.

AEs or SAEs assigned a causality assessment by the Investigator of "probably related" or "possibly related" will be considered by the Sponsor to be related for the purpose of defining adverse reactions and thereby also expedited reporting.

An AE is considered "unexpected" if the nature, severity, or outcome is not consistent with the reference safety information section (see current edition of the IB).

A **serious adverse event** (**SAE**) is any untoward medical occurrence that at any dose:

- Results in death;
- Is life threatening (an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability or incapacity;
- Consists of a congenital anomaly or birth defect; or
- Is another medical event.
    - Important medical events that may not be immediately life threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious. This is based on the medical and scientific judgment of the Investigator.

Other Reportable Information

Certain information, although not considered an SAE, must be recorded, reported, and followed up as indicated for an SAE (see Section 7.5.2). This includes:

- Pregnancy during exposure to a trial treatment. If a pregnancy is confirmed, use of the trial treatment must be discontinued immediately. Information about pregnancy exposure includes the entire course of pregnancy and delivery, and perinatal and neonatal outcomes, even if there are no abnormal findings. Both maternal and paternal exposures are considered other reportable information. For exposure involving the female partner of a male patient, the necessary information must be collected from the patient, while respecting the confidentiality of the partner.
- Lactation exposure to a trial treatment with or without an AE.
- Overdose of a trial treatment as specified in this protocol with or without an AE.
- Inadvertent or accidental exposure to a trial treatment with or without an AE.

Any new event, sign or symptom occurring in the period between Screening and Baseline (Day 1) will be recorded in the same manner as an AE.

7.5.2 Eliciting, Documenting, and Reporting of Adverse Events

The Investigator is responsible for ensuring that all AEs and SAEs are recorded on the AE page of the eCRF and reported to the Sponsor. AEs will be assessed from the time of informed consent until completion of all trial procedures and discharge from the trial. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

At every clinic visit, patients will be asked a standard question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalised, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications).

Information to be collected includes drug treatment, type of event, time of onset, dosage, Investigator-specified assessment of severity and relationship to trial treatment, time of resolution of the event, seriousness, as well as any required treatment or evaluations, and outcome. The AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs should be followed until they have reached a "final outcome" (recovered, recovered with sequelae, recovering, not recovered, fatal, or unknown) or the patient's participation in the trial ends, whichever comes first. Serious AEs and severe, non-serious AEs assessed as "possibly related" or "probably related" to IMP, still ongoing after ended trial participation, should be followed on a regular basis according to the Investigator's clinical judgment until a "final outcome" has been established (see Section 7.5.6).

The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition that is present at the time that the patient is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the trial, it should be recorded as an AE.

Reporting of Serious Adverse Events

Any AE which meets any of the SAE criteria (Section 7.5.1) must be reported to the Sponsor immediately (within 24 hours after the Investigator has confirmed the occurrence of the SAE) to contact details listed below, using the trial-specific SAE report form. The Investigator will assess whether there is a reasonable possibility that the trial treatment caused the SAE. Other reportable information as defined in Section 7.5.2 should also be reported to the below contact immediately (at least 3 calendar days after the Investigator has confirmed the occurrence of the information).

The Sponsor will be responsible for notifying the relevant regulatory authorities of any SAEs according to applicable legislation. The investigator is responsible for notifying the IEC directly.

The following contact information is to be used for SAE reporting:

Email: safety@camurus.com
or
International SAE fax no.: +46 46 27 07 060

7.5.3 Assessment of Severity

Severity is defined as a measure of the intensity of an AE or SAE and will be classified as mild, moderate, or severe using the following criteria:

- **Mild**: Awareness of symptoms, sign, illness, or event that is easily tolerated.
- **Moderate**: Discomfort sufficient to cause interference with usual activity.
- **Severe**: Incapacitating, with inability to work or undertake further normal activities.

Note that a severe reaction is not necessarily an SAE (e.g. a severe headache would probably not constitute an SAE; however, a mild myocardial infarction may constitute an SAE).

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. An AE characterised as intermittent requires documentation of onset and duration of each episode.

7.5.4 Assessment of Outcome

The outcome of an AE or SAE will be classified using the following outcome ratings:

0 = unknown

1 = recovered/resolved

2 = recovering/resolving

3 = not recovered/not resolved/ongoing

4 = recovered/resolved with sequelae

5 = fatal

7.5.5 Assessment of Causality

The Investigator will assess relationship to trial treatment for all AEs and SAEs. The relationship will be characterised using the following causality ratings:

- **Probably related**: An AE with a reasonable time sequence to administration of the trial treatment, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfil this definition.
- **Possibly related**: An AE with a reasonable time sequence to administration of the trial treatment, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
- **Not related**: An AE with a temporal relationship to drug administration which makes a causal relationship improbable, or in which other drugs, chemicals, or underlying disease provide plausible explanations. There is no reasonable possibility that the event was caused by the trial treatment.
- **Not applicable**: This assessment can be used, for example, in cases where the patient did not receive any treatment with trial treatment.

7.5.6 Follow-up of Adverse Events

All AEs should be followed until they have reached a “final outcome” (recovered, recovered with sequelae, recovering, not recovered, fatal, or unknown) or the patient’s participation in the trial ends, whichever comes first.

SAEs and severe, non-serious AEs assessed as “possibly related” or “probably related” to trial treatment, still ongoing after ended trial participation, should be followed on a regular basis according to the Investigator’s clinical judgment until a “final outcome” has been established.

The outcome “recovering” can be used as the “final outcome” for events that are stabilised (i.e., no further worsening is expected) and expected by the Investigator to resolve over time.

The outcome “not recovered” can be used as the “final outcome” for events that are not expected to resolve over time (e.g., cancer).

SAEs occurring after the patient has completed the clinical trial and for which a reasonable possibility (assessed as “possibly” or “probably” related) of a causal relationship is assessed by the Investigator, should be reported to the Sponsor by the Investigator regardless of the time that has elapsed (post-trial events).

8 STATISTICAL CONSIDERATIONS

8.1 Statistical and Analytical Plans

Complete details of the statistical analyses to be performed will be documented in a statistical analysis plan (SAP), which will be completed prior to database lock. This document will include more detail of analysis populations, summary strategies, and any amendments to the proposed analyses listed here, if necessary. Any changes to the SAP will be outlined in the final trial report.

8.2 Determination of Sample Size

All endpoints will be analysed using descriptive statistics, including 95% confidence intervals (CIs) for the treatment difference. As the primary outcome measure (TSQM) has not previously been used in this type of trial with these substances, the residual standard deviation from an analysis using a Mixed Model Repeated Measures (MMRM) method in a trial studying the treatment of multiple sclerosis has been used (47). The derived standard deviation at 48 weeks was approximately 26 units, but the standard deviation is assumed to be relevant also at 24 weeks. The 95% CI for the treatment difference would then extend approximately 9.3 units from the estimated difference in either direction, with 60 patients per treatment group. To put this into context, under the same assumptions and with a true treatment difference of 13.4 units, the power would be approximately 80%. A sample size of 60 patients per treatment arm is hence overall judged to be sufficient for characterizing the treatment effect in the current trial.

8.3 Patient Disposition

All patients screened and randomised will be accounted for. All post-randomisation discontinuations will be summarised by time of, and reason for, discontinuation. Patients screened but not randomised will be listed.

8.4 Protocol Deviations

Major protocol deviation criteria will be established prior to the database lock.

8.5 Analysis Sets

8.5.1 Intention-to-Treat (ITT) Analysis Set

The intention-to-treat (ITT) analysis set comprises all patients who have been randomised to a treatment group. Analyses based on this population will group patients according to the treatment they were randomised to receive, regardless of actual treatment received.

8.5.2 Full Analysis Set (FAS)

The Full Analysis Set (FAS) comprises all randomised patients who were administered at least one dose of trial treatment and for which data for the endpoints to be analysed are available.

The efficacy analyses will be based on the FAS.

8.5.3 Per Protocol (PP) Analysis Set

The PP analysis set is defined as all patients in the FAS with no major protocol deviations that will impact the efficacy assessment.

8.5.4 Safety Analysis Set

The safety analysis set comprises all randomised and patients who were administered at least one dose of trial treatment. Analyses based on this population will group patients according to the actual treatment the patients received.

8.6 Trial Population

8.6.1 Demographics and other Baseline Characteristics

Descriptive statistics of demographics and other baseline characteristics will be presented for all randomised and treated patients by treatment group.

8.6.2 Medical History and Concomitant Medication

Medical history (recorded at the screening visit) will be coded using MedDRA. Prior and concomitant medication will be summarised separately by Anatomical Therapeutic Chemical (ATC) classification 1st level (alphabetically), ATC classification 2nd level (in decreasing order of frequency) and treatment group.

8.6.3 Substance Use and Treatment History

Substance use and treatment history will be summarised by treatment group.

8.6.4 Other Screening and Baseline Assessments

Clinical safety laboratory values, physical examinations, and vital signs will be summarised by treatment group.

8.7 Efficacy Endpoints

8.7.1 General Considerations

For all efficacy endpoints, descriptive measures and 95% CI for the difference between the 2 treatment arms will be presented, unless otherwise specified.

All efficacy analyses will be based on the FAS.

8.7.2 Missing Values

Imputation methods to handle dropouts and/or missing data will be detailed in the SAP.

8.7.3 Primary Endpoint

The Week 24 assessment in TSQM global satisfaction score, is the primary variable and will be analysed over time by a longitudinal data analysis method using MMRM methods. All post-baseline observations will be utilised; missing values will remain as missing, i.e. no attempt will be made to impute missing values, and only observed values will be used in the data analysis. The model will include treatment, post-baseline weeks, treatment by week interaction as fixed effects. The covariance will be assumed to be unstructured. If the estimates do not converge, Statistical Analysis System default covariance structure (Variance Components) may be assumed.

The estimated treatment effects, treatment differences, and the two-sided 95% confidence intervals of the treatment differences at all post baseline time points will be presented. The primary comparison will be the treatment difference at Week 24.

8.7.4 Secondary Endpoints

The secondary endpoints are listed in Table 6. The following statistical methodology will be used:

- For continuous endpoints, the same methodology as for the primary endpoint will be used, where appropriate, with further details provided in the SAP.
- For variables based on UDS, the percent weeks will be analysed in an analysis of variance with treatment as factor. The cumulative distribution function of these variables will be compared between treatments with a Wilcoxon test. In addition, the responder rate defined as 75% negative UDS (with and without self-reports) will be calculated and compared with a 95% CI for the difference. This will also include a description of the relative risk with the associated 95 % CI.
- Retention in treatment will be compared between treatments with a log-rank test.
- Health-economic endpoints will be summarised using descriptive statistics.

Table 6. Secondary Endpoint Categories

Endpoint	Category
TSQM effectiveness score (items 1 to 3)	1
TSQM side effects score (items 5 to 8)	1
TSQM convenience score (items 9 to 12)	1
Patient satisfaction with treatment VAS	1
Illicit opioid use measured by UDS and self-reports of illicit opioid use by TLFB	2
Illicit drug use measured by UDS and self-reports of drug use by ATOP	2
Retention in treatment	3
Trial drug adherence measured by dispensing records (for CAM2038) and self-reports of drug accountability (for BPN standard of care)	2
SURE	1
EQ-5D 3L	1
OSTQOL	1
PGIC	1
TBQ	1
ORBIT	1
SF-36	1
DASS-21	1
WPAI:GH	1
Estimates of HRU through the AD-SUS questionnaire	4
Estimates of social service utilisation through the AD-SUS	4
Estimation of QALYs (using Australian weights)	4
Criminal offences and incarcerations measured using the AD-SUS questionnaire	4
Self-reported overdoses	1
COWS	1
Craving VAS	1

Abbreviations: AD-SUS = Alcohol & Drug adapted Adult Service Use Schedule, ATOP = Australian Treatment Outcomes Profile, BPN = buprenorphine, COWS = Clinical Opiate Withdrawal Scale, DASS-21 = Depression, Anxiety and Stress Scale 21, EQ-5D = EuroQol five dimensions health questionnaire, HRU = healthcare resource utilisation, ORBIT = Opioid Related Behaviours In Treatment, OSTQOL = Opioid Substitution Treatment Quality of Life scale PGIC = Patient Global Impression of Change, QALY = quality-adjusted life year, SURE = Substance Use Recover Evaluator, TBQ = Treatment Burden Questionnaire, TLFB = timeline follow-back, TSQM = Treatment Satisfaction Questionnaire for Medication, UDS = urine drug screen, VAS= visual analogue scale
Endpoint categories: 1 = Continuous endpoint, 2 = Endpoint based on UDS or self-report, 3 = Retention in treatment, 4 = Health economic endpoint

8.7.5 Adjustments for Multiplicity

No adjustments for multiplicity will be made.

8.8 Extent of Exposure and Treatment Compliance

Exposure and compliance will be calculated per patient and summarised by treatment group.

8.9 Safety

8.9.1 General Considerations

Safety parameters will be evaluated for the safety analysis set.

8.9.2 Adverse Events

An overview of all AEs including severity, relationship to IMP, SAEs and AEs leading to withdrawals or death will be presented by treatment group.

AEs will be summarised by treatment group, system organ class (according to MedDRA) and preferred term (according to MedDRA) displaying number of patients in treatment group, number and percentage of patients having the AE as well as number of AEs. Furthermore, AEs will be summarised according to severity, relationship, outcome and seriousness.

Summary tables will in addition be prepared for AEs with an incidence of at least 5% or lower threshold as applicable for reporting.

SAEs and AEs leading to withdrawal will be listed and tabulated, if appropriate.

Any new event, sign or symptom occurring in the period between Screening and Baseline will be listed.

8.10 Interim Analyses

No interim analyses are planned for this trial.

9 DATA HANDLING

9.1 Source Data and Source Documents

The Investigator must maintain patient records.

The Investigator should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial patients. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry and should be explained if necessary (e.g., via an audit trail).

What constitutes source data is described in a Source Data Agreement.

Items which are directly entered in the eCRF which have no prior written or electronic record will be considered as source data. The same applies to electronic PROs (ePROs) which will be considered as source data.

9.2 Case Report Form

An eCRF system provided and hosted by an independent third-party CRO will be used for data capture. The system is validated and access at all levels to the system is granted/revoked following Sponsor and vendor procedures, in accordance with regulatory and system requirements.

Trial data should be entered into the eCRF in a timely manner after the patient has attended a visit or after the data become available, as applicable.

The Investigator or a designee will approve/authorise the eCRF entries for each patient with an electronic signature which is equivalent to a handwritten signature.

Entry errors occurring in the eCRF will be corrected electronically. Such corrections/modifications will be automatically tracked by an audit trail detailing the date and time of the correction and the name of the person making the correction.

9.3 Data Management

A data management plan will be created and will describe all functions, processes, and specifications for data collection, cleaning and validation.

The relevant data management documents will define the data entry, data validation, electronic data capture (EDC) system settings, EDC user permission, reconciliation requirement, coding dictionary, coding setup, etc.

10 MONITORING PROCEDURES

10.1 Periodic Monitoring

The monitor will contact and visit the Investigator periodically to ensure adherence to the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice (ICH GCP), standard operating procedures and applicable regulatory requirements, maintenance of trial-related source records, completeness, accuracy and verifiability of eCRF entries compared to source data, verification of drug accountability and compliance to safety reporting instructions.

The Investigator will permit the monitor direct access to all source data, including electronic medical records, and/or documents in order to facilitate data verification. Key trial personnel must be available to assist the monitor during these visits.

The source data verification process and definition of key variables to be monitored will be described in detail in the Monitoring Plan for the trial.

10.2 Audit and Inspection

The Investigator will make all the trial-related source data and records available at any time to auditor(s) mandated by the Sponsor, or to domestic/foreign regulatory inspectors or representatives from IECs who may audit/inspect the trial.

The patients must be informed by the Investigator and in the ICF that authorised Sponsor representatives and representatives from regulatory authorities and IECs may wish to inspect their medical records. During audits/inspections the auditors/inspectors may copy relevant parts of the medical records. No personal identification apart from the screening/randomisation number will appear on these copies.

The Investigator should notify the Sponsor without any delay of any inspection by a regulatory authority or IEC.

10.3 Data Protection and Confidentiality of Patient Data

The Investigator will ensure that the confidentiality of the patients' data will be preserved. On the eCRF or any other documents submitted to the Sponsor, the patients will not be identified by their names, but by their screening/randomisation number. Documents that are not for submission to Sponsor, e.g. the confidential patient identification code and the signed Informed Consent Documents, will be maintained by the Investigator in strict confidence.

11 CHANGES IN THE CONDUCT OF THE TRIAL

11.1 Protocol Amendments

Any change to this protocol will be documented in a protocol amendment, issued by the Sponsor, and agreed upon by the Investigator and Sponsor prior to its implementation. Amendments may be submitted for consideration to the approving IEC(s) and regulatory authorities, in accordance with local regulations. Changes to the protocol to eliminate immediate hazard(s) to trial patients may be implemented prior to IEC approval/favourable opinion.

11.2 Deviations from the Protocol

If deviations from the protocol occur, the Investigator must inform the monitor, and the implications of the deviation must be reviewed and discussed. Any deviation must be documented. A log of protocol deviations will be maintained by the CRO. The protocol deviation log and supporting documentation must be kept in the Investigator's File and the Trial Master File (TMF).

11.3 Premature Trial Termination

Both the Investigator (with regards to his/her participation) and the Sponsor reserve the right to terminate the trial at any time. Should this become necessary, the procedures will be agreed upon after consultation between the two parties. In terminating the trial, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the best interests of the patients. Regulatory authorities and IECs will be informed.

In addition, the Sponsor reserves the right to terminate the participation of individual trial sites. Conditions that may warrant termination include, but are not limited to, insufficient adherence to protocol requirements and failure to enter patients at an acceptable rate.

12 ETHICAL AND REGULATORY ASPECTS

12.1 IEC

Before implementing this trial, the protocol, the proposed Patient Information and ICF, and other documents as required, will be reviewed by properly constituted IECs and by the national regulatory authorities.

A signed and dated statement that the protocol, Patient Information and ICF, and other documents as required have been approved by the IECs and regulatory authorities will be obtained before trial initiation.

IECs will receive updates on trial progress according to local regulations.

12.2 Regulatory Authority Authorisation / Approval / Notification

The regulatory permission to perform the trial will be obtained in accordance with applicable regulatory requirements. All ethical and regulatory approvals must be available before a patient is exposed to any trial-related procedure, including screening tests for eligibility.

12.3 End-of-Trial

The end of trial for an individual patient is defined as the last protocol-specified contact with that patient. The overall end of trial is defined as the last protocol-specified contact with the last patient ongoing in the trial.

12.4 Ethical Conduct of the Trial

This trial will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki (2013), in compliance with the approved protocol, ICH GCP and applicable regulatory requirements (48, 49).

12.5 Patient Information and Consent

The Investigator (or authorised designee) will obtain a freely given written consent from each patient after an appropriate explanation of the aims, methods, sources of funding, any possible conflicts of interest, anticipated benefits, potential risks of the trial and the discomfort it may entail, post-trial provisions and any other aspects of the trial which are relevant to the patient's decision to participate. The patient must be given ample time to consider participation in the trial, before the consent is obtained. The ICF must be signed and dated by the patient and the Investigator who has provided information to the patient regarding the trial before the patient is exposed to any trial-related procedure, including screening tests for eligibility. Patients must be given the option of being informed about the general outcome and the results of the trial.

The Investigator (or authorised designee) will explain that the patient is completely free to refuse to enter the trial or to withdraw from it at any time, without any consequences for his/her further care and without the need to justify his/her decision.

The patient will receive a copy of the Patient Information and his/her signed ICF.

If new information becomes available that may be relevant to the trial patient's willingness to continue participation in the trial, a new Patient Information and ICF will be forwarded to the IECs (and regulatory authorities, if required). The patients will be informed about this new information and re-consent will be obtained.

Each patient will be informed that the monitor(s), quality assurance auditor(s) mandated by the Sponsor, IEC representatives or regulatory authority inspector(s), in accordance with applicable regulatory requirements, may review his/her source records and data. Data protection will be handled in compliance with national/local regulations.

12.6 Patient Card

Patients will receive a patient card to be carried at all times. The patient card will state that the patient is participating in a clinical research trial, type of treatment, and contact details for the Investigator and the Sponsor. The card should be presented to healthcare providers in the event of an emergency or if medications are required. Sample patient cards will be provided for IEC submission.

13 LIABILITIES AND INSURANCE

13.1 ICH GCP Responsibilities

The responsibilities of the Sponsor, the monitor and the Investigator are defined in the ICH E6 GCP (Note for Guidance on Good Clinical Practice) consolidated guideline, and applicable regulatory requirements in the country where the trial takes place. The Investigator is responsible for adhering to the ICH GCP responsibilities of Investigators, for dispensing the trial treatment in accordance with the approved protocol or an approved amendment, and for its secure storage and safe handling throughout the trial.

13.2 Liabilities and Insurance

The Sponsor has obtained an insurance covering, in its terms and provision, its legal liability for injuries caused to participating subjects and arising out of trial procedures performed in accordance with this protocol, in accordance with applicable law and with ICH GCP.

14 ARCHIVING

14.1 Investigator File

The Investigator is responsible for maintaining all the records, which enable the conduct of the trial at the site to be fully understood, in compliance with ICH GCP. The trial documentation including all the relevant correspondence should be kept by the Investigator for at least 15 years, unless local regulations or institutional policies require a longer retention period, after the completion or discontinuation of the trial, if no further instructions are given by Sponsor.

No trial site document may be destroyed without prior written agreement between the Investigator and the Sponsor. Should the Investigator elect to assign the trial documents to another party, or move them to another location, the Sponsor must be notified. If the Investigator retires and the documents can no longer be archived by the site, the Sponsor can arrange having the Investigator File archived at an external archive.

14.2 Trial Master File

The Sponsor will archive the TMF in accordance with ICH GCP and applicable regulatory requirements.

15 REPORTING AND PUBLICATION

15.1 Clinical Trial Report

Upon completion of the trial, a clinical trial report will be prepared by the Sponsor or a CRO.

15.2 Confidentiality and Ownership of Trial Data

Any confidential information relating to the trial treatment or the trial, including any data and results from the trial will be the exclusive property of the Sponsor. The Investigator and any other persons involved in the trial must protect the confidentiality of this proprietary information belonging to the Sponsor.

15.3 Publications and Public Disclosure

15.3.1 Publication Policy

The results of this trial may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts in due time to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of trial results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter trials only in their entirety and not as individual site data

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

15.3.2 Public Disclosure Policy

The Sponsor will register the trial in an appropriate public registry according to applicable regulations. The trial results may be made publicly available in accordance with applicable regulatory requirements.

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