CLINICAL STUDY PROTOCOL

A RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, 6-PERIOD, PLACEBO-CONTROLLED, CROSSOVER STUDY TO EXPLORE AND COMPARE THE VENTILATORY RESPONSE TO HYPERCAPNIA (VRH), OF BELBUCA, OXYCODONE HYDROCHLORIDE, AND PLACEBO IN RECREATIONAL OPIOID USERS

CONFIDENTIAL

Sponsor code: BUP-401
PRA code: BDL673SL-186739

Investigational product:	Belbuca (buprenorphine buccal film)
Clinical phase:	Phase 1 study
Indication to be studied:	Not applicable
Sponsor:	BioDelivery Sciences International, Inc. 4131 ParkLake Avenue, Suite 225 Raleigh, NC 27612 USA
Contract Research Organization:	PRA Health Sciences (PRA) – Early Development Services (EDS) 9755 Ridge Drive Lenexa, KS 66219 USA
Clinical Site:	PRA-EDS 1255 East 3900 South Salt Lake City, UT 84124 USA
Principal Investigator:	[redacted]
Protocol Authors:	[redacted]

Version 2.0, 6 Aug 2019

[redacted]

This study will be performed in compliance with the principles of Good Clinical Practice (GCP).

[redacted]

SPONSOR AUTHORIZATION OF CLINICAL STUDY PROTOCOL

The Sponsor and the Contract Research Organization agree to conduct the study as outlined in this clinical study protocol (CSP). Any modification of the CSP must be agreed upon by the Sponsor and the Contract Research Organization and must be documented in writing.

Name/Position: Date: Signature:

Sponsor: BioDelivery Sciences International, Inc.

[redacted]

Sponsor's Contact

AUTHORIZATION OF CLINICAL STUDY PROTOCOL BY CONTRACT RESEARCH ORGANIZATION

The Sponsor and the Contract Research Organization agree to conduct the study as outlined in this CSP. Any modification of the CSP must be agreed upon by the Sponsor and the Contract Research Organization and must be documented in writing.

Name/Position: Date: Signature:

Contract Research Organization: PRA Health Sciences – EDS

[redacted]

[redacted]

[redacted]

SERIOUS ADVERSE EVENT CONTACT INFORMATION

In case of a serious adverse event (See Appendix 8.2), the Principal Investigator will send a report within 24 hours of notification to:

Sponsor

[redacted]

Medical Monitor

[redacted]

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CONTACT INFORMATION

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Laboratories

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SUMMARY OF CHANGES

The following changes have been introduced in Version 2.0 of the protocol:

- **Change:** To enhance subject recruitment, the restrictions for tobacco and nicotine use have been relaxed so that only subjects who have smoked on a daily basis within the 30 days prior to the first dose of medication will be excluded from participation in the study. Subjects will not be excluded from the study for occasional nicotine use in the form of cigarettes, cigars, or vape pens (defined as less than half a pack of cigarettes (10 cigarettes), equivalent vaping (100 puffs), or no more than 2 cigars per week). In addition, nicotine replacement therapies may be used without restriction. The original protocol excluded subjects who had used tobacco, nicotine, or nicotine-containing products within 30 days prior to admission and throughout the study.
  Rationale: Given the age and characteristics of the targeted subject population, complete abstinence from smoking is unlikely. Infrequent smoking is unlikely to have any effect on the collection and interpretation of VRH data. Thus, a change of the exclusion criteria to allow infrequent smokers who were previously excluded will allow for better enrollment of the targeted population. The original intent of the criteria was to exclude individuals where smoking history could possibly affect interpretation of VRH data.

- **Change:** To enhance subject recruitment, the definition for adequate contraception was revised so that subjects were not required to use hormonal contraceptives or an intrauterine device in combination with a diaphragm, cervical cap or condom. In the amended protocol, adequate contraception (for both males and females) is defined as using spermicide with a single barrier method: diaphragm, cervical cap, or condom. For female participants and female partners of male participants, being surgically sterilized or using hormonal contraception or intrauterine device is also acceptable. Also, total abstinence, in accordance with the lifestyle of the subject, is acceptable.
  Rationale: Being surgically sterilized or using a single barrier method with spermicide represents an adequate minimum for contraception in this single-dose crossover study of buprenorphine and oxycodone. A serum pregnancy test will be performed at screening and urine pregnancy tests will be done prior to check-in for each study period; tests must be negative for the subjects to continue with study procedures.

- **Change**: The duration of the exclusion criterion for female subjects or male subjects with female partners planning or attempting to become pregnant is extended to during this study or within 90 days after the follow-up visit (previously during study or within 90 days of the last dose of study drug).
  Rationale: The criterion is clarified for consistency throughout the protocol.

- The instructions for processing blood samples for PK analysis of oxycodone and buprenorphine/nor-buprenorphine have been revised to match the instructions in the PK laboratory manual.

A detailed summary of changes showing revisions to the text is provided in Attachment 1: Summary of Changes for Version 1.0 to 2.0 for Protocol BUP-401.

SYNOPSIS

Study Title

A RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, 6-PERIOD, PLACEBO-CONTROLLED, CROSSOVER STUDY TO EXPLORE AND COMPARE THE VENTILATORY RESPONSE TO HYPERCAPNIA (VRH), OF BELBUCA, OXYCODONE HYDROCHLORIDE, AND PLACEBO IN RECREATIONAL OPIOID USERS

Short Study Title

A single-dose, 6-period crossover study to compare the respiratory drive after administration of Belbuca, oxycodone hydrochloride, and placebo

Study Codes

Sponsor code : BUP-401
PRA code : BDL673SL-186739

Sponsor

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Contract Research Organization and Clinical Site

PRA-EDS, 9755 Ridge Drive, Lenexa, KS 66219, USA

Clinical Site

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Principal Investigator

[redacted]

Objectives

Primary : Respiratory drive will be evaluated by measuring the ventilatory response to hypercapnia (VRH) by maximum decrease in minute ventilation after administration of Belbuca, oxycodone hydrochloride, and placebo.

Secondary : Pupil diameter will be assessed by pupillometry predose and at multiple timepoints after completion of Belbuca, oxycodone hydrochloride, and placebo dosing.

Change in ratio of minute ventilation over end-tidal CO_2 predose and multiple timepoints after oral administration of Belbuca, oxycodone hydrochloride, and placebo.

Clinical safety data from adverse event (AE) reporting, clinical observations, 12-lead electrocardiograms (ECGs), vital signs (blood pressure [BP], heart rate [HR], respiratory rate, and oral temperature), oxygen saturation, and safety laboratory tests following administration of Belbuca, oxycodone hydrochloride, and placebo will be summarized, and any clinically significant abnormalities will be described.

[redacted]

Exploratory : Blood samples will be collected on evaluate pharmacokinetic (PK) and blood levels of Belbuca and oxycodone hydrochloride at important pharmacodynamic (PD) endpoints.

Design and Treatments

This is a single-center, double-blind, double-dummy, placebo-controlled randomized crossover study in up to 18 men and women self-identifying as recreational drug users. This study will consist of a screening phase, treatment phase, which includes the Naloxone Challenge Test, and a follow-up visit.

Screening Phase:

Approximately 40 subjects will be screened to randomize 16 subjects and 2 back-up subjects. Screening will begin no more than 28 days prior to the first dose of study medication. After completing the informed consent process and signing the informed consent form (ICF), subjects will undergo study-specific screening procedures. A physical examination (PE), including measurement of height, weight, and vital signs; blood and urine laboratory testing; review of medical and medication history; and a 12-lead ECG will be performed. Subjects will also undergo the VRH procedure to determine tolerability of procedure and demonstrate adequate VRH. The VRH procedure may occur on a separate screening day within the screening phase window, if necessary.

Treatment Phase:

Subjects will check-in on Day -1 as long as they have a negative urine drug screen test (a positive test for delta-9-tetrahydrocannabinol is permitted and will not lead to exclusion from the study). Subjects with positive urine drug screen test for opioids will be screen failed and dismissed from the research clinic. Subjects who remain in the clinic on Day -1 will undergo a Naloxone Challenge Test to exclude the possibility of physical dependence on opioids.

On Day 1, after subjects have completed and passed the screening phase and Naloxone Challenge Test, they will be eligible to enter the treatment phase. The treatment phase is a double-blind, double-dummy, oral/buccal, 6-treatment, 6-period, placebo-controlled, randomized, crossover design with the following treatments, each separated by an approximate 7-day washout period:

- **Treatment A**: Belbuca 300 µg and oral placebo
- **Treatment B**: Belbuca 600 µg and oral placebo
- **Treatment C**: Belbuca 900 µg and oral placebo
- **Treatment D**: Oxycodone 30 mg and buccal placebo
- **Treatment E**: Oxycodone 60 mg and buccal placebo
- **Treatment F**: Oral placebo and buccal placebo

Pharmacodynamic (PD) assessments will include pupillometry and VRH. Subjects will undergo several assessments prior to and after administration of the study drug on Days 1 and 2. Subjects will be discharged from the clinic approximately 24 hours after dosing at the discretion of the investigator. After an approximately 7-day washout period, subjects will return to the clinic on Day -1 for dosing in the subsequent treatment period.

Follow-up Visit:

A follow-up call will be completed approximately 7 ±2 days after the final study dose.

Study Schedule

Screening	: Between Day -28 and Day -2
Confinement period	: An anticipated 6 periods in the clinic each lasting from Day -1 (admission) to approximately 24 hours after study drug administration (Day 2).
Follow-up	: 7 ±2 days after the last study drug administration.

Subjects

A total of 18 subjects who are recreational opioid users that are not dependent on opioids will be enrolled with the intention to complete the study with 16 subjects.

Main Criteria for Inclusion

Age	: 18 to 55 years, inclusive, at screening
Weight	: >50 kg, inclusive
Body mass index (BMI)	: 18.0 to 33.0 kg/m^2, inclusive

Study Drug

Test preparation

Active substance	: Belbuca (buprenorphine)
Strength	: 300 µg, 600 µg, and 900 µg
Dosage form	: Oral buccal film
Manufacturer	: BioDelivery Sciences International, Inc.

Reference medication

Active substance	: Oxydocone hydrochloride, immediate-release
Strength	: 30 mg and 60 mg
Dosage form	: Oral tablets that will be overencapsulated in gelatin capsules (Swedish orange DB capsules, size AA) for blinding process
Manufacturer	: Commercially acquired by the clinical research site from a local vendor

Placebo (visually matching Belbuca)

Substance	: Placebo
Strength	: 0 µg
Dosage form	: Oral buccal film
Manufacturer	: BioDelivery Sciences International, Inc.

Placebo (visually matching oxycodone hydrochloride)

Substance	: Placebo
Strength	: 0 mg
Dosage form	: Oral capsules matching overencapsulated oxycodone hydrochloride
Manufacturer	: Pharmacy at PRA

Variables

Safety	: AEs, clinical laboratory, vital signs, 12-lead ECG, continuous oxygen saturation monitoring, Columbia-Suicide Severity Rating Scale (C-SSRS), cardiac telemetry, and PE.

Pharmacokinetics	:	During the treatment phase, blood samples for pharmacokinetic (PK) evaluation will be collected predose and at 0.5, 1, 2, 3, 4, and 6 hours postdose. Cmax, Tmax, AUClast, and abuse quotient (AQ) will be calculated using noncompartmental PK methods.
Pharmacodynamics	:	Pupillometry and VRH

Statistical Methods

Sample size calculation	:	Approximately 40 subjects will be screened to randomize 16 subjects with 2 back-up subjects. No prospective calculations of statistical power have been made.
Safety parameters	:	Safety and tolerability assessments will be listed and summarized descriptively by treatment group and time point.
Pharmacokinetic parameters	:	Individual and mean plasma concentrations of buprenorphine, nor-buprenorphine, and oxycodone at each sampling time point will be presented by listings and descriptive summary statistics. Time profile plots, linear and semi-logarithmic plots of the mean (± standard deviation [SD]) at each time measurement will be generated for plasma concentration data. All PK parameters will be presented by individual listings and summary statistics for each dose cohort.
Pharmacodynamic parameters	:	All PD data will be listed and summarized descriptively by time of evaluation. The PD effects of Belbuca, oxycodone, and placebo will be assessed using data derived from the pupillometry and VRH. Pairwise treatment comparisons will be performed using a mixed-model analysis of variance (ANOVA).

Table 1 Schedule of Assessments

	Screening	Inpatient Visit			Early Termination	Follow-Up Call
Visit ID	**V1**	**V2-V7[a]**			**ET**	**V9**
Study Day(s) **Procedures**	**-28 to -2**	**-1**	**1**	**2**		7 days from final IMP (+/- 2 days)
Informed consent	X					
Eligibility criteria	X	confirm				
Demographics	X					
Medical history, including recreational drug use history	X	update				
Physical examination	X			X	X[b]	
Oral mucosa examination	X	X				
Pregnancy test[c]	X	X				
Follicle stimulating hormone and estradiol level[d]	X					
Height, weight, BMI	X					
Blood pressure, heart rate, and respiration rate	X	X	X[e]	X	X	
Temperature	X	X	X[e]	X	X	
O_2 saturation	X	X	X[f]	X	X	
Continuous pulse oximetry			X[f]			
12-lead ECG	X	X		X	X	
Continuous cardiac telemetry			X[g]			
Chemistry and hematology labs[h]	X	X			X	
Viral serology (HBsAG, anti-HCV, HIV)	X					
Urinalysis	X	X			X	
Alcohol breathalyzer/urine drug screen	X	X				
Naloxone Challenge[i]		X				
Randomization (first treatment period only)			X			
IMP administration			X			
Pupillometry			X[e]			

Ventilatory Response to Hypercapnia	X		X[j]			
PK[k]			X			
C-SSRS[l]	X	X			X	
Adverse events			X	X	X	X
Prior/Concomitant medications	X	X	X	X	X	X
Discharge from clinic				X		

BMI=body mass index; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ET=early termination; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; ID=identification; IMP=investigational medicinal product; PK=pharmacokinetics

[a] Each treatment period will be separated by at least 7 days.

[b] Physical examination to be completed at ET at discretion of investigator. Unscheduled symptom-directed PEs may be conducted at any time per the investigator's discretion.

[c] Serum pregnancy test will be done for all female subjects at screening. Urine pregnancy test will be done for all female subjects at check-in to each period.

[d] Postmenopausal female subjects only to confirm postmenopausal status.

[e] Vital signs, and pupillometry collected at predose and 0.5, 1, 1.5, 2, 2.5, 3, and 4 hours postdose. Body temperature collected once predose each treatment period.

[f] Continuous pulse oximetry from at least 15 minutes predose through 8 hours postdose, and recorded at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, and 8 hours postdose.

[g] Continuous cardiac telemetry during VRH procedures from at least 15 minutes predose until at least 4 hours postdose.

[h] Creatinine clearance and thyroid stimulating hormone (TSH) will be measured at screening only.

[i] Naloxone challenge will be done during Treatment Period 1 and will consist of vital signs (BP, HR, RR and O_2 Saturation) at least 30 minutes before naloxone administration and at 5 minutes, 30 minutes and 60 minutes after administration. Clinical Opiate Withdrawal Scale (COWS) associated with the naloxone challenge will occur immediately predose and within 1 minute and 5 minutes after administration of naloxone.

[j] VRH at predose and 0.5, 1, 2, 3, and 4 hours postdose.

[k] PK at predose, 0.5, 1, 2, 3, 4, and 6 hours postdose.

[l] C-SSRS Baseline version will be used at screening. At the subsequent visits, C-SSRS Since Last Visit version will be used.

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LIST OF ABBREVIATIONS

AE	adverse event
BP	blood pressure
CHMP	Committee for Medicinal Products for Human Use (formerly: Committee for Proprietary Medicinal Products [CPMP])
CI	confidence interval
COWS	Clinical Opiate Withdrawal Scale
CSP	clinical study protocol
CSR	clinical study report
C-SSRS	Colombia Suicide Severity Rating Scale
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EDS	Early Development Services
ET	early termination
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
ICF	informed consent form
ICH	International Council for Harmonisation (formerly: International Conference on Harmonisation)
IRB	Institutional Review Board
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
MRHD	maximum recommended human dose
MSE	morphine sulfate equivalents
OD	oculus dexter
OS	oculus sinister
OTC	over-the-counter
PD	pharmacodynamic(s)
PEF	peak expired follow
PK	pharmacokinetic(s)
PRA	PRA Health Sciences
PRA-EDS	PRA Early Development Services
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOA	Schedule of Assessments
SOP	standard operating procedure
SpO_2	peripheral capillary oxygen saturation
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
THC	delta-9-tetrahydrocannabinol
TSH	thyroid stimulating hormone
V_E	expired minute volume
VRH	ventilatory response to hypercapnia
V_T	expired tidal volume
WBC	white blood cell / leukocyte
WMA	World Medical Association

Note: Definitions of pharmacodynamic (PD) parameters are provided in Section 3.5.3

1. INTRODUCTION

1.1 Background

Belbuca is a buccal film providing transmucosal delivery of buprenorphine hydrochloride, a partial opioid agonist and a Schedule III controlled substance. [1]

Belbuca exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with long-acting opioid formulations, Belbuca is to be used in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.

1.1.1 Nonclinical Toxicology

Carcinogenesis: Buprenorphine was administered in the diet to Sprague-Dawley rats at doses of 0.6, 5.5, and 56 mg/kg/day for 27 months (estimated exposure was approximately 3, 29, and 299 times the maximum recommended human dose [MRHD] of buccal Belbuca of 1.8 mg on a mg/m^2 basis, respectively), in which the rats exhibited statistically significant dose-related increase in testicular interstitial cell tumors. In an 86-week study in CD-1 mice, buprenorphine was not carcinogenic at dietary doses up to 100 mg/kg/day (estimated exposure was approximately 267 times the MRHD).

Mutagenesis: Buprenorphine was studied in a series of tests using gene, chromosome, and deoxyribonucleic acid (DNA) interactions in prokaryotic and eukaryotic systems. The results were negative in yeast for recombinant, gene convertant, or forward mutations; negative in Bacillus subtilis “rec” assay, negative for clastogenicity in the Chinese hamster ovary cells, Chinese hamster bone marrow and spermatogonia cells, and negative in the mouse lymphoma L5178Y assay.

Results were ambiguous in the Ames test: negative in studies in two laboratories, but positive for frame shift mutation at a high dose (5 mg/plate) in a third study. Results were positive in the Green-Tweets (*E.coli*) survival test, positive in a DNA synthesis inhibition test with testicular tissue from mice, for both in vivo and in vitro incorporation of [^{3}H]thymidine, and positive in unscheduled DNA synthesis test using testicular cells from mice.

Impairment of Fertility: Reproduction studies of buprenorphine in rats demonstrated no evidence of impaired fertility at daily oral doses of up to 80 mg/kg/day (estimated exposure approximately 427 times the MRHD) or up to 5 mg/kg/day intramuscular or subcutaneous (estimated exposure was approximately 27 times the MRHD).

1.1.2 Clinical Pharmacology

Mechanism of Action: Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor.

Pharmacodynamics (PD): The principal action of therapeutic value of buprenorphine is analgesia and is thought to be due to buprenorphine binding with high affinity to opioid receptors on neurons in the brain and spinal cord. Buprenorphine may also cause sedation or somnolence. Buprenorphine causes miosis, even in total darkness, and little tolerance develops to this effect. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (eg, pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen with worsening hypoxia in the event of buprenorphine overdose.

Buprenorphine causes an increase in biliary tract pressure, constipation, reduction in blood pressure (BP), inhibition of secretion of adrenocorticotropic hormone, cortisol, and luteinizing hormone in humans, and stimulation of prolactin, growth hormone secretion, and pancreatic secretion of insulin and glucagon. In controlled and open-label chronic pain trials at doses up to 900 µg every 12 hours, 2% of the patients demonstrated a prolongation of QTcF to a post-baseline value between 450 to 480 msec during therapy. In vitro and in animal models, the overall effect of opioids was modestly immunosuppressive.

Pharmacokinetics (PK):
Absorption: Systemic plasma levels of Belbuca increased in a linear manner (C_{max} and AUC) over the single-dose range of 75 to 1200 µg. The absolute bioavailability of Belbuca ranged from 46% to 65%. Following the multiple dose administration of Belbuca (60-240 µg every 12 hours), apparent steady-state buprenorphine plasma concentrations were achieved prior to the sixth dose. Buprenorphine steady-state C_{max} and AUC increased proportional to dose. Systemic exposure to buprenorphine from Belbuca film was reduced by 23% to 27% by the ingestion of liquids (cold, hot, and room temperature water) during film administration; additionally coadministration with low pH liquid, such as decaffeinated cola, decreased buprenorphine exposure from Belbuca by approximately 37%. Therefore, consumption of liquids should be avoided until the buccal film has completely dissolved.

Distribution: Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin.

Elimination: Based on multiple dose studies performed with Belbuca, the mean plasma elimination half-life of buprenorphine was 27.6 hours±11.2 hours.

1.1.3 Clinical Studies

The efficacy of Belbuca was evaluated in two 12-week double-blind, placebo-controlled clinical trials in opioid-naïve and opioid-experienced patients with moderate-to-severe

chronic low back pain using pain scores as the primary efficacy variable. Both studies demonstrated efficacy in pain relief in patients with low back pain.

In a 12-week study in opioid-naïve patients, 749 patients with chronic low back pain entered an open-label dose-titration period for up to 8 weeks. Patients started therapy with a single 75 µg dose of Belbuca on Day 1 and continued taking Belbuca 75 µg either once daily or every 12 hours for 4 to 8 days as tolerated. The dose was then increased to 150 mcg every 12 hours, and patients could continue to dose escalate in 150 µg dose increments every 4 to 8 days for up to 6 weeks if the adverse effects were tolerable and the analgesic effects were not adequate. Patients who achieved adequate analgesia and tolerable adverse effects on Belbuca for at least 2 weeks were then randomized to continue their titrated dose of Belbuca or matching placebo. Sixty-one percent (61%) of the patients who entered the open-label dose-titration period were able to titrate to a tolerable and effective dose and were randomized into a 12-week, double-blind treatment period. Fifteen percent (15%) of patients discontinued due to an adverse event (AE) and 4% discontinued due to lack of a therapeutic effect. The remaining 20% of patients discontinued due to various non-drug related administrative reasons. Seventy-six percent (76%) of the patients treated with Belbuca completed the 12-week treatment compared to 73% of the patients treated with placebo. Four percent (4%) of the patients randomized to Belbuca discontinued due to lack of efficacy and 8% due to AEs. Eleven percent (11%) of the patients randomized to placebo discontinued due to lack of efficacy and 4% due to AEs. A higher proportion of Belbuca patients (62%) had at least a 30% reduction in pain score from prior to open-label titration to study endpoint when compared to patients who received placebo buccal film (47%). A higher proportion of Belbuca patients (41%) also had at least a 50% reduction in pain score from prior to open-label titration to study endpoint compared to patients who received placebo (33%).

In a 12-week study in opioid-experienced patients, 810 patients on chronic opioid therapy (total daily dose 30 to 160 mg in oral morphine sulfate equivalents [MSE] for at least 4 weeks) entered an open-label, dose-titration period with Belbuca for up to 8 weeks, following taper of their prior opioids to 30 mg oral MSE daily. Patients started with Belbuca 150 µg every 12 hours if they were on 30 to 89 mg oral MSE daily, and 300 µg every 12 hours if they were on 90 to 160 mg oral MSE daily prior to taper. If a patient tolerated the AEs and the analgesic effects were not adequate, the dose was increased in increments of 150 mcg every 12 hours after 4 to 8 days for up to 6 weeks. After a dose was reached with adequate analgesia and tolerable adverse effects for a period of 2 weeks, patients were randomized to continue their titrated dose of Belbuca or matching placebo. Sixty-three percent (63%) of the patients who entered the open-label titration period were able to titrate to a tolerable and effective dose and were randomized into a 12-week double-blind treatment phase. Ten percent (10%) of patients discontinued due to an AE, 8% discontinued due to lack of therapeutic effect, and 0.1% discontinued due to opioid withdrawal during the open-label titration period. The remaining 20% of patients discontinued due to various non-drug related administrative reasons. Eighty-three percent (83%) of patients treated with

Belbuca and 57% of patients treated with placebo buccal film completed the 12-week treatment period. Eight percent (8%) of the patients randomized to Belbuca discontinued due to lack of efficacy and 2% due to AEs. Twenty-five percent (25%) of the patients randomized to placebo discontinued due to lack of efficacy and 5% due to AEs. A higher proportion of Belbuca patients (64%) had at least a 30% reduction in pain score from prior to open-label titration to study endpoint when compared to patients who received placebo buccal film (31%). A higher proportion of Belbuca patients (39%) also had at least a 50% reduction in pain score from prior to open-label titration to study endpoint compared to patients who received placebo (17%).

1.2 Risk-Benefit Assessment

This is a study of Belbuca in recreational opioid users who are not dependent on opioids. Subjects will receive no known health benefit from participating in this study beyond that of an assessment of overall health status. The information obtained in this study will be used to better understand the respiratory effects of Belbuca.

Possible risks for subjects who will participate in this study are side effects that are commonly seen with opioids. Detailed information about the known and expected side effects of both Belbuca and oxycodone hydrochloride, as well as safety pharmacology data, are presented in the package inserts for each of these drugs. The study design, inclusion/exclusion criteria, and procedures have been developed in a manner to protect subject safety.

Overall, on the basis of the available nonclinical and clinical data, and prior knowledge, the risk-benefit profile of Belbuca is judged acceptable for the proposed clinical study.

1.3 Study Rationale

Approximately 90% of the US opioid market for chronic pain is comprised of Schedule II drugs. Increasing the dose for Schedule II drugs to address the needs of chronic pain patients also increases the safety risks, especially the risk of respiratory depression. Buprenorphine is a Schedule III drug which has shown to have a ceiling effect such that, at a certain dose, further increases in dose, do not further depress respiratory function.[2,3] As respiratory depression is the most significant safety concern of any central nervous system-depressant, the rationale for this study is to compare the effects of increasing dose and respiratory depression between a Schedule II and Schedule III opioid. In this study, the effect of 300 µg, 600 µg, and 900 µg doses of Belbuca (Schedule III), 30 mg and 60 mg of oxycodone hydrochloride (Schedule II), and placebo, on the respiratory drive will be evaluated by measuring the ventilatory response to hypercapnia (VRH).

2. OBJECTIVES

2.1 Primary

- Respiratory drive will be evaluated by measuring the VRH by maximum decrease in minute ventilation after administration of Belbuca, oxycodone hydrochloride, and placebo.

2.2 Secondary

- Pupil diameter will be assessed by pupillometry predose and at multiple time points after administration of Belbuca, oxycodone hydrochloride, and placebo.
- Change in ratio of minute ventilation over end-tidal CO_2 predose and at multiple time points after oral administration of Belbuca, oxycodone hydrochloride, and placebo.
- Clinical safety data from AE reporting, clinical observations, 12-lead electrocardiograms (ECGs), vital signs (BP, heart rate [HR], respiratory rate [RR], and oral temperature), oxygen saturation, and safety laboratory tests following administration of Belbuca, oxycodone hydrochloride, and placebo will be summarized, and any clinically significant abnormalities will be described.

2.3 Exploratory

- Blood samples will be collected to evaluate PK and blood levels of Belbuca and oxycodone hydrochloride at important PD endpoints.

3. INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

3.1.1 Type of Study

This is a single-center, double-blind, double-dummy, placebo-controlled randomized crossover study in up to 18 men and women self-identifying as recreational drug users.

The treatments planned in this study are described in Section 3.4.1.

3.1.2 Screening Phase

Approximately 40 subjects will be screened to randomize 16 subjects and 2 back-up subjects. Screening will begin no more than 28 days prior to the first dose of study medication. After completing the informed consent process and signing the informed consent form (ICF), subjects will undergo study-specific screening procedures. A physical examination (PE), including measurement of height, weight, and vital signs; blood and urine laboratory testing; review of medical and medication history; and a 12-lead ECG will be performed. The subjects will also undergo the VRH procedure to determine tolerability of procedure and demonstrate adequate VRH. The VRH procedure may occur on a separate screening day within window, if necessary.

3.1.3 Treatment Phase

Subjects will check-in on Day -1 as long as they have a negative urine screen test (a positive test for delta-9-tetrahydrocannabinol [THC] is permitted and will not lead to exclusion from the study). Subjects with a positive urine drug screen test for opioids will be screen failed and dismissed from the research clinic. If a subject has a positive urine drug screen (except THC) upon admission to the clinic (V3-V7) the subject will be dismissed from the clinic and will be allowed to return at a later date (+14 days) to participate in the missed treatment period. A subject may only test positive once (except THC) and be allowed to return. . Subjects who remain in the clinic on Day -1 will undergo a Naloxone Challenge Test to exclude the possibility of physical dependence on opioids.

On Day 1, after subjects have completed and passed the screening phase and Naloxone Challenge Test, they will be eligible to enter the treatment phase. The treatment phase is a double-blind, double-dummy, oral/buccal, 6-treatment, 6-period, placebo-controlled, randomized, crossover design with the following treatments, each separated by an approximate 7-day washout period.

- **Treatment A:** Belbuca 300 µg and oral placebo
- **Treatment B:** Belbuca 600 µg and oral placebo
- **Treatment C:** Belbuca 900 µg and oral placebo
- **Treatment D:** Oxycodone 30 mg and buccal placebo
- **Treatment E:** Oxycodone 60 mg and buccal placebo
- **Treatment F:** Oral placebo and buccal placebo

Pharmacodynamic assessments will include pupillometry and VRH. Subjects will undergo several assessments prior to and after administration of the study drug on Days 1 and 2. Subjects will be discharged from the clinic approximately 24 hours after dosing at the discretion of the investigator. After an approximately 7-day washout period, subjects will return to clinic on Day -1 for dosing in the subsequent treatment period.

3.1.4 Follow-up

A follow-up call will be completed approximately 7±2 days after the final study dose.

Assessments during follow-up will be performed as presented in the Schedule of Assessments (SOA) (Table 1).

3.2 Discussion of Study Design

This is a randomized, double-blind, double-dummy, 6-period, 6-treatment, placebo-controlled, crossover study to explore and compare the VRH of Belbuca, oxycodone hydrochloride, and placebo in recreational opioid users. This study will consist of a screening phase, a treatment phase including Naloxone Challenge Test, and a follow-up phase.

This study design has been chosen to decrease variability by allowing each subject to serve as his/her own control.

Based on the PK data of previous studies in humans, a washout period of at least 7 days is scheduled between consecutive treatment periods to avoid possible carry-over effects. Dose selection is presented in Section 3.4.4.

3.3 Selection of Study Population

Approximately 40 subjects will be screened to randomize 16 subjects and 2 back-up subjects. Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be considered for enrollment into the study. A completed subject is defined as a subject who completes dosing and provides data for the primary study endpoint in all 6 treatment periods. A partial completer is defined as a subject who completes at least 2 of the study treatment periods (this population will be used for the sensitivity analyses). Subjects that are disqualified in the Naloxone Challenge Test may be replaced.

3.3.1 Inclusion Criteria

The following inclusion criteria must be met for a subject to be eligible for inclusion in the study:

1. Male or female subjects 18 to 55 years of age, inclusive.
2. Subjects are in good health as indicated by medical history, PE, vital signs, oxygen saturation, clinical laboratory tests, and 12-lead ECG. A status of good health will be

defined by the absence of evidence of any clinically significant, active or chronic disease based on these assessments, in the opinion of the investigator.

3. Subjects with a body mass index (BMI) of 18.0 to 33.0 kg/m^2, inclusive, and body weight greater than 50 kg, inclusive.
4. Subject is able to speak, read, and understand English and voluntarily provide written informed consent to participate in the study.
5. Subjects have healthy oral mucosa as determined by examination at screening and admission to the clinical facility.
6. Subject must be a recreational opioid user who is not currently dependent on opioids (based on self-reported DSM-5 criteria and a Clinical Opiate Withdrawal Scale [COWS] score ≤5 on the Naloxone Challenge) but has experience in the use of opioids for non-therapeutic purposes (ie, for psychoactive effects) on at least 10 occasions within the last year and at least once in the 12 weeks prior to the screening visit.
7. Subject demonstrates adequate VRH at screening during VRH assessment, defined as a minimum increase in ET_{CO2} of 10 mmHg and an increase in minute ventilation appropriate per investigator's discretion.
8. Ability and willingness to abstain from alcohol-, caffeine-, and xanthine-containing beverages or food (eg, coffee, tea, cola, chocolate, energy drinks) as well as poppy seeds from 48 hours (2 days) prior to each admission to the clinical facility until study discharge (including clinic furloughs).
9. Female subjects who are non-pregnant, non-lactating, and either postmenopausal for at least 1 year or surgically sterile for at least 3 months, or, if of childbearing potential, will agree to use adequate contraception from 28 days and/or their last confirmed menstrual period prior to study enrollment (whichever is longer) until 90 days after the follow-up visit. Male subjects, if not surgically sterilized, must agree to use adequate contraception and not donate sperm from first admission to the clinical research center until 90 days after the follow-up visit. Adequate contraception (for both males and females) is defined as using spermicide with a single barrier method: diaphragm, cervical cap, or condom. For female participants and female partners of male participants, being surgically sterilized or using hormonal contraception or an intrauterine device is also acceptable. Also, total abstinence, in accordance with the lifestyle of the subject, is acceptable.
10. For female subjects: a negative pregnancy test at screening and Day -1 of each treatment period.
11. Postmenopausal females: defined as 12 months with no menses prior to screening and a serum follicle stimulating hormone (FSH) >40 IU/L at screening.
12. All prescribed medications, over-the-counter (OTC) medications, dietary supplements or herbal supplements (eg, St. John's Wort extract) must have been stopped at least 14 days prior to the first admission to the clinical research center. An exception is made for acetaminophen, which is allowed up to admission to the clinical research center. An exception is also made for hormonal contraceptives, which may be used throughout the study. Antiemetics may be allowed after the 4-hour VRH assessments while confined in the clinical research unit.

3.3.2 Exclusion Criteria

A subject who meets any of the following exclusion criteria will not be eligible for inclusion in the study:

1. Employee of PRA or the Sponsor.
2. Women who are pregnant, lactating, or planning to attempt to become pregnant during this study or within 90 days after the follow-up visit.
3. Male subjects with female partners who are pregnant, lactating, or planning to attempt to become pregnant during this study or within 90 days after the follow-up visit.
4. Has received study medication in another clinical trial within 30 days prior to the first dose of study medication.
5. Having any disease that, in the opinion of the investigator, poses an unacceptable risk to the subjects.
6. History of drug allergy diagnosed by a physician. Confirmatory circumstances would include treatment with epinephrine or an Emergency Department.
7. Subjects who have smoked on a daily basis within 30 days prior to the first dose of study medication. Occasional nicotine use in the form of cigarettes, cigars, or vape pen is allowable (defined as less than half a pack of cigarettes (10 cigarettes), equivalent vaping (100 puffs), or no more than 2 cigars per week). Nicotine replacement therapies (ie, patches and/or gum) may be used without restriction.
8. Routine or chronic use of more than 3 grams of acetaminophen daily.
9. Strenuous activity and contact sports within 48 hours (2 days) prior to first admission to the clinical facility and for the duration of the study.
10. History of donation of more than 450 mL of blood within 60 days prior to dosing in the clinical research center or planned donation before 30 days has elapsed since intake of study drug.
11. Plasma or platelet donation within 7 days of first dose administration and throughout the entire study.
12. History of or presence of alcohol dependence. This includes subjects who have never been to a drug rehabilitation program. Alcohol consumption will be prohibited 48 hours prior to admission to the clinical facility and throughout the entire study until discharge.
13. Positive screening test for hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV) antibodies, or antihuman immunodeficiency virus (HIV)-1 and -2 antibodies.
14. History or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, oncologic, or psychiatric disease, or any other condition, which, in the opinion of the investigator, would jeopardize the safety of the subject or the validity of the study results.
15. Has any condition in which an opioid is contraindicated (eg, significant respiratory depression, acute or severe bronchial asthma or hypercarbia, or has or is suspected of having paralytic ileus).
16. Have a history of chronic obstructive pulmonary disease or any other lung disease (eg, asthma, bronchitis, obstructive sleep apnea, exercise-induced asthma) that would cause CO_2 retention.

17. Has participated in (within the last 5 years), is currently participating in, or is seeking treatment for substance-related disorders (excluding nicotine and caffeine).
18. A positive result for drugs of abuse (amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine, and opioids, including oxycodone) at screening is acceptable as long as the urine drug screen is negative for these drugs at admission to the clinical facility. A positive test for THC is not exclusionary at screening or at admission to the clinical facility. If a subject has a positive urine drug screen (except THC) upon admission to the clinic (V3-V7) the subject will be dismissed from the clinic and will be allowed to return at a later date (+14 days) to participate in the missed treatment period. A subject may only test positive once (except THC) and be allowed to return.
19. Has oral sores, mucositis, or inflammation in oral cavity at screening and check-in.

3.3.3 Removal of Subjects from Assessment

Participation in the study is strictly voluntary. A subject has the right to withdraw from the study at any time for any reason.

The investigator has the right to terminate participation of a subject for any of the following reasons: difficulties in obtaining blood samples, violation of the protocol, severe AEs or serious adverse events (SAEs), or for any other reason relating to the subject's safety or integrity of the study data.

If a subject is withdrawn from the study, the Sponsor/study monitor will be informed immediately. If there is a medical reason for withdrawal, the subject will remain under the supervision of the investigator until satisfactory health has returned.

Subjects who drop out or withdraw for any reason without completing all screening evaluations successfully will be considered screen failures.

An enrolled/randomized subject who is withdrawn or voluntarily withdraws from the study for any reason, whether related to the study drug or not, after having received a subject/randomization number, will be considered an early-termination subject. If a subject is withdrawn for a reason related to the study drug, according to the judgment of the investigator, the early-termination subject will not be replaced. If a subject does not complete the study for a reason not related to the study drug, the early-termination subject may be replaced after mutual agreement between the Sponsor and PRA.

The decision regarding the replacement of subjects will be documented.

PRA will make every effort to ensure that early-termination subjects who have received study drug complete the safety follow-up assessments.

3.4 Treatments

3.4.1 Treatments Administered

Naloxone Challenge Test

During the Naloxone Challenge Test, all subjects will receive an initial dose of naloxone hydrochloride 0.2 mg by intravenous bolus, followed by an assessment of signs of withdrawal. The subject will be assessed by a medical provider for signs or symptoms of withdrawal through assessments of the COWS scores. If no evidence of withdrawal occurs within 30 seconds, an additional 0.6 mg naloxone will be administered by intravenous bolus. A second COWS assessment will be done 5 minutes after the 0.6 mg naloxone dose administration. A COWS score of >5 will result in a failed naloxone challenge. Subject safety will be monitored for 60 minutes after the administration of naloxone.

3.4.2 Identity of Investigational Products

Active medication

Active substance	:	Belbuca (buprenorphine)
Strength	:	300 µg, 600 µg, and 900 µg
Dosage form	:	Oral buccal film
Manufacturer	:	BioDelivery Sciences International, Inc.

Reference medication

Active substance	:	Oxycodone hydrochloride, immediate-release
Strength	:	30 mg and 60 mg
Dosage form	:	Oral tablets that will be overencapsulated in gelatin capsules (Swedish orange DB capsules, size AA) for blinding purposes
Manufacturer	:	Commercially acquired by the clinical research site from a local vendor

Placebo buccal film (visually matching Belbuca)

Substance	:	Placebo
Strength	:	0 µg
Dosage form	:	Buccal film
Manufacturer	:	BioDelivery Sciences International, Inc.

Placebo capsules (visually matching oxycodone hydrochloride)

Substance	:	Placebo
Strength	:	0 mg
Dosage form	:	Oral capsules matching overencapsulated oxycodone hydrochloride
Manufacturer	:	Pharmacy at PRA

For details concerning drug storage and drug accountability see Appendix 8.1.

3.4.3 Method of Assigning Subjects to Treatment Groups

After obtaining informed consent, subjects will be screened according to the inclusion and exclusion criteria. Subjects who have met all eligibility criteria will receive a subject number upon inclusion in the study. The subject number will be assigned just prior to dosing and according to the randomization code generated by the Biostatistics Department of PRA. The subject number will ensure identification throughout the study. Randomization numbers will range from 1001 to 1018. Replacement subjects will receive the number of the subject to be replaced, increased by 1000 (eg, 2001 replacement number for subject number 1001), and will be administered the same (or remaining) treatments in the same order.

On Day 1, subjects will be randomized to 1 of 6 treatment sequences in a 1:1:1:1:1:1 ratio. Up to approximately 18 eligible subjects will be randomized to 1 of 6 treatment sequences using a computer-generated randomization scheme based on a Williams design (where every treatment follows every other treatment at least once). Study drug will be prepared for each subject based on the randomization scheme. Subjects will receive all six treatments in the order specified by the treatment sequence. The following is an example of a Williams design that might be generated for this 6-treatment, 6-period, 6-sequence crossover trial.

Table 2 Assignment of Subjects to Treatments

Sequence	Period 1	Period 2	Period 3	Period 4	Period 5	Period 6
1	Treatment C	Treatment A	Treatment D	Treatment B	Treatment F	Treatment E
2	Treatment D	Treatment C	Treatment F	Treatment A	Treatment E	Treatment B
3	Treatment F	Treatment D	Treatment E	Treatment C	Treatment B	Treatment A
4	Treatment E	Treatment F	Treatment B	Treatment D	Treatment A	Treatment C
5	Treatment B	Treatment E	Treatment A	Treatment F	Treatment C	Treatment D
6	Treatment A	Treatment B	Treatment C	Treatment E	Treatment D	Treatment F

Treatment A= Belbuca 300 µg and oral placebo; Treatment B= Belbuca 600 µg and oral placebo; Treatment C= Belbuca 900 µg and oral placebo; Treatment D= Oxycodone 30 mg and buccal placebo; Treatment E= Oxycodone 60 mg and buccal placebo; Treatment F= Oral placebo and buccal placebo

Subjects who drop out or withdraw for any reason without completing all screening evaluations successfully will be considered screen failures.

3.4.4 Selection of Doses in the Study

The doses selected for this study were based on an estimate of equivalent doses of Belbuca and oxycodone required to produce a similar analgesic effect and to compare the effect of these doses on respiration. Because there is no known dose equivalence between buprenorphine and a pure mu agonist like oxycodone, it is not known whether 30 mg oxycodone is roughly equivalent to 300 µg or 450 µg buprenorphine. However, the range of 300 to 900 µg buprenorphine is believed to be equivalent to 30 to 60 mg oxycodone.

The dose range of oxycodone was selected based on the fact that 30 mg is a high therapeutic dose and 60 mg is a supratherapeutic dose for acute pain in subjects without opioid tolerance.

The doses of naloxone HCl to be administered in this study (i.e., 0.2 mg IV bolus followed by an additional 0.6 mg IV bolus dose if no reaction) are commonly employed in human abuse liability studies. The naloxone challenge administered as part of qualification ensures that subjects are not dependent on opioids.

3.4.5 Timing of Doses in the Study

On Day 1 of each period, the study drugs will be administered with the subject in the upright position. Study drugs will be administered to subjects between 08:00 and 11:00 hours in the morning. Before each morning dose, subjects will fast overnight for at least 10 hours following a standardized supper on the evening before. Oxycodone and placebo capsules will be swallowed with 240 mL room temperature water. Belbuca and placebo buccal film will be applied to the buccal mucosa. The buccal films should remain in the foil pouches (primary packaging container) until the time of administration. Subjects will receive the capsule first followed by the application of buccal film, inside of moist cheek pocket free of lesions or skin irritation. Subjects will be instructed not to chew the capsules or chew/swallow the film, to keep the mouth closed for the duration of buccal film placement, and to not use the tongue to manipulate the film. For oral capsule dosing, a mouth check will be performed immediately following the dose administration to confirm subjects' proper and complete swallowing of the capsule. For buccal application, an oral cavity check for complete dissolution will be performed prior to the start of the 0.5-hour assessments, allowing for dissolution of the buccal film. If the film is still visibly present after the initial check, a second inspection may be performed before or after 0.5-hour assessments provided the check does not interfere with other planned assessments. Treatment will be double-blind, double-dummy whereby subjects will receive both buccal film (active or placebo) and a capsule (active or placebo). Fasting will continue for a period of 4 hours after drug administration. During fasting, no fluids are allowed except water; however, water is not allowed from 2 hours predose until 1 hour postdose (apart from the water taken with the capsule dose as described above).

3.4.6 Meals During the Study

A fasting period of at least 10 hours is required before obtaining clinical laboratory samples at all time points outlined in the SOA (Table 1).

With the exception of the restrictions with respect to methylxanthine- and alcohol-containing beverages or food as described in Section 3.4.8 and what has been described in Section 3.4.5, there are no special requirements related to food and beverage intake. When not fasting, meals and snacks (such as decaffeinated coffee, herbal tea, fruit, biscuits) will be provided according to PRA standard operating procedures (SOPs). A standardized supper will be provided on the evening before those days where fasting is required until lunchtime.

Subjects will fast for at least 10 hours prior to dosing and for 4 hours after drug administration.

3.4.7 Blinding

This is a randomized, double-blind, placebo-controlled study with limited access to the randomization code. The treatment that each subject will receive will not be disclosed to the investigator, study center personnel, the subject, PRA, or the Sponsor.

The following controls will be employed to maintain the double-blind status of the study:

- Subjects will be blindfolded during initial administration of buccal film.
- Limited staff who administer the buccal films will be considered unblinded and are restricted from study conduct except for study drug administration.
- All oral study medication including placebo and oxycodone will be overencapsulated to ensure study blind is maintained.
- Placebo capsules will be indistinguishable in appearance from the overencapsulated active drug with the same number of capsules and weight as the corresponding active doses.
- The buccal film containing active drug or placebo will be indistinguishable in appearance and taste.
- The randomization code will be provided to the pharmacist at PRA for dispensing purposes and kept in the pharmacy, accessible to the pharmacists and the pharmacy technicians only.

The Sponsor and PRA must be notified immediately if unblinding occurs during the course of the study. Pertinent information regarding the circumstances of unblinding of a subject's treatment code must be documented in the subject's source documents and electronic case report form (eCRF).

3.4.8 Concomitant Medication and Other Restrictions During the Study

Note: Restrictions that apply to the period before the first admission are described in Section 3.3.1 and Section 3.3.2.

The use of all prescribed medications, OTC medications, dietary supplements or herbal supplements (eg, St John's Wort) is not allowed within 14 days before the first check-in to the clinical research center until follow-up. An exception is made for hormonal contraceptives, which are allowed throughout the study. An exception is made for acetaminophen, which is allowed up to admission to the clinical research center. The investigator may permit a limited amount (up to 3 grams daily) acetaminophen for the treatment of headache or any other pain. Other medication to treat AEs may only be prescribed if deemed necessary by the investigator. Use of antiemetics will be allowed after the 4-hour VRH assessments. If medication is used, the name of the drug, the dose, and dosage regimen will be recorded in the eCRF.

The use of alcohol, methylxanthine-containing beverages or food (coffee, tea, cola, chocolate, energy drinks) is not allowed from 2 days prior to each admission and during the stay in the clinical research center. Occasional nicotine use in the form of cigarettes, cigars, or vape pen is allowable (defined as less than half a pack of cigarettes (10 cigarettes), equivalent vaping (100 puffs), or no more than 2 cigars per week). Nicotine replacement therapies (ie, patches and/or gum) may be used without restriction. Subjects who have smoked on a daily basis within 30 days prior to the first dose will not be eligible to participate in the study.

Strenuous exercise and contact sports are not allowed within 48 hours (2 days) prior to the first admission in the clinical research center and for the duration of the study.

Subjects should not consume any foods containing poppy seeds within 48 hours (2 days) prior to each admission to the clinical research center as this could cause a false-positive drug screen result.

Male subjects, if not surgically sterilized, are required to use adequate contraception (see description below) and not donate sperm from first admission to the clinical research center until 90 days after the follow-up visit.

Female subjects of childbearing potential, with a fertile male sexual partner, are required to use adequate contraception (see description below) from 28 days and/or their last confirmed menstrual period prior to study enrollment (whichever is longer) until 90 days after the follow-up visit.

Adequate contraception (for both males and females) is defined as using spermicide with a single barrier method: diaphragm, cervical cap, or condom. For female participants and female partners of male participants, being surgically sterilized or using hormonal contraception or an intrauterine device is also acceptable. Also, total abstinence, in accordance with the lifestyle of the subject, is acceptable.

Subjects must not donate plasma or platelets within 7 days from first dose administration and throughout the study.

- As a general rule, no concomitant medication will be permitted, except acetaminophen, unless the rationale for the exception is discussed and clearly documented between the investigator and the Sponsor. Medications (other than acetaminophen) to treat AEs may only be prescribed after consultation with the Sponsor unless there is an emergency situation that does not allow discussion.
- No new concomitant medications will be allowed during the study unless they are prescribed in response to treatment-emergent AEs (TEAEs). If medication is used, the name of the drug, the dose, and dosage regimen will be recorded in the source documents.

- All medications (prescription and OTC) taken within 30 days of study screening or during the study will be recorded in the appropriate section of the eCRF and in the source documents.

3.4.9 Treatment Compliance

Study drug will be administered in the clinical research center. To ensure treatment compliance, administration of the study drug will be supervised by the investigator or authorized designee.

The exact times of study drug administration and the number of units administered will be recorded in the eCRF.

3.5 Pharmacodynamic, Pharmacokinetic, and Safety Measurements and Variables

3.5.1 Pharmacodynamic, Pharmacokinetic, and Safety Measurements Assessed and Schedule of Assessments

A SOA is presented in Table 1.

3.5.1.1 Pharmacodynamic Measurements

The following PD assessments will be performed at the time points defined in the SOA.

3.5.1.1.1 Ventilatory Response to Hypercapnia

Opioids are well known to reduce the responsiveness of the respiratory centers to carbon dioxide and slopes of the hypercapnic ventilatory response are decreased and shifted to the right.[4] Clinical methods for assessing the ventilatory response to both hypoxia and carbon dioxide were developed in the late 1960s and early 1970s. [5]The VRH challenge has been widely used over the past 25 years and more recently has been used to evaluate whether opioid-induced ventilatory depression can be antagonized by various compounds without reduction of analgesia.[6,7] The VRH test is an experimental model used to evaluate the effect of medications on respiratory drive.

The VRH test will be performed with the subjects comfortably seated or semi-supine in a hospital bed and breathing through a facemask.[8,9] The VRH assessment will be performed once at Screening and 6 times on Day 1. The intervals between each assessment will be a minimum of 20 minutes. At each time point, subjects will be allowed an acclimation period of ambient air to establish regular breathing pattern; immediately followed by hypercapnic gas mixture (21% O_2, 72% N_2, 7% CO_2) for a 5-minute capture period, unless the subject reaches an end-tidal CO_2 of 60 mmHg for three consecutive breaths at which point the procedure will be terminated.

3.5.1.1.2 Pupillometry

The procedure for the pupillometer test will be performed as described in the neuroptic VIP 200 pupillometer reference manual. The subject will be instructed to focus on a distant object

keeping his/her head straight, looking forward with both eyes wide open during both targeting and measurement steps. The oculus dexter (OD) (right eye) or oculus sinister (OS) (left eye) scan button is pressed to start the process. Then, the instrument is positioned so that there is good seal of the rubber portion of the pupillometer head against the subject's orbital rim. The instrument must not be tilted during the measurement process. The pupillometer will automatically detect the pupil, which will show up with its periphery as a highlighted green circle enclosed in a green bracket. During the entire duration, the pupillometer is kept steady on the subject's eye. To initiate the measurement, the OD or the OS button is released; the green bracket will disappear and the results will be displayed. After the measurement process, the center button on the pupillometer is pressed and the subject record being displayed in the results window will be printed.

3.5.1.1.3 Clinical Opiate Withdrawal Scale

The COWS, which will be used only during the Naloxone Challenge Test, is a clinical assessment performed by the investigator to evaluate symptoms of opioid withdrawal. The scale contains 11 items to rate signs and symptoms of opioid withdrawal including pulse rate, gastrointestinal upset, sweating, tremor, restlessness, yawning, pupil size, anxiety or irritability, bone or joint aches, gooseflesh skin, runny nose, and tearing. Each symptom is rated on a unique scale. Total scores for the scale range from 0 to 48 with scores of 5 to 12 indicating mild withdrawal; scores of 13 to 24 indicating moderate withdrawal; scores of 25 to 36 indicating moderately severe withdrawal; and score >36 indicating severe withdrawal.

3.5.1.2 Pharmacokinetic Measurements

3.5.1.2.1 Blood Sampling

During all study periods, blood samples (approximately 6 mL for oxycodone, and 10 mL for buprenorphine and nor-buprenorphine) will be collected to provide at least 3 mL and 6 mL plasma for PK analysis of oxycodone and buprenorphine/nor-buprenorphine, respectively. Samples for oxycodone analysis will be collected into appropriately labeled tubes containing dipotassium ethylenediaminetetraacetic acid (K_2EDTA) and samples for buprenorphine/nor-buprenorphine analysis will be collected in tubes containing sodium heparin. Pharmacokinetic collection times are: at predose, 0.5, 1, 2, 3, 4, and 6 hours postdose.

Pharmacokinetic samples for postdose assessments should be collected ± 10 minutes from the nominal time point.

Samples for both oxycodone and buprenorphine/nor-buprenorphine will be gently inverted 8 to 10 times for complete mixing with the anticoagulant. Samples for oxycodone analysis will be placed in an ice water bath immediately after collection until centrifugation. Samples for buprenorphine/nor-buprenorphine will be maintained at ambient temperature under UV-shielded light until centrifugation.

The PK laboratory manual provides additional detailed instructions on collection and handling for oxycodone and buprenorphine/nor-buprenorphine plasma samples.

Samples will be analyzed using a validated analytical method in compliance with SOPs at the bioanalytical laboratory.

3.5.1.3 Safety and Tolerability Measurements

Safety and tolerability assessments will consist of AEs, clinical laboratory tests, vital signs, 12-lead ECG, continuous oxygen saturation monitoring, Columbia-Suicide Severity Rating Scale (C-SSRS), cardiac telemetry, and PE. Assessments will be performed in accordance with the SOA.

3.5.1.3.1 Adverse Events

All AEs and SAEs encountered during the clinical study will be reported in detail in the source documents and documented in the eCRF from the time of first dose administration, throughout the clinical conduct, and up to 7±2 days after the last study dose (a definition for AEs is given in Appendix 8.2.1). Prior and concomitant medications will be continuously monitored starting after the time of informed consent through the follow-up visit. AEs will be followed until they have returned to the baseline status or stabilized. If a clear explanation of cause is established, it should be recorded in the eCRF.

Pregnancy of female subjects and female partners of male subjects will be monitored along with follow-up, if warranted (see Appendix 8.3).

3.5.1.3.2 Clinical Laboratory

Blood and urine samples for clinical laboratory assessments will be collected according to PRA SOPs. All blood and urine specimens will be sent to a local reference laboratory for analysis and testing.

The following parameters will be measured at the time points noted in the SOA (Table 1):

- Hematology: erythrocytes (red blood cells), leukocytes (white blood cells [WBCs]) with differential (neutrophils, eosinophils, lymphocytes, monocytes, and basophils), hemoglobin, hematocrit, and platelet count.
- Blood chemistry: sodium, potassium, chloride, bicarbonate, creatinine, creatine kinase, amylase, lipase, glucose (fasting), urea, albumin, calcium, magnesium, inorganic phosphorus, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, indirect and direct bilirubin, total protein, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, and uric acid. Creatinine clearance and thyroid stimulating hormone (TSH) will be measured at screening only.
- Urinalysis: A midstream, clean-catch urine specimen will be collected for dipstick analysis of protein, blood, glucose, WBCs, and pH (to be captured in the database). Microscopic analysis will be performed on abnormal results for blood, protein, or WBCs.

The following parameters will also be measured at the time points noted in the SOA (Table 1):

- Urine will be collected for the assessment of the following drugs of abuse: amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine, and opioids, including oxycodone. Results must be available and reviewed before dosing on Day 1.
- An alcohol breathalyzer test will be performed.
- Serology will be collected for the measurement of HIV-1 and -2 antibodies, HBsAg, and anti-HCV.
- For all females, a serum pregnancy test will be collected at screening and urine pregnancy tests will be done prior to check-in to each period. Results must be available and reviewed before dosing on Day 1.
- An FSH panel will be performed and estradiol level will be measured on all postmenopausal female subjects.

In case of unexplained or unexpected clinical laboratory test values, the tests will be repeated as soon as possible and followed up until the results have returned to the normal range and/or an adequate explanation for the abnormality is found. The clinical laboratory will clearly mark all laboratory test values that are outside the normal range, and the investigator will indicate which of these deviations are clinically significant. These clinically significant laboratory result deviations will then be recorded as AEs and the relationship to the treatment will be indicated (see also Appendix 8.2).

The procedures for the collection, handling, and shipping of laboratory samples are specified in the laboratory manual(s) provided to the study site.

3.5.1.3.3 Vital Signs

Complete vital signs will be taken at screening. Vital signs will be recorded after the subject has been resting for at least 5 minutes in the supine position. Complete vital signs will include BP, HR, RR, oral temperature, and pulse oximetry. These assessments will be made using an automated device.

3.5.1.3.4 Electrocardiogram

A standard 12-lead ECG will be recorded after the subject has been resting for at least 5 minutes in the supine position. The ECG will be recorded using an ECG machine equipped with computer-based interval measurements. The following ECG parameters will be recorded: HR, PR-interval, QRS-duration, QT-interval, QTc-interval (Fridericia's), and the interpretation of the ECG profile by the investigator.

3.5.1.3.5 Continuous Oxygen Saturation Monitoring

During VRH tests, from at least 15 minutes predose until at least 8 hours postdose, subjects will have their peripheral capillary oxygen saturation (SpO_2) measured by pulse oximetry.

Because of the intensity of the VRH testing procedure, and because the study drug can lead to respiratory depression, it is important to continuously monitor SpO_2 by telemetry.

3.5.1.3.6 Columbia-Suicide Severity Rating Scale

Suicide-related thoughts and behaviors will be assessed using the C-SSRS. Regulatory agencies have been interested in examining suicide-related thoughts and behaviors in patients receiving antidepressant and other drugs used in psychiatric illnesses. In February 2009, the Food and Drug Administration's (FDA's) Division of Psychiatry Products communicated that information regarding suicide-related thoughts and behaviors should be prospectively collected in a standardized format (Columbia Classification Algorithm or Suicide Assessment) from all clinical studies, including Phase 1 studies, for all drugs in development to enable the analysis of suicide-related thoughts and behaviors in an aggregated fashion. [10] The tool was developed by a National Institute of Mental Health trial group for the purpose of being a counterpart to the FDA's categorization of suicidal events.

The C-SSRS captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period. [10,11,12] The scale includes suggested questions to solicit the type of information needed to determine if a suicide-related thought or behavior occurred. The C-SSRS will be administered by appropriately trained site personnel. A referral to a psychiatrist will be made in the event of a significant finding on the C-SSRS. The C-SSRS Baseline version will be used at screening and the Since Last Visit version will be used at subsequent visits.

All AEs obtained through the questionnaire are recorded. The Sponsor or its designee will be alerted within 24 hours of the investigator's awareness of any SAEs from these questionnaires.

3.5.1.3.7 Cardiac Telemetry

During the period of VRH tests, from at least 15 minutes predose until at least 4 hours postdose, subjects will have their HR and rhythm monitored by telemetry. Because of the intensity of the VRH testing procedure, it is important to use continuous cardiac telemetry.

3.5.1.3.8 Physical Examination

A complete PE will be performed consisting of all body systems (with the exception of genitalia, anus/rectal, and breast examinations, which will only be performed if medically indicated). Unscheduled symptom-directed PEs may be conducted at any time per the investigator's discretion.

3.5.1.4 Total of Blood Volume

Table 3 presents the number and volume of blood samples and the total volume of blood that will be collected throughout the study per subject.

If deemed necessary by the investigator or the Sponsor, the number and/or volume of blood samples per assessment may be increased.

Table 3 Number and Volume of Blood Samples and Total Blood Volume Collected per Subject

Assessment	Maximum # Samples	Volume of Blood per Sample (mL)	Total Volume of Blood (mL)
Pharmacokinetics			
• Oxycodone	42	6	252
• Buprenorphine/nor-buprenorphine	42	10	420
Clinical Chemistry	7	8.5	59.5
Hematology	7	4	28
Serology	1	8.5	8.5
Total Volume of Blood Drawn			**768**

3.5.2 Appropriateness of Measurements

The assessments that will be made in this study are standard and generally recognized as reliable, accurate, and relevant.

3.5.3 Pharmacodynamic, Pharmacokinetic, and Safety Variables

3.5.3.1 Pharmacodynamic Variables

Pharmacodynamic assessments will include pupillometry and VRH.

During VRH the following parameters will be recorded continuously as inhaled oxygen and CO_2 are administered:

- Minute ventilation (expired minute volume, V_E; L/min): volume of gas exhaled per minute from the lungs)
- Respiratory rate (breaths/min)
- Flow rates (peak expired flow, PEF; L/min): maximum speed of expiration
- Tidal volume (expired tidal volume, V_T; mL): volume of gas displaced between normal inhalation and exhalation when extra effort is not applied
- End-tidal CO_2 (ET_{CO2}, mmHg): partial pressure of carbon dioxide at the end of an exhaled breath

For each measurement during pupillometry, a single pupil diameter will be recorded.

3.5.3.2 Pharmacokinetic Variables

Plasma samples will be analyzed for buprenorphine, nor-buprenorphine, and oxycodone using liquid chromatography with tandem mass spectrometric detection according to validated analytical methods. The samples will be analyzed regardless of whether the

subject completed all treatments or not. Full details of the methodology will be presented in a bioanalytical report, which will be appended to the clinical study report (CSR).

The following PK parameters will be calculated for buprenorphine, nor-buprenorphine, and oxycodone using standard noncompartmental methods:

- T_{max}: The time to maximum observed plasma concentration for each subject.
- C_{max}: The maximum observed plasma concentration for each subject.
- AUC_{last}: Area under the plasma concentration versus time curve from 0 to last measurable concentration.
- Abuse quotient (AQ): C_{max}/T_{max}.

3.5.3.3 Safety Variables

The safety variables to be measured include but are not limited to the variables as given below. A complete list of safety variables will be provided in the Statistical Analysis Plan (SAP).

- AEs
- Clinical laboratory tests
- Vital signs
- ECGs
- Continuous oxygen saturation monitoring
- C-SSRS
- Cardiac telemetry
- PEs

3.6 Statistical Procedures and Determination of Sample Size

3.6.1 Analysis Sets

3.6.1.1 Safety Set

All subjects who have received at least 1 dose of the study drug.

3.6.1.2 Pharmacokinetic Set

All enrolled subjects treated who have at least 1 concentration (PK sample) in the treatment phase. The PK parameter analysis population will include all enrolled subjects treated who have at least 1 of the PK parameters of interest.

3.6.1.3 Pharmacodynamic Set

All subjects belonging to the safety set and for whom the PD data are considered to be sufficient and interpretable. The primary analysis will be performed on PD completers. A sensitivity analysis will be performed on PD partial completers (subjects who complete at least 2 treatment periods).

3.6.2 Statistical and Analytical Plan for Pharmacodynamics, Pharmacokinetics, and Safety Evaluation

An SAP will be generated by the Biostatistics Department of PRA; the SAP will be finalized prior to database lock and unblinding of study treatment codes. Full details of the analyses to be performed will be included in the SAP.

Any deviation from the SAP will be reported in the section "Changes in Planned Analysis" in the CSR.

3.6.2.1 Pharmacodynamic Evaluation

The PD parameters and their statistical evaluation will be included in the CSR for this study.

In addition to the measured VRH parameters (see Section 3.5.3.1), the following derived PD parameter will be calculated: The V_E values will be plotted versus the ET_{CO2} values or each subject/treatment per time point, and the intercept and slope (S) will be determined by linear regression. S is the derived PD parameter, i.e., the Hypercapnic Ventilatory Response (L/min per mm Hg).

For all measured and derived PD parameters, mean and standard error (SE) for the actual value and change from baseline for each of the PD parameters, for each treatment group and time point, will be calculated and tabulated, and will be plotted as a function of time after dosing.

For all PD parameters, descriptive statistics including the number of observations (n), mean, standard deviation (SD), minimum, and maximum, as well as quartiles, will be calculated by treatment group. For the VRH PD parameters, pairwise comparisons between treatments will be performed using a mixed-model Analysis of Variance (ANOVA) model with fixed effects for sequence, period, and treatment, and a random effect for subject nested within sequence. Least Square means with 95% confidence intervals (CI) will be provided for each treatment comparison.

More details of the statistical analyses will be defined in the SAP. Prior to the analysis of the final study data, a detailed SAP will be written describing all analyses that will be performed. The SAP may contain any modifications to the PD calculations and analyses described in this protocol.

3.6.2.2 Pharmacokinetic Evaluation

The PK analyses will be based on all available PK concentration-time data. For each subject, the PK parameters will be determined using noncompartmental methods.

Individual and mean plasma concentrations of buprenorphine, nor-buprenorphine, and oxycodone at each sampling time point will be presented by listings and descriptive

summary statistics. Pharmacokinetic parameters including C_{max}, T_{max}, AQ (C_{max}/T_{max}), and AUC_{last} will be calculated and summarized by treatment using descriptive statistics appropriate for the parameter (eg, n, arithmetic mean, median, SD, minimum and maximum, coefficient of variation, geometric mean and geometric CV% [C_{max}, T_{max}, AUC, and AQ (C_{max}/T_{max})]).

3.6.2.3 Evaluation of Safety and Tolerability

Safety and tolerability will be assessed through AEs, clinical laboratory tests, vital signs, ECGs, continuous oxygen saturation monitoring, C-SSRS, cardiac telemetry, and PE findings, and any other parameter that is relevant for safety assessment.

3.6.2.3.1 Adverse Events

Summary tables of TEAEs will be presented by system organ class based on the Medical Dictionary for Regulatory Activities (MedDRA) terminology list (preferred terms): a table containing the number of subjects experiencing the AE by treatment, a table by treatment and relationship, and a table by treatment and severity.

3.6.2.3.2 Clinical Laboratory

Clinical laboratory data will be listed accompanied by an indication if the parameter is outside the reference range. A summary of all data outside the reference range of the clinical laboratory will be provided. Clinical laboratory data will be presented descriptively by treatment, where applicable.

3.6.2.3.3 Vital Signs and Electrocardiograms

Vital signs and ECG parameters will be listed, and they will be presented descriptively by treatment, where applicable.

3.6.2.3.4 Continuous Oxygen Saturation Monitoring

Continuous oxygen saturation monitoring results will be listed and presented descriptively by treatment, where applicable.

3.6.2.3.5 Columbia-Suicide Severity Rating Scale

C-SSRS results will be listed and summarized by treatment.

3.6.2.3.6 Cardiac Telemetry

Cardiac telemetry results will be listed and presented descriptively by treatment, where applicable.

3.6.2.3.7 Physical Examination

Changes from baseline for PE will be described by treatment where applicable and listed.

3.6.3 Determination of Sample Size

An adequate number of subjects will be screened to randomize 18 subjects with the intention to complete the study with 16 subjects. No prospective calculations of statistical power have been made.

3.7 Data Quality Assurance

The study may be audited by the Quality Assurance Department at PRA to assess adherence to the clinical study protocol (CSP) and Quality System. During the conduct of the study, process-related audits may be performed. An audit certificate will be provided in the appendices of the final CSR outlining any audits and other related activities performed.

The clinical research site will be monitored by the study monitor to ensure correct performance of the study procedures and assure that the study is conducted according to the relevant regulatory requirements. The eCRF entries will be verified with the source documentation.

Regulatory authorities, the Institutional Review Board (IRB), and/or the Sponsor's clinical quality assurance group may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

Quality control principles will be applied throughout the performance of this study. Review procedures will be followed at PRA for all documents that are generated in relation with the study.

An explanation will be given for all missing, unused, and spurious data in the relevant sections of the CSR.

4. ETHICS

4.1 Institutional Review Board

The CSP and the ICFs will be submitted for review and approval by an IRB prior to the eligibility screening. The composition of the IRB will be in accordance with 21 CFR 56 and the recommendations of the International Council for Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP). [13]

PRA will keep the IRB informed about the progress of the study. All changes in research activities and all unanticipated problems involving risks to human subjects will be immediately reported to the IRB. PRA will inform the subjects and the IRB if anything occurs on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal, or if further recruitment of subjects in the study has been put on hold for that reason, whichever occurs first. The study may be suspended pending further review by the IRB, except insofar as suspension would jeopardize the subjects' health. PRA will take care that all subjects are kept informed.

No changes will be made in the study without IRB approval, except when required to eliminate apparent immediate hazards to human subjects.

Notification of the end of the study will be sent to the IRB within 90 days after completion of follow-up for the last subject. In case a study is temporarily halted, PRA will notify the IRB immediately, including the reason for this. In case a study is ended prematurely, the IRB will be notified within 15 days, including the reasons for the premature termination. A summary of the results of the study will be sent to the IRB within 1 year after the end of the study. The end of the study is defined as the date of receipt of the last data point for statistical analysis of the last subject participating in the study.

4.2 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that have their origin in the World Medical Association (WMA) Declaration of Helsinki, adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and subsequent amendments. [14]

This study is also designed to comply with ICH E6 Guideline for GCP (European Medicines Agency [EMA]/Committee for Medicinal Products for Human Use [CHMP]/ICH/135/1995). [13]

Guidelines adopted by the ICH and other relevant international guidelines, recommendations, and requirements will be taken into account as comprehensively as possible, as long as they do not violate local law.

Whenever the term “investigator” is noted in the CSP text, it may refer to either the investigator at the site or an appropriately qualified, trained, and delegated individual of the investigational site.

4.3 Subject Information and Consent

All subjects will be informed verbally and in writing regarding the objectives, procedures, and risks of study participation. The subjects will sign the ICF that contains information about the objectives of the study, the procedures followed during the study, and the risks and restrictions of the study, with special reference to possible side effects of the medication and potential interactions.

4.4 Privacy

All personal details of subjects will be treated as confidential by the investigator and staff at PRA, and handling of personal data will be in compliance with the Health Insurance Portability and Accountability Act of 1996.[15]

5. STUDY ADMINISTRATIVE STRUCTURE

5.1 Documentation

5.1.1 Archiving

All documents concerning the study will be kept on file in the Central Archives of PRA for at least 15 years after conduct of the study. The Sponsor will receive the completed eCRFs (upon request, as PDF file).

5.1.2 Recording of Data in Source Documents and CRFs

All data will be collected on source documents and then entered in the eCRFs.

6. CONFIDENTIALITY AND PUBLICATION POLICY

By signing this CSP, the investigator reaffirms to the Sponsor that he/she will maintain in confidence all information furnished to him/her or resulting from this study. The investigator will only divulge such information as may be necessary to the IRB, the members of the staff, and the subjects who are involved in this study.

All relevant aspects regarding publication will be part of the contract (or similar document) between the Sponsor and PRA.

7. REFERENCES

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Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Note for Guidance on Clinical Safety Data Management, June 1995.

8. APPENDICES

8.1 Drug Accountability

The investigator is responsible for the control of drugs under investigation. Adequate records of the receipt (eg, Drug Accountability Forms) and disposition (eg, Drug Dispensing Forms) of the study drug must be maintained. The Drug Dispensing Forms must be kept current and should contain the following information:

- The identification of the subject to whom the study drug was administered
- The date(s) and quantity of the study drug administered to the subject (when applicable)
- The date(s) and quantity of the study drug returned by the subject (when applicable)

All records and drug supplies must be available for inspection by the monitor at every monitoring visit. Unused medication will be returned to the Sponsor at the end of the study or will be locally destroyed according to study site procedures. The investigator's copy of the Drug Accountability Form(s) must accurately document the return of all study drug supplies to the Sponsor, if applicable.

8.2 Adverse Events and Serious Adverse Events Evaluation and Reporting

8.2.1 Adverse Events

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. AE definitions will be followed as stated in the "Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting" (ICH topic E2A). [16]

All AEs reported by the subjects or apparent from their physical appearance during the clinical study will be reported on the AE eCRF page.

The severity of AEs will be graded using the most current version of MedDRA 3-point scale:

- **Mild**: An AE that is easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities.
- **Moderate**: An AE that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed.
- **Severe**: An AE that prevents normal everyday activities; treatment or other intervention usually needed.

If an AE has multiple aspects, the aspect with the highest severity will be graded.

It is emphasized that the term severe is a measure of severity; thus, a severe AE is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

In addition, clinically significant changes in PE findings and abnormal objective test findings (eg, laboratory, x-ray, ECG) should also be recorded as AEs. Test findings and PE findings can result in AEs if they:

- Are associated with accompanying symptoms, and/or
- Require additional diagnostic testing or medical/surgical intervention, and/or
- Lead to a change in study dosing or discontinuation from the study; result in the addition of significant additional concomitant drug treatment or other therapy, and/or
- Lead to any of the outcomes included in the definition of an SAE, and/or
- Are considered to be an AE by the investigator or Sponsor.

Reporting as an AE should not be triggered by:

- Merely repeating an abnormal test, or
- Any abnormal test result that is determined to be an error.

The relationship of any AE to the study drug will be assessed and graded on a 5-point scale: none, unlikely, possibly, likely, or definitely.

Relationship between use of study drug and AE (Causality)					
AE (is)	**None**	**Unlikely**	**Possibly**	**Likely**	**Definitely**
Clearly the result of an external factor	Yes	No	No	No	No
Probably/possibly the result of another factor	No	Yes	Yes	No	No
Has a chronological relationship with the time of study drug administration and/or represents a known reaction to study drug	No	No	Yes	Yes	Yes
Disappears or decreases after discontinuation of the study drug	NA	NA	NA	Yes	Yes
Recurs on renewed administration (re-challenge)	No	No	NA	NA	Yes or NA**

** A rechallenge is not required; if done, rechallenge would be expected to be positive

NA Not applicable

8.2.2 Serious Adverse Events

An SAE is any untoward medical occurrence that, on the basis of medical and scientific judgment:

- Results in death, or
- Is life-threatening (this refers to 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 were more severe), or
- Requires inpatient hospitalization for a medical reason or prolongation of existing hospitalization (this refers to hospital admission required for treatment of the AE). (Note: this does not include confinement in, for example, a respite unit; a skilled nursing unit; rehabilitation facility; the clinical research center; or confinement due to planned or unplanned reason unrelated to study), or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization.
SAEs will be collected from the time of first dose administration until the final study visit. SAEs that are related to the investigational drug and continue beyond the normal collection period (ie, are ongoing at the time a subject exits the study) will be followed until resolution or until stabilized with sequelae. SAEs that begin after the subject's participation in the study is complete, but that the investigator considers to be related to study drug, may be reported at any time.

The investigator or clinical site personnel must notify the Medical Monitor or Clinical Drug Safety Officer of all SAEs, regardless of relationship to the investigational drug, within 24 hours of clinical site personnel becoming aware of the event. The investigator will provide the initial notification by sending a completed "SAE Notification Form," which must include the investigator's assessment of the relationship of the event to investigational drug and must be signed by the investigator.

In addition, notification is sent by PRA to the IRB.

Follow-up information, or new information regarding an ongoing SAE, must be provided promptly to the Medical Monitor or Clinical Drug Safety Officer.

All SAE reports should be sent to the contacts provided on Page 4: SAE Contact Information.

8.2.3 Suspected Unexpected Serious Adverse Reactions

An SAE that is also an unexpected adverse drug reaction is called a suspected unexpected serious adverse reaction (SUSAR). Unexpected adverse reactions are adverse reactions of which the nature or severity is not consistent with the applicable product information (eg, IB for an unapproved investigational medicinal product or the labeling for an authorized medicinal product).

The Sponsor or its representative (eg, PRA if agreed to before start of the study) will report promptly (expedited reporting) the following SUSARs to the IRB:

- SUSARs that have arisen in the current clinical study that was assessed by the IRB.
- SUSARs that have arisen in other clinical studies of the same Sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the current clinical study that was assessed by the IRB.

Expedited reporting will occur no later than 15 calendar days after the Sponsor or its representative has first knowledge of the adverse reactions. For fatal or life-threatening cases, the term will be maximally 7 calendar days for a preliminary report with another 8 days for completion of the report.

8.2.4 Follow-up of Adverse Events

Follow-up of AEs will continue until resolution, stabilization, or death. In case of ongoing AEs at database closure, the data obtained at database closure will be used in the statistical analysis. The follow-up of the AE will be documented in the source documents and will be described in the final CSR only if considered relevant by the investigator.

8.3 Pregnancy

A female clinical study subject must be instructed to stop taking the study drug and immediately inform the investigator if she becomes pregnant during the study. Pregnancies occurring up to 90 days after the completion of the study drug must also be reported to the investigator. The investigator will make arrangements for the subject to be counseled by a specialist, to discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the subject should continue until the outcome of the pregnancy is known.

The investigator should report all pregnancies of female clinical study subjects to the Sponsor within 1 working day of becoming aware of them.

If the investigator becomes aware of a pregnancy occurring in the partner of a male subject participating in the study, the pregnancy should be reported to the Sponsor within 1 working day of obtaining written consent from the pregnant partner. Monitoring of the partner should continue until the outcome of the pregnancy is known.

Attachment 1: Summary of Changes for Version 1.0 to 2.0 for Protocol BUP-401

The following changes have been introduced in Version 2.0 of the protocol. Additions are shown as underlined text, and deleted text is given as ~~strikethrough text.~~

Pages 26 and 27—Section 3.3.1 Inclusion Criteria

9. Female subjects who are non-pregnant, non-lactating, and either postmenopausal for at least 1 year or surgically sterile for at least 3 months, or, if of childbearing potential, will agree to use adequate contraception from 28 days and/or their last confirmed menstrual period prior to study enrollment (whichever is longer) until 90 days after the follow-up visit. Male subjects, if not surgically sterilized, must agree to use adequate contraception and not donate sperm from first admission to the clinical research center until 90 days after the follow-up visit. Adequate contraception (for both males and females) is defined as using ~~hormonal contraceptives or an intrauterine device combined with at least 1 of the following forms of contraception~~ spermicide with a single barrier method: ~~a~~ diaphragm, ~~or~~ cervical cap, or ~~a~~ condom. For female participants and female partners of male participants, being surgically sterilized or using hormonal contraception or an intrauterine device is also acceptable. Also, total abstinence, in accordance with the lifestyle of the subject, is acceptable.

Page 28—Section 3.3.2 Exclusion Criteria

1. Women who are pregnant, lactating, or planning to attempt to become pregnant during this study or within 90 days after ~~dosing of study drug~~ the follow-up visit.

2. Male subjects with female partners who are pregnant, lactating, or planning to attempt to become pregnant during this study or within 90 days after ~~the last dose of study drug~~ the follow-up visit.

7. Subjects who have smoked on a daily basis within 30 days prior to the first dose of study medication. Occasional nicotine use in the form of cigarettes, cigars, or vape pen is allowable (defined as less than half a pack of cigarettes (10 cigarettes), equivalent vaping (100 puffs), or no more than 2 cigars per week). Nicotine replacement therapies (ie, patches and/or gum) may be used without restriction. ~~Use of tobacco, nicotine, or nicotine-containing products within 30 days prior to the admission to the clinical research center and for the duration of study participation~~.

Pages 33 and 34—Section 3.4.8 Concomitant Medication and Other Restrictions During the Study

3rd Paragraph

The use of alcohol, methylxanthine-containing beverages or food (coffee, tea, cola, chocolate, energy drinks) is not allowed from 2 days prior to each admission and during the stay in the clinical research center. ~~The use of tobacco, nicotine, and nicotine-containing products is not allowed from 30 days prior to admission to the clinical research center and for the duration of study participation.~~ Occasional nicotine use in the form of cigarettes, cigars, or vape pen is allowable (defined as less than half a pack of cigarettes [10 cigarettes], equivalent vaping [100 puffs], or no more than 2 cigars per week).

Nicotine replacement therapies (ie, patches and/or gum) may be used without restriction. Subjects who have smoked on a daily basis within 30 days prior to the first dose will not be eligible to participate in the study.

7th Paragraph

Female subjects of childbearing potential, with a fertile male sexual partner, are required to use adequate contraception (see description below) from 28 days and/or their last confirmed menstrual period prior to study enrollment (whichever is longer) until 90 days after the ~~last drug administration~~ follow-up visit.

8th Paragraph

Adequate contraception (for both males and females) is defined as using ~~hormonal contraceptives or an intrauterine device combined with at least 1 of the following forms of contraception~~ spermicide with a single barrier method: ~~a~~ diaphragm, ~~or~~ cervical cap, or ~~a~~ condom. For female participants and female partners of male participants, being surgically sterilized or using hormonal contraception or an intrauterine device is also acceptable. Also, total abstinence, in accordance with the lifestyle of the subject, is acceptable.

Pages 36 and 37—Section 3.5.1.2.1 Blood Sampling

During all study periods, blood samples (approximately 6 mL for oxycodone, and 10 mL for buprenorphine and nor-buprenorphine) will be collected to provide at least 3 mL and 6 mL plasma for PK analysis of oxycodone and buprenorphine/nor-buprenorphine, respectively. Samples for oxycodone analysis will be collected into appropriately labeled tubes containing dipotassium ethylenediaminetetraacetic acid (K_2EDTA) and samples for buprenorphine/nor-buprenorphine analysis will be collected in tubes containing sodium heparin. All samples will be stored on wet ice until processing. Pharmacokinetic collection times are: at predose, 0.5, 1, 2, 3, 4, and 6 hours postdose.

Pharmacokinetic samples for postdose assessments should be collected ± 10 minutes from the nominal time point.

~~Within 45 minutes of collection, samples will be centrifuged at approximately 1700 x g for about 10 minutes at approximately 4°C. The plasma will be stored in appropriately labeled screw capped polypropylene tube at approximately 20°C or lower within 90 minutes of collection.~~

Samples for both oxycodone and buprenorphine/nor-buprenorphine will be gently inverted 8 to 10 times for complete mixing with the anticoagulant. Samples for oxycodone analysis will be placed in an ice water bath immediately after collection until centrifugation. Samples for buprenorphine/nor-buprenorphine will be maintained at ambient temperature under UV-shielded light until centrifugation.

The PK laboratory manual provides additional detailed instructions on collection and handling for oxycodone and buprenorphine/nor-buprenorphine plasma samples.

Samples will be analyzed using a validated analytical method in compliance with SOPs at the bioanalytical laboratory.