1.0 STUDY SYNOPSIS

Name of Sponsor	Opiant Pharmaceuticals
Name of Investigational Product:	Nalmefene hydrochloride nasal spray
Title of Study:	A Two-Period, Two-Treatment, Randomized Crossover Study of the Pharmacokinetics of Nalmefene by Intranasal and Intramuscular Administration in Healthy Volunteers
Clinical Phase:	Phase I (Healthy Volunteers)
Protocol Number:	OPNT003-PK-001
Study Design:	Open-label, randomized, 2-period, 2-treatment, 2-sequence, crossover study in 68 healthy volunteers. Subjects will be assigned to each of the 2 possible sequences. Each subject will receive 2 treatments during the 2 dosing periods: Intranasal (IN) dose of 3 mg nalmefene hydrochloride and intramuscular (IM) dose of 1.0 mg nalmefene, with a 4 day washout period between doses. Screening can occur up to 28 days before baseline admission, subjects will then stay in the inpatient facility for 7 days to complete the treatment phase of the study and will be discharged following completion of the discharge procedures at the end of the last period. Subjects will be called 3 to 5 days after discharge to inquire concerning Adverse Events (AEs) and concomitant medications since discharge. All subjects who have given their written informed consent and who satisfy all of the relevant inclusion criteria and none of the exclusion criteria will be screened for eligibility to participate in the study including medical history, demographics, concomitant medications, physical examination, height, weight, body mass index (BMI), nasal passage examination, smell test, clinical chemistry, coagulation markers, hematology, serum Follicle Stimulating Hormone (FSH) levels (females postmenopausal only), infectious disease serology, urinalysis, urine drug, urine cotinine and urine alcohol toxicology screen, serum pregnancy test (females only), vital signs and electrocardiogram (ECG). On the day of clinic admission (Day -1) the following procedures will be performed to review eligibility, update on medical history, update on concomitant medications, physical examination, nasal passage examination, 12-lead ECG, vital signs, urine pregnancy test (females only), urine drug, urine cotinine and urine alcohol toxicology screen. After eligibility of established and admission procedures complete, patients will be randomized. On the day after admission subjects, in a fully supine position, will be administered the IN or IM dose randomized to a sequence order of receipt. Subjects should be instructed to hold their breath during administration of the nasal spray into the nose. Blood will then be collected prior to dosing (within 15 minutes) and approximately 2.5, 5, 7.5, 10, 15, 20, 30, 45 minutes and 1, 2, 3, 4, 6, 8, 12, 18, 24, 36 and 48 hours after drug administration. Actual blood collection times can vary as follows: ± 1 minutes for the 1 to 30 minute samples, ± 2 minutes for the 45 to 90 minute samples, and ± 5 minutes for the 120 minute or greater samples. Actual sampling times will be recorded. On days of study drug administration (days 1 and 5):

	A numerical rating scale (NRS) to assess acute nasal pain will be completed pre-dose, and at approximately 15 (± 2) and 60 (± 10) minutes post-dose (IN dose only). Continuous cardiac monitoring (telemetry) will be performed from approximately one hour (± 30 minutes) pre-dose to 10 hours (± 30 minutes) post-dose. ECG assessment will be conducted within ± 5 minutes of the nominal blood collection at 20 minutes, and ± 15 minutes of the nominal blood collections at 1 and 10 hours post-dose. Vital signs will be measured pre-dose and at approximately 15 and 30 minutes, and ± 15 minutes of the nominal blood collections at 1, 2, 4 and 8 hours post-dose. Vital signs will also be measured if the subject displays any change in condition including lightheadedness, dizziness, syncope, nausea, vomiting or tachy/bradyarrhythmia as noted on continuous cardiac monitoring. Nasal passage examination (IN dose only) will be conducted pre-dose, at approximately 5 minutes and ± 15 minutes of the nominal blood collections at 1 and 8 hours post-dose. Smell test (IN dose only) will be conducted pre-dose and ± 15 minutes of the nominal blood collections at 1 and 4 hours post-dose. Tolerability assessed via AE query and concomitant medications will be reviewed. On the day after dosing (day 2 and 6) tolerability via AE querry will be assessed, concomitant medications reviewed, vital signs measured, the smell test (IN dose only) will be conductedand examination of the nasal passage performed (IN dose only) at approximately 24 hours post-dose. On the second day after dosing (day 3) tolerability via AE query will be assessed, concomitant medications reviewed, vital signs measured and examination of the nasal passage performed (IN dose only) at approximately 48 hours post-dose. On the day before the next dosing (day 4) tolerability will be assessed, concomitant medications reviewed, a urine pregnancy test (females only) and 12-lead ECG performed. On the day of clinic discharge (day 7) from the inpatient stay the following procedures will be performed: assess tolerability via AE query, update on concomitant medications, vital signs at approximately 48 hours post-dose, physical examination, weight, examination of the nasal passage (IN dose only) at approximately 48 hours post-dose, smell test, 12-lead ECG, serum pregnancy test (females only), urine cotinine, clinical chemistry, coagulation markers, hematology and urinalysis. AEs will be assessed by spontaneous reports by subjects, by examination of the nasal mucosa and by measuring vital signs, ECG and clinical laboratory parameters.
Planned Sample Size:	Sixty eight subjects
Trial Subjects Selection Criteria:	*Inclusion criteria:* The subject must satisfy the following criteria for entry into the study: 1. Male or female aged 18 to 55 years inclusive, having provided written, informed consent prior to any study specific procedure being conducted *2.* BMI ranging from 18 to 30 kg/m^2, inclusive 3. Adequate venous access, as determined by the investigator 4. Subjects must be non-smokers

	5. On screening and admission, the following are the vital signs criteria that need to be met before dosing (with subject sitting at least 5 minutes before obtaining measures): • Systolic blood pressure: 140 mmHg or less and equal to or greater than 90 mmHg • Diastolic blood pressure: 90 mmHg or less and equal to or greater than 55 mmHg • Heart rate: 100 bpm or less and equal to or greater than 40 beats per minute (bpm) • Respiratory rate: 20 respirations per minute (rpm) or less and equal to or greater than 8 rpm Vital signs may be repeated once. *Exclusion criteria:* The subject will be excluded from the study if any of the following applies: 1. A history of clinically significant gastrointestinal, renal, hepatic, neurologic, hematologic, endocrine, oncologic, pulmonary, immunologic, psychiatric, or cardiovascular disease, severe seasonal or non-seasonal allergies, nasal polyps or any nasal passage abnormality that could interfere with nasal spray administration, or any other condition which, in the opinion of the Principal Investigator, would jeopardize the safety of the subject or impact the validity of the study results 2. Subject has had significant traumatic injury, major surgery or open biopsy within 30 days prior to study screening 3. Subjects who (for whatever reason) have been on an abnormal diet (such as one that severely restricts specific basic food groups [e.g., ketogenic diet], limits calories [e.g., fast], and/or requires the use of daily supplements as a substitute for the foods typically eaten at mealtimes), during the four (4) weeks preceding screening 4. Taking prescribed or over the counter medications, dietary supplements, herbal products, vitamins or recent use of opioid analgesics for pain relief within 14 days before initial dosing and throughout the duration of the study 5. Treatment with any known enzyme altering drugs such as barbiturates, phenothiazines, cimetidine, carbamazepine, etc., within 30 days prior to the first dose of study drug or during the study 6. Use of over the counter or prescription nasal products within 28 days of initial dosing and throughout the duration of the study 7. Experimental agents must have been discontinued at least 8 weeks prior to initial dosing for a period equivalent to 5 half-lives of the agent (whichever is longer) 8. Positive urine drug test for alcohol, opioids, cocaine, methamphetamine, benzodiazepines, tetrahydrocannabinol (THC), barbiturates, or methadone at screening or admission/baseline 9. Previous or current opioid, alcohol, or other drug dependence (excluding nicotine and caffeine), based on medical history 10. Positive urine screen for cotinine (smoking and the use of tobacco products is not permitted for four (4) weeks prior to the first dose of Study Drug and throughout the duration of the study)

	11. On standard 12-lead ECG, a QTcF interval >450 msec for males and >470 msec for females 12. Clinically significant concurrent medical conditions considered by the investigator, determined by medical history, physical examination, clinical laboratory examination, vital signs and 12 lead-ECG 13. Donated or received blood or underwent plasma or platelet apheresis within the 30 days before initial dosing 14. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant; unless surgically sterile or use effective contraception (either combined estrogen and progestogen containing hormonal contraception associated with inhibition of ovulation [oral, intravaginal, transdermal], progestogen only hormonal contraception associated with inhibition of ovulation [oral, injectable, implantable], intrauterine device [IUD], intrauterine hormone-releasing system [IUS], vasectomised partner, sexual abstinence (only considered an acceptable method of contraception when it is in line with the subjects' usual and preferred lifestyle), combination of male condom with either cap, diaphragm or sponge with spermicide [double barrier methods]), and willing and able to continue contraception for 1 month after the last administration of Investigational Medicinal Product (IMP). Women using oral contraception must have started using it at least 2 months prior to screening. Women are not considered to be of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum follicle stimulating hormone (FSH) levels that have been confirmed to be in the "postmenopausal range". Or have had a surgical bilateral oophorectomy (with or without hysterectomy) or bilateral tubal ligation at least six weeks before the screening visit. In case of oophorectomy alone, the reproductive status of the woman should have been confirmed by follow-up hormone level assessment 15. Women who are pregnant or breastfeeding at screening and prior to each administration of study drug 16. Positive test for HBsAg, HCVAb, or HIVAb at screening 17. Current or recent (within 7 days prior to screening) upper respiratory tract infection 18. Current or recent (within 14 days prior to first dose) use of any decongestants 19. Allergic to nalmefene or any of the excipients 20. Subjects who will not abstain from engaging in strenuous exercise during the inpatient stay of the study 21. Subjects who will not abstain from consuming poppy seed or similar opium derived food stuff during the study 22. Subjects who will not abstain from ingesting alcohol, drinks containing xanthine >500mg/day (eg. Coca Cola®, coffee, tea, etc.), or grapefruit/grapefruit juice 72 hours before initial dosing and throughout the duration of the study 23. Subject is deemed unlikely to be able to comply with the requirements of the protocol 24. Subjects with any laboratory tests from samples taken at screening considered clinically significant

	25. Subjects with a known intolerance to continuous ECG lead adhesive exposure considered clinically significant by the investigator 26. Brief Smell identification Test (BSIT) < 9 27. Subjects with a known hypersensitivity reaction to plastics
Study Objectives:	The primary objective is to determine the pharmacokinetics (PK) of 3mg nalmefene hydrochloride IN compared to a 1.0 mg dose of nalmefene administered IM, to demonstrate systemic exposure comparable to an approved IM dose. A secondary objective of this study is to evaluate the safety and tolerability of IN nalmefene.
Investigational medicinal product, route of administration and dosage:	Nalmefene hydrochloride 3mg nasal spray Nasal (IN) 1 spray in 1 nostril delivers 0.1 millilitres (mL) of 30mg/mL nalmefene hydrochloride
Reference product, route of administration and dosage:	Nalmefene hydrochloride 1.108 mg/mL solution given intramuscularly (IM) 1.0 mL IM delivers 1.0 mg nalmefene
Maximum Duration of Treatment	Screening can occur up to 28 days before baseline admission. The total subject inpatient stay is 7 days, during which the treatment will be administered. Subjects will be called 3 to 5 days after final discharge to inquire concerning adverse events and concomitant medications since discharge. Total subject duration is up to 40 days to complete the entire study.
Blood and urine sampling	Blood for PK assessments will be obtained via direct venipuncture or through an Intravenous (IV) catheter in the forearm. Four mL of blood will be collected in a K2EDTA-containing vacutainer tube for each time point for determination of nalmefene. Blood samples will be taken at Screening and after last blood draw prior to Final Discharge (or early termination) after the second dosing for clinical chemistry, coagulation markers and hematology. Urine samples will also be taken at screening and clinic admission for urinalysis, urine drug, urine cotinine and urine alcohol toxicology screen. Urine sample will also be taken at discharge for urine cotinine. Female subjects of child-bearing potential will be asked to provide a blood sample at screening, a urine sample prior to each dose and a blood sample prior to study discharge (or early termination) after the second dosing for a pregnancy test.
Pharmacokinetic Endpoints:	The following plasma pharmacokinetic parameters for nalmefene will be calculated using non-compartmental analysis: maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under the curve to the final time with a concentration equal to or greater than the lower limit of quantitation [$AUC_{(0\text{-}t)}$], to infinity [$AUC_{(inf)}$], and during the first 30 minutes [$AUC_{0\text{-}2.5\ mins}$, $AUC_{0\text{-}5\ mins}$, $AUC_{0\text{-}10\ mins}$, $AUC_{0\text{-}15\ mins}$, $AUC_{0\text{-}20\ mins}$ and $AUC_{0\text{-}30\ mins}$], terminal elimination rate constant (λz), half-life ($t_{½}$), clearance (CL/F) and volume of distribution (Vz/F) uncorrected for bioavailability (F).
Safety Endpoints:	Adverse events will be elicited by a verbal probe. Any events spontaneously reported by the subject or observed by investigator staff (physical examinations and nasal cavity examinations) will be recorded.

	Vital signs, clinical laboratory results and ECG abnormalities will be reported as an adverse event if considered clinically significant. Objective evaluations of nasal irritation will be assessed after each administration of study drug using a 6-point (0 to 5) score. A NRS will also be used to assess acute nasal pain following each administration of study drug.
Statistical Analyses:	Individual subject plasma concentrations, actual sampling times, and pharmacokinetic parameters will be listed by analyte and treatment. Descriptive statistics will be calculated by analyte and treatment for plasma concentrations and pharmacokinetic parameters. Individual subject and mean plasma concentrations will be displayed on linear and semi-logarithmic axes. The pharmacokinetic parameters C_{max} and $AUC_{(inf)}$, $AUC_{0\text{-}2.5\ mins}$, $AUC_{0\text{-}5\ mins}$, $AUC_{0\text{-}10\ mins}$, $AUC_{0\text{-}15\ mins}$, $AUC_{0\text{-}20\ mins}$ and $AUC_{0\text{-}30\ mins}$ for nalmefene will be compared between the treatments using an analysis of variance (ANOVA) model with treatment, period, sequence, and subject within sequence as the factors using the natural logarithms (ln) of the data. Confidence intervals (CI) (90%) will be constructed for the geometric mean ratios, nalmefene intranasal (test formulations) to intramuscular on a dose adjusted basis, using the log-transformed data and the two one-sided t-tests procedure. The point estimates and confidence limits will be exponentiated back to the original scale. Comparability between the nalmefene intranasal (test formulation) and nalmefene intramuscular (reference formulation) will be assessed from the geometric mean ratios and 90% confidence intervals. Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and will be grouped by system, organ, class (SOC) designation. Adverse events will be presented as a listing including the start date, stop date, severity, relationship, outcome, and duration. Vital signs, ECG, and clinical laboratory parameters will be presented as summary statistics.

1.1 Schedule of Events

	Screening	Admission /Baseline	Period 1	Washout			Period 2	Washout	Discharge or Early term	Follow-Up Phone call
Study Day(s)	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**+3 to 5 days after discharge**
Informed Consent	X									
Medical History (includes smoking history)	X	X								
Demographics	X									
Eligibility (Inclusion/Exclusion)	X	X								
Physical Examination	X	X							X	
Nasal Passage Examination	X	X	X[a]	X[b]	X[c]		X[a]	X[b]	X[c]	
NRS			X[r]				X[r]			
Smell test	X		X[t]	X[u]			X[t]	X[u]	X	
12-lead ECG[s]	X	X				X			X	
Continuous cardiac monitoring (telemetry)			X[v]				X[v]			
ECG assessment			X[d]				X[d]			
Vital Signs	X[e]	X[e]	X[f]	X[g]	X[h]		X[f]	X[g]	X[e]	
Weight	X								X	
Height, BMI	X									
Clinical Chemistries & Coagulation parameters[i]	X								X	
Hematology[j]	X								X	
Urinalysis[k]	X								X	
Serum FSH levels (females postmenopausal)	X									
Serum Pregnancy test (females)	X								X	
Urine Pregnancy test (females)		X				X				
Urine drug and alcohol toxicology screen[l]	X	X								
Urine cotinine screen	X	X							X	
HIV, Hepatitis B and C	X									
PK blood sampling			X[m]	X[n]	X[o]		X[m]	X[n]	X[o]	
AEs			X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Randomization		X								
Study drug administration[p]			X				X			

Meals [q]		X	X	X	X	X	X	X	X	

[a] Nasal passage examination pre-dose, and at approximately 5 minutes and ± 15 minutes of the nominal blood collections at 1 and 8 hours post-dose (IN Period).
[b] Nasal passage examination at approximately 24 hours post dose (IN Period).
[c] Nasal passage examination at approximately 48 hours post dose (IN Period).
[d] ECG assessment will be conducted within ± 5 minutes of the nominal blood collection at 20 minutes, and ± 15 minutes of the nominal blood collections at 1 and 10 hours post-dose.
[e] Sitting (5 mintues) blood pressure, heart rate, respiration rate, and temperature.
[f] Blood pressure, heart rate, respiration rate, pre-dose (sitting, 5 minutes) and at approximately 15 and 30 minutes (supine), and ± 15 minutes of the nominal blood collections at 1, 2, 4 and 8 hours (sitting, 5 minutes) post-dose.
[g] Sitting (5 minutes) blood pressure, heart rate, respiration rate, at approximately 24 hours post-dose.
[h] Sitting (5 minutes) blood pressure, heart rate, respiration rate, at approximately 48 hours post-dose.
[i] Chemistry parameters include: total protein, albumin, blood urea nitrogen, creatinine, alkaline phosphatase, ALT, AST, total bilirubin, glucose, sodium, potassium, chloride, CO_2, total cholesterol, and calcium. Coagulation parameters include PT and aPTT.
[j] CBC with differentials and platelet count will be performed.
[k] Urinalysis includes: pH, specific gravity, blood, ketones, nitrites, glucose, bilirubin, leukocyte esterase, protein.
[l] Urine toxicology screen for alcohol, opioids, cocaine, amphetamine/methamphetamine, benzodiazepines, barbiturates, THC, or methadone.
[m] Pre-dose (within 15 mins), 2.5, 5, 7.5, 10, 15, 20, 30, 45 minutes and 1, 2, 3, 4, 6, 8, 12, 18 hours post-dose. Actual blood collection times windows can vary as follows: ± 1 minutes for the 1 to 30 minute samples, ± 2 minutes for the 45 to 90 minute samples, and ± 5 minutes for the 120 minute or greater samples.
[n] 24 and 36 hours post dose.
[o] 48 hours post dose. At discharge, collect sample after last blood draw prior to Final Discharge (or early termination) after the second dosing for clinical chemistry, coagulation markers and hematology.
[p] Subjects will receive either a 3 mg nalmefene hydrochloride (one 0.1 mL spray of 30 mg/mL nalmefene hydrochloride) IN dose or a 1.0 mg nalmefene (1.0 mL injection of 1.108 mg/mL nalmefene hydrochloride) IM dose . Subjects must be in a fully supine position at dosing and for 1 hour post-dose. Subjects should be instructed to hold their breath during administration of the nasal spray into the nose.
[q] Subjects will fast from midnight the day before nalmefene dosing until one hour after dosing. Water will be provided *ad libitum*.
[r] Pre-dose, 15 (± 2) and 60 (± 10) minutes post-dose (IN Period).
[s] Subjects will be supine for at least 5 minutes prior to obtaining ECGs
[t] Smell test will be conducted pre-dose and ± 15 minutes of the nominal blood collections at 1 and 4 (IN period)
[u] Smell test wil be conducted at approximately 24 hours post-dose (IN Period)
[v] Continuous cardiac monitoring will be performed from approximately one hour (± 30 minutes) pre-dose to 10 hours (± 30 minutes) post-dose