1) STUDY SYNOPSIS

Name of Sponsor	Opiant Pharmaceuticals
Name of Investigational Product:	Nalmefene hydrochloride nasal spray
Title of Study:	An Open-Label, Three-Period, Three-Treatment, Six-Sequence, Randomized Crossover Study of the Pharmacokinetics of Intranasal Nalmefene in Healthy Volunteers using Three Dosing Regimens
Clinical Phase:	Phase I (Healthy Volunteers)
Protocol Number:	OPNT003-PK-002
Study Design:	Open-label, randomized, 3-period, 3-treatment, 6-sequence, randomized crossover study in **24** healthy volunteers. Subjects will be assigned to each of the 6 possible sequences. Each subject will receive **3 intranasal (IN) Nalmefene doses**: • 3mg IN dose (one 0.1mL spray of a 30mg/mL solution in one nostril) • 6mg IN dose (one 0.1mL spray of a 30mg/mL solution in each nostril) • 6mg IN dose (two 0.1mL sprays of a 30mg/mL solution in one nostril) There will be a **6 day** washout period between doses. Screening can occur up to 28 days before admission, subjects will then stay in the inpatient facility for 16 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 has been reviewed by an investigator, patients will be randomized. On the day after admission subjects, in a fully supine position, will be administered the IN 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 and 48 hours after drug administration. Pre-dose blood sample will be collected within 15 minutes before dosing. Actual blood collection times can vary as follows: ±30 seconds for the 2.5, 5 & 7.5 samples, ±1 minute for the 10 to 30-minute samples, ±3 minutes for the 45 to 120-minute samples, and ±5 minutes for the 180 minute or greater samples. Actual sampling times will be recorded. On days of study drug administration (days 1, 7 and 13): 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. Continuous cardiac monitoring (telemetry) will be performed from approximately one hour (± 30 minutes) pre-dose to 6 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 6 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 will be conducted in both nostrils pre-dose, at approximately 5 minutes and ± 15 minutes of the nominal blood collections at 1 and 8 hours post-dose. Smell test 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 2,8 and 14) tolerability via AE query will be assessed, concomitant medications reviewed, vital signs measured, the smell test will be conducted and examination of the nasal passage performed in both nostrils at approximately 24 hours post-dose. On the second day after dosing (day 3 and day 9) tolerability via AE query will be assessed, concomitant medications reviewed, vital signs measured and examination of the nasal passage performed in both nostrils at approximately 48 hours post-dose. On days 4, 5, 10 and 11 tolerability will be assessed, and concomitant medications reviewed. On the days before the next dosing (days 6 and 12) 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 15) 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 both nostrils at approximately 48 hours post-dose, smell test,,

	12-lead ECG, serum pregnancy test (females only), 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:	Twenty-four subjects
Investigational medicinal product, route of administration and dosage:	Nalmefene hydrochloride 3mg nasal spray Nasal (IN) **Period 1**: 3mg (one 0.1 mL spray of 30 mg/mL nalmefene hydrochloride in one nostril) **Period 2**: 6mg (one 0.1 mL sprays of 30 mg/mL nalmefene hydrochloride in each nostril) **Period 3**: 6mg (two 0.1 mL sprays of 30 mg/mL nalmefene hydrochloride in one nostril)
Maximum Duration of Treatment	Screening can occur up to 28 days before admission. The total subject inpatient stay is 16 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 48 days to complete the entire study.

1) SCHEDULE OF EVENTS

	Screening	Admission	Period 1	Washout					Period 2	Washout					Period 3	Washout	Discharge or Early term	Follow-Up Phone call
Study Day(s)	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**+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]				X[a]	X[b]	X[c]	
NRS			X[r]						X[r]						X[r]			
Smell test	X		X[t]	X[u]					X[t]	X[u]					X[t]	X[u]	X	
12-lead ECG[s]	X	X						X						X			X	
Continuous cardiac monitoring (telemetry)			X[v]						X[v]						X[v]			
ECG assessment			X[d]						X[d]						X[d]			
Vital Signs	X[e]	X[e]	X[f]	X[g]	X[h]				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						X				
Urine drug and alcohol toxicology screen[l]	X	X																
Urine cotinine screen	X	X																
HIV, Hepatitis B and C	X																	
PK blood sampling			X[m]	X[n]	X[o]				X[m]	X[n]	X[o]				X[m]	X[n]	X[o]	
AEs			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X																
Study drug administration[p]			X						X						X			
Meals[q]		X	X	X	X	X			X	X	X	X			X	X	X	
COVID-19 PCR Test		X																

[a] Nasal passage examination on both nostrils will be performed at pre-dose, and at approximately 5 minutes (± 1 minute) and at 1 and 8 hours post-dose (± 15 minutes).
[b] Nasal passage examination on both nostrils will be performed at approximately 24 hours post dose (± 30 minutes).
[c] Nasal passage examination on both nostrils will be performed at approximately 48 hours post dose (± 30 minutes).
[d] ECG assessment will be conducted at 20 (± 5 minutes) minutes, and at 1(± 15 minutes) and 6 (± 15 minutes) hours post-dose.
[e] Sitting (5 mintues) blood pressure, heart rate, respiration rate, and temperature.
[f] Blood pressure, heart rate, respiration rate, pre-dose (within 30 minutes; sitting) and at approximately 15 and 30 minutes (supine), and at 1, 2, 4 and 8 (± 15 minutes; sitting) hours post-dose, after at least 5 minutes rest.
[g] Blood pressure, heart rate, respiration rate, at approximately 24 hours (± 30 minutes; sitting) post-dose, after at least 5 minutes rest.
[h] Blood pressure, heart rate, respiration rate, at approximately 48 hours (± 30 minutes; sitting) post-dose, after at least 5 minutes rest.
[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. Pre-dose blood sample will be collected within 15 minutes before dosing. Actual blood collection times can vary as follows: ±30 seconds for the 2.5, 5 & 7.5 samples, ±1 minute for the 10 to 30-minute samples, ±3 minutes for the 45 to 120-minute samples, and ±5 minutes for the 180 minute or greater samples.
[n] 24 (± 5 minutes) hours post dose.
[o] 48 hours post dose (± 5 minutes). At discharge, collect sample after last blood draw prior to Final Discharge (or early termination) after the third dosing for clinical chemistry, coagulation markers and hematology.
[p] Subjects will receive either 3 mg nalmefene hydrochloride IN (one 0.1 mL spray of 30 mg/mL nalmefene hydrochloride in one nostril), 6 mg nalmefene hydrochloride IN (one 0.1 mL spray of 30 mg/mL nalmefene hydrochloride in each nostril) or 6 mg nalmefene hydrochloride IN (two 0.1 mL sprays of 30 mg/mL nalmefene hydrochloride in one nostril). 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] NRS will be performed at pre-dose, at approximately 15 (± 2) minutes and 1 (± 10 minutes) hour post-dose.
[s] Subjects will be supine for at least 5 minutes prior to obtaining ECGs.
[t] Smell test will be conducted pre-dose and at 1 and 4 hours post dose (± 15 minutes).