Clinical Study Protocol TR08

A Randomized, Double-Blind, Double-Dummy, Active- and Placebo-Controlled, Two-Part, 7-Way Crossover Study to Evaluate the Oral Abuse Potential of Nalbuphine Solution and Extended-Release Intact Tablets Relative to Hydromorphone Solution and Placebo in Non-Dependent, Recreational Opioid Users

INC Research Project #1008910
Initial protocol: Version 1.0, 09-Apr-2018
Protocol Amendment 1: Version 2.0, 18-May-2018
Protocol Amendment 2: Version 3.0, 10-Sep-2018

Short Title	Oral Abuse Potential Study of Nalbuphine
Protocol Number	TR08
INC Research Project Number	1008910
Phase	Phase I
Sponsor	Trevi Therapeutics, Inc. 195 Church Street, 14th Floor New Haven, CT, United States 06510
Test Products	Part A ▪ Nalbuphine hydrochloride (HCl) 10 mg/mL (equivalent to 9 mg/mL of the free base) Part B ▪ Nalbuphine HCl 10 mg/mL (equivalent to 9 mg/mL of the free base) ▪ Nalbuphine extended-release (ER) tablets, 162 mg ▪ Nalbuphine matching placebo tablets ▪ Hydromorphone HCl, 2 mg/mL
Dose/Route of Administration	Oral administration ▪ Nalbuphine single doses from 81 mg (corresponding to 90 mg of the HCl salt) up to a maximum safe dose (MSD) coadministered with a flavored beverage as a 150 mL solution ▪ Nalbuphine ER single dose 162 mg (1 × 162 mg ER tablet) ▪ Hydromorphone HCl single dose 8 mg, 12 mg, and 16 mg (4 mL, 6 mL, and 8 mL × 2 mg/mL, respectively) coadministered with a flavored beverage as a 150 mL solution
CRO/Study Center	INC Research Toronto, Inc. (part of Syneos Health™) 720 King Street West, Suite 700 Toronto, Ontario, Canada M5V 2T3
Clinical Laboratory (Safety)	Dynacare Medical Laboratories 115 Midair Court Brampton, Ontario, Canada L6T 5M3
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Medical Monitor	Thomas Sciascia, M.D. Trevi Therapeutics 195 Church Street New Haven, CT, United States 06510
Version	3.0
Date	10-Sep-2018

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SPONSOR APPROVAL PAGE

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Version: 3.0

Date: 10-Sep-2018

Trevi Therapeutics, Inc.

A. Hawi — Sep 13, 2018

Amale Hawi, Ph.D.
Senior VP, CMC, Nonclinical & Clinical Pharmacology

Date

Thomas Sciascia, M.D.
Chief Medical Officer

Date

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Amale Hawi, Ph.D.
Senior VP, CMC, Nonclinical & Clinical Pharmacology

Date

Thomas Sciascia MD

Thomas Sciascia, M.D.
Chief Medical Officer

Sept 13, 2018

Date

PRINCIPAL INVESTIGATOR PROTOCOL AGREEMENT PAGE

A Randomized, Double-Blind, Double-Dummy, Active- and Placebo-Controlled, Two-Part, 7-Way Crossover Study to Evaluate the Oral Abuse Potential of Nalbuphine Solution and Extended-Release Intact Tablets Relative to Hydromorphone Solution and Placebo in Non-Dependent, Recreational Opioid Users

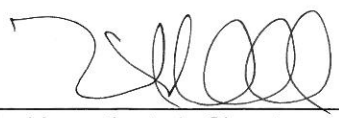
I agree, as an Investigator conducting this study:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, with any future amendments, and with any other written study conduct procedures provided and reviewed and approved by Trevi Therapeutics, Inc.
- Not to implement any deviations from or changes to this protocol without agreement from the sponsor and the prior review and written approval from the Institutional Review Board, except where necessary to eliminate an immediate hazard to the patients/subjects or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- That I am thoroughly familiar with the appropriate use of the investigational drug, as described in this protocol, and any other information provided by the sponsor including, but not limited to, the current Investigator's Brochure or equivalent document provided by Trevi Therapeutics, Inc.
- That I am aware of, and will comply with, Good Clinical Practice and all applicable regulatory requirements, including the regulations governing the use of controlled substances.
- To ensure that all persons assisting me with the study are adequately informed about the investigational drug, and that they are qualified to perform their study-related duties and functions, as described in this protocol.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply details about the Qualified Investigator's ownership interest in the sponsor or the study drug and more generally about his/her financial ties with the sponsor. Trevi Therapeutics, Inc. will obtain and disclose any relevant information in this regard solely for the purpose of complying with regulatory requirements.

Hence, I

- Agree to supply Trevi Therapeutics, Inc. with all information regarding ownership interest and financial ties with Trevi Therapeutics, Inc. (including those of my spouse and dependent children);
- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study; and
- Agree that Trevi Therapeutics, Inc. may disclose this information about such ownership interests and financial ties to regulatory authorities.

Principal Investigator's Name (please print): MICHAEL MADONICH



Principal Investigator's Signature

12 Sep 2018.

Date

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AMENDMENT SUMMARY

Version	Date	Description
1.0	09-Apr-2018	Initial release
2.0	18-May-2018	Amendment 1. The protocol was amended based on feedback from Health Canada on contraception use for male subjects and dose escalation stopping rules. Minor clarifications were also incorporated into the protocol. Details of all changes and the rationale are provided in Section 12.1.
3.0	10-Sep-2018	Amendment 2. The dose escalation scheme in Part A was amended to allow an incremental increase in the dose of nalbuphine based on a percentage of up to 50% from the last dose (rather than an absolute 27 mg dose increase), if supported by the safety data of the preceding cohorts up to a 2-3-fold the therapeutic dose. Doses of nalbuphine are not to exceed 486 mg (ie, 3-fold the therapeutic dose). The amendment is proposed based on the preliminary safety results of the first 4 cohorts indicating a lower than expected incidence of adverse events and mildness (all Grade 1 except for 1 event of Grade 2 nausea) of the adverse event profile up to a dose of 162 mg nalbuphine. Any episode of vomiting (instead of Grade 2 or higher) will be considered as a possible signal of intolerance in the evaluation of the maximum safe dose. In addition, an option to use both pharmacokinetic and safety data to identify the maximum safe dose was included. Additional protocol clarifications were also added regarding urine drug screens, the statistical analyses of the pharmacodynamic data in Part B, and data listings of the Columbia-Suicide Severity Rating Scale. Details of all changes and the rationale are provided in Section 12.2.

ACRONYMS & ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
Alu	aluminum
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{0\text{-}inf}$ or AUC_{inf}	area under the plasma drug concentration time curve extrapolated to infinity
AUC_{last}	area under the plasma drug concentration time curve from the time of dosing to the last measurable concentration
BID	2 times daily
BLQ	below the limit of quantification
BMI	body mass index
bpm	beats per minute
CI	confidence interval
CL/F	apparent clearance
C_{max}	maximum observed plasma drug concentration
CNS	central nervous system
COWS	Clinical Opiate Withdrawal Scale
CRF	case report form (electronic or paper)
CRU	clinical research unit
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DAT	divided attention test
DRC	Data Review Committee
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition – Text

	Revision
DSST	digit symbol substitution test
ECG	electrocardiogram
EDC	electronic data capture
E_{max}	maximum effect
E_{min}	minimum effect
ER	extended-release
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HAP	human abuse potential
HCl	hydrochloride
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IR	immediate release
IRB	Institutional Review Board
IV	intravenous
kel	first-order elimination rate constant
MedDRA	Medical Dictionary for Regulatory Activities
MPC	maximum pupil constriction
MSD	Maximum Safe Dose
PD	pharmacodynamics
PK	pharmacokinetics
Q1	first quartile
Q3	third quartile
QD	once per day

RMS	root mean square
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SpO_2	blood oxygen saturation
SSTM	Sternberg short-term memory test
$t_{½}$	elimination half-life
TA_AUE	time-averaged area under the effect curve
TA_PAOC	time-averaged pupillometry area over the curve
TBD	to be determined
TEAE	treatment-emergent adverse event
TE_{max}	time to maximum effect
TE_{min}	time to minimum effect
T_{max}	time to maximum observed plasma drug concentration
TMPC	time to maximum pupil constriction
THC	tetrahydrocannabinol
VAS	visual analog scale
Vd/F	apparent volume of distribution

1. STUDY BACKGROUND

Nalbuphine is a derivative of 14-hydroxymorphine and is structurally related to the opioid μ-receptor agonist oxymorphone and the opioid μ-receptor antagonist naloxone.[1] Nalbuphine is a competitive antagonist of the μ-opioid receptor while producing agonist effects at the κ-opioid receptor and is therefore classified as an 'opioid agonist-antagonist'. Unlike morphine and other potent mu-agonists, nalbuphine produces an agonist-antagonist "ceiling effect" and does not produce a dose-dependent increase in respiratory depression as the dose is increased.[2]

In the US, nalbuphine was approved in 1979 as nalbuphine hydrochloride (HCl) for injection (originally marketed as Nubain®) and is medically indicated to treat moderate to severe pain, a supplement to balanced anesthesia, for pre-operative and post-operative analgesia and obstetrical analgesia during labor and delivery. No oral formulations of nalbuphine have been approved for any indication; the drug is available only in generic, parenteral formulations. Presently, nalbuphine is not a controlled substance under the Controlled Substances Act (CSA; 21 U.S.C. 812) in the US[3] and is a Schedule IV controlled drug substance under the Controlled Drugs and Substances Act in Canada.[4]

Trevi Therapeutics, Inc. is developing an oral, extended-release (ER) tablet formulation of nalbuphine. Nalbuphine has not been studied in an oral abuse potential study. From the literature, the abuse potential of parenteral formulations of nalbuphine has been evaluated in dependent and non-dependent opioid users[1] and results from some of these studies showed that nalbuphine produced abuse-related positive subjective responses that were similar to those of the opioid, morphine. In a randomized, placebo-controlled, double-blind, crossover trial,[5] 16 healthy volunteers not dependent on opioids received injections of 2.5, 5.0 or 10 mg/70 kg nalbuphine, 10 mg/70 kg morphine, or saline over a 15-second interval. Subjective and objective measures were tested between 5 and 300 minutes post-injection. The results demonstrated that the administration of nalbuphine produced dose-related effects on subjective, psychomotor and physiological variables. The profiles of subjective and physiological responses were similar between the 10 mg/70 kg doses of nalbuphine and morphine: both produced statistically significant ($P < 0.001$) differences in subjective effects (eg, drug liking), pupil constriction, and induced impaired psychomotor performance (number of digit symbols drawn) when compared to saline. In another study conducted in 8 subjects not dependent on opioids and with a history of opioid abuse, parenteral doses of 8 mg/70 kg nalbuphine produced pupil constriction comparable to 10 mg/70 kg morphine; however, increasing the dose of nalbuphine up to 72 mg/70 kg (a nine-fold dose increase) did not result in a dose-dependent increase in pupil constriction (equivalent higher doses of morphine were not tested).[6]

1.1 Previous Human Experience

The sponsor has completed 13 clinical studies with oral nalbuphine to date. A total of 706 subjects have received at least one dose of nalbuphine. Trevi has conducted 7 Phase 1 clinical studies of nalbuphine ER tablets (6 studies in healthy volunteers and 1 study in hemodialysis patients with age-, gender- and weight-matched healthy subjects). Two analgesic efficacy and safety studies have been conducted.[1] Two (2) anti-pruritic efficacy and safety

studies in hemodialysis patients with uremic pruritus have been conducted[1] and 2 anti-pruritic efficacy and safety studies in prurigo nodularis subjects.[1] No human abuse potential studies of nalbuphine ER tablets have been conducted.

The most common adverse events (AEs) following single or multiples doses of nalbuphine ER tablets were known to occur with other drugs with opioid pharmacologic properties and were primarily in the system organ categories related to nervous system disorders (eg, dizziness, headache, somnolence) and gastrointestinal disorders (eg, nausea and vomiting).[1] Most of the AEs were mild to moderate in severity.[1] In order to minimize these AEs, in-clinical efficacy patients were titrated from a low dose of 27 mg to the highest clinical tested dose of 162 mg over a 2-week period. However, when administered as a single 108 mg or 162 mg oral dose, the incidence of these AEs was relatively high (approximately 20 to 40% dose). Specifically, when administered as a single dose nalbuphine ER ranging between 27 mg and 162 mg in studies in healthy subjects, the incidence of AEs increased with increasing dose.[1] Most of these single dose related AEs were mild or moderate in AE grade intensity. One subject administered a single 108 mg oral dose of nalbuphine ER tablets under fasting conditions experienced sedation (ie, unresponsive to pain and verbal stimuli but had normal blood pressure and respiration) that was reported as a serious adverse event (SAE) attributed to drug-related sedation effects. The subject received treatment with naltrexone (2 x 0.4 mg intramuscular [IM] injections) and recovered.

One (1) study (NAL 20) evaluated opiate withdrawal-related effects in subjects with osteoarthritis after administration of nalbuphine ER tablets for 21 days followed by abrupt study drug discontinuation.[1] The objective opiate withdrawal scale (OOWS) scores obtained from the study showed an absence of any physical withdrawal symptoms in most active arm subjects scored (85% of subjects scored) or minimal evidence of physical withdrawal symptoms.

Nalbuphine was well absorbed following oral administration of nalbuphine ER tablets in healthy volunteers.[1] The median time of observed peak concentrations (T_{max}) was 3 to 6 hours after oral doses of up to 162 mg nalbuphine ER tablets, while the median T_{max} of nalbuphine was 0.5 hours after oral administration of 54 mg nalbuphine as a solution (Nubain®) (equivalent to 60 mg nalbuphine HCl solution). Exposure (area under the curve; AUC) of nalbuphine after single dose administration of Nalbuphine ER tablet and oral solution was shown to be comparable with a relative bioavailability of 94% under fasting conditions. However, as expected, the rate of absorption for the ER tablet is slower than the rate of the oral solution with a reduced maximum observed plasma drug concentration (C_{max}) and delayed T_{max} (5.8 hours compared to 0.5 hours, respectively), which would be expected from the ER mechanism of this formulation.

Coadministration of nalbuphine ER tablets with a high caloric meal did not affect T_{max} but C_{max} values were approximately 1.5-fold higher compared to dosing under fasting conditions (Study NAL 06). However when administered as a nalbuphine solution, the food effect was less pronounced with an 11% decrease in C_{max} and approximately 24% increase in AUC under fed relative to fasting conditions.

The mean elimination half-life ($t_{1/2}$) of nalbuphine varied between 6.6 and 9.6 hours across clinical studies. Nalbuphine is metabolized by the liver, possibly undergoes enterohepatic circulation, and is excreted via the kidneys. Nalbuphine metabolites are reported to be pharmacologically inactive.

Following a single oral dose, nalbuphine exposure was dose-dependent and increased with increasing dose in a near dose proportional manner in healthy subjects. The mean exposure of nalbuphine ranged between 4.13 to 21.6 ng/mL and 58.8 to 328 ng.hr/mL for C_{max} and the area under the curve extrapolated to infinity ($AUC_{0\text{-}inf}$), respectively, over the 27 mg to 162 mg dose range. Drug exposure in healthy female subjects was consistently higher (~ 1.3-1.6 fold at the 162 mg dose) than that in male subjects; however, the differences were not statistically significant (*P* value > 0.05) (Study NAL07). The $t_{1/2}$ was similar between males (8 to 9 hours) and females (7 to 11 hours), and was independent of dose and gender. In an open-label multiple escalating dose study of nalbuphine ER (TR01), 15 hemodialysis patients with pruritus and 9-matched healthy subjects were evaluated. Subjects were titrated every 3-4 days from 27 mg once per day (QD) on Day 1 to 27 mg 2 times daily (BID) then 54 mg BID, 108 mg BID and finally 162 mg BID over a 13-day period. Exposure (C_{max} and are under the curve over the dosing interval [AUC_{tau}]) increased in a dose proportional fashion over the 27-mg to 162-mg BID dose range: 2-, 4-, and 6-fold increases in dose resulted in approximately 2-, 5-, and 6-fold increases, respectively, in mean C_{max}, and AUC_{tau}.[7]

1.2 Study Rationale

Nalbuphine is an opioid agonist-antagonist and produces effects related to the central nervous system (CNS). Drug products with CNS activity are associated with abuse potential.[8] Therefore, this protocol will evaluate the abuse potential, as well as the pharmacokinetics (PK) and safety, of nalbuphine solution and intact ER tablets administered orally in non-dependent, recreational opioid users. The abuse potential of nalbuphine will be evaluated against placebo and the μ-agonist opioid analgesic hydromorphone HCl solution administered orally. The active drugs (ie, nalbuphine and hydromorphone) will be administered as solutions in order to maximize the peak exposure (C_{max}). As described in the Food and Drug Administration (FDA) Guidance for Industry,[8] the assessment of abuse potential requires the examination of doses ranging from minimally effective to supratherapeutic; however, a maximum (supratherapeutic) dose of nalbuphine that can be safely administered in a healthy population has not been identified. Therefore, this study will include a Dose Selection Study (Part A) in order to identify the appropriate doses of nalbuphine to administer in the Main Study (Part B).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

The primary and secondary study objectives will be addressed in the Main Study (Part B). The exploratory objectives will be addressed in the Dose Selection Study (Part A).

2.1.1 Primary Objective

The primary objective of the Main Study is to evaluate the abuse potential of orally administered nalbuphine solution and nalbuphine ER intact tablets relative to hydromorphone solution (the active comparator) and placebo in non-dependent, recreational opioid users.

2.1.2 Secondary Objectives

The secondary objectives of the Main Study are:

- To assess the cognitive and psychomotor effects of orally administered nalbuphine solution and nalbuphine ER intact tablets relative to hydromorphone solution and placebo in non-dependent, recreational opioid users.
- To assess the PK of orally-administered nalbuphine solution and nalbuphine ER tablets in non-dependent, recreational opioid users.
- To assess the safety and tolerability of orally-administered nalbuphine solution and nalbuphine ER tablets relative to hydromorphone solution and placebo in non-dependent, recreational opioid users.

2.1.3 Exploratory Objectives

The exploratory objectives that will be evaluated in the Dose Selection Study are:

- To assess the safety and tolerability of various doses of orally-administered nalbuphine solution and determine the maximum safe dose (MSD) in non-dependent, recreational opioid users.
- To assess the PK and pharmacodynamics (PD; pupillometry) of various doses of orally-administered nalbuphine solution in non-dependent, recreational opioid users.

2.2 Endpoints

2.2.1 Primary Endpoint

The primary endpoint for the Main Study is the peak (maximum) effect (E_{max}) for Drug Liking ("at this moment"), assessed on a bipolar, 0 to 100 point visual analog scale (VAS).

2.2.2 Key Secondary Endpoints

The key secondary endpoints for the Main Study are the following measures of global effects:

- Overall Drug Liking VAS (E_{max} and peak minimum effect [E_{min}])
- Take Drug Again VAS (E_{max})

2.2.3 Other Secondary Endpoints

The other secondary endpoints for the Main Study are described below.

2.2.3.1 Pharmacodynamic Endpoints

- Balance of effects:
  - Drug Liking VAS (E_{min}, time to maximum/minimum effect [TE_{max}/TE_{min}], and time-averaged area under the effect curve [TA_ AUE])
- Positive drug effects:
  - High VAS (E_{max}, TE_{max}, and TA_AUE)
  - Good Drug Effects VAS (E_{max}, TE_{max}, and TA_AUE)
- Negative drug effects:
  - Bad Drug Effects VAS (E_{max}, TE_{max}, and TA_AUE)
- Other effects:
  - Hallucination VAS (E_{max}, TE_{max}, and TA_AUE)
  - Any Drug Effects (E_{max}, TE_{max}, and TA_AUE)
  - Drowsiness/Alertness VAS (E_{min}, TE_{min} and TA_AUE)
  - Bowdle VAS (E_{max}, TE_{max}, and TA_AUE)
  - Drug Similarity VAS (score at 12 hours)
- Objective measure:
  - Pupillometry (maximum pupil constriction [MPC], time to MPC [TMPC], and time-averaged pupillometry area over the curve [TA_PAOC])
- Cognitive and psychomotor effects:
  - Divided Attention Test (DAT)
    - Root mean square (RMS) distance: the RMS distance from the center of the road (pixels) (E_{max})
    - Percentage over road: percentage of time over the road (%); (E_{min})
    - Greatest distance: the maximum distance from the center of the road (pixels) (E_{max})
    - Response latency of correct responses (msec) (E_{max})
    - Average number of false alarms (E_{max})
    - Percentage of target hits (%) (E_{min})
  - Digit Symbol Substitution Test (DSST)
    - Number of symbols completed (E_{min})
    - Number of errors (symbols completed incorrectly) (E_{max})

- Sternberg Short-Term Memory Test (SSTM)
  - d'Prime (d') pooled, for all valid responses (E_{min})
  - Mean reaction time pooled, for all valid responses (E_{max})

2.2.3.2 Pharmacokinetic Endpoints

The PK parameters that will be evaluated for nalbuphine, as applicable, include:

- C_{max}: maximum observed plasma concentration
- T_{max}: time to maximum observed plasma concentration
- AUC_{last}: area under the plasma concentration time curve from 0 to last measurable concentration

The following parameters will be derived for nalbuphine if sufficient data are available:

- AUC_{inf}: area under the plasma concentration versus time curve extrapolated to infinity
- kel: first-order elimination rate constant associated with the terminal (log-linear) portion of the curve
- t½: apparent first-order terminal elimination half-life will be calculated as 0.693/kel
- CL/F: apparent clearance
- Vd/F: apparent volume of distribution

2.2.3.3 Safety Endpoints

- AEs (type, incidence, and severity)
- Vital signs (blood pressure, respiratory rate, heart rate, oxygen saturation [SpO_2], and oral temperature)
- Electrocardiograms (ECGs) (heart rate and the PR, QRS, QT, QTcB, and QTcF intervals)
- Clinical laboratory tests (hematology, clinical chemistry, urinalysis)
- Physical examination

2.2.4 Exploratory Endpoints

- Safety Assessments: AEs, vital signs (blood pressure, respiratory rate, heart rate, SpO_2, and oral temperature), ECGs (heart rate and the PR, QRS, QT, QTcB, and QTcF intervals), clinical laboratory tests (hematology, clinical chemistry, urinalysis), and physical examination
- Identification of an MSD of nalbuphine administered as nalbuphine oral solution
- Concentration-versus-time profiles of nalbuphine in plasma and PK parameters C_{max}, T_{max}, and AUC_{last}. If data allow then the PK parameters AUC_{inf}, kel, $t_{1/2}$, CL/F and Vd/F will be calculated.
- Pupillometry (MPC, TMPC, and TA_PAOC)

3. INVESTIGATIONAL PLAN

3.1 Study Design

This study will be a single-dose, randomized, double-blind, active- and placebo-controlled, double-dummy, 2-part, 7-way crossover study to determine the abuse potential of orally administered nalbuphine solution and nalbuphine ER intact tablets relative to hydromorphone solution and placebo, in non-dependent, recreational opioid users. The study will be conducted in a single clinical research unit (CRU).

In order to determine the appropriate MSD of nalbuphine solution to be used in the main study, the study will be conducted in 2 parts: Part A (Dose Selection Study) and Part B (Main Study). The purpose of Part A will be to conduct an exploratory dose selection study to identify the appropriate low, intermediate, and high doses of nalbuphine solution to be administered as single doses in the Treatment Phase of the Main Study (Part B).

In the Main Study Treatment Phase in Part B, the total estimated duration between each dose of study drug is approximately up to 7 days, of which the subject will spend 3 days/2 nights in the CRU and approximately up to 4 days at home.

The study will comprise the following visits:

Dose Selection Study (Part A)

- Screening Visit (Visit 1)
- Dose Selection Phase (naloxone challenge and dose selection) (3-days/2-nights; Visit 2)

Main Study (Part B)

- Screening Visit (Visit 1)
- Qualification Phase (naloxone challenge and drug discrimination test) (4-days/3-nights; Visit 2)
- Treatment Phase; treatment periods 1-7 (3-days/2-nights; Visits 3-9)
- Follow-up Visit (Visit 10)

3.1.1 Screening (Part A and Part B)

Subjects will undergo a screening visit, which will include a review of their medical history and recreational drug use history against the study inclusion and exclusion criteria (Section 4.2 and Section 4.3, respectively). The same screening procedures and requirements will be applicable to both Part A and Part B of this study.

Eligible subjects who participate in Part A may also participate in Part B (after informed consent to participate in Part B is obtained) and will only require re-screening if a duration of 60 days or greater has passed between the screening visit in Part A and the first visit in Part B. If a duration of more than 4 days and less than 60 days has passed between the screening visit in Part A and

the first visit in Part B, then the following assessments will be performed: blood samples will be collected from these subjects for clinical laboratory tests of hemoglobin, hematocrit, and liver enzymes (ie, alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), serology (human immunodeficiency virus [HIV], hepatitis B and hepatitis C), and, for females only, a serum pregnancy test.

New subjects enrolling into Part B of this study will be required to undergo all screening procedures.

3.1.2 Dose Selection Study (Part A)

Within 30 days of Screening, eligible subjects will enter the Dose Selection Phase that will include 1) a naloxone challenge to confirm that subjects are not opioid dependent, and 2) a dose escalation scheme to evaluate the safety and tolerability of single escalating oral doses of nalbuphine solution to non-dependent, recreational drug users.

During the naloxone challenge, subjects will receive 0.2 mg of naloxone via an intravenous (IV) bolus followed by 0.6 mg naloxone IV if no withdrawal signs are observed, as described in Section 4.4. The Clinical Opiate Withdrawal Scale (COWS) will be administered to confirm non-dependence. Subjects with a COWS score of <5 will be eligible to continue participation in the Dose Selection Phase.

At least 12 hours after completing the naloxone challenge, eligible subjects will receive a single oral dose of nalbuphine or placebo solution in a randomized, double-blind manner, after at least an 8-hour overnight fast, as described in Section 5.1.1. Each dosing cohort will comprise 8 unique subjects who will be randomized to nalbuphine or placebo in a ratio of 6:2 nalbuphine:placebo. All subjects within a cohort will receive the same dose of nalbuphine if randomized to active study drug.

At least 5 unique dosing cohorts are planned and the proposed single doses of nalbuphine solution will increase by at least 27 mg increments or will increase in an amount up to 50% of the dose administered in the previous cohort, as deemed appropriate by the safety and tolerability data: eg, 81 mg, 108 mg, 135 mg, 162 mg, and 243 mg (corresponding to 90 mg, 120 mg, 150 mg, 180 mg, and 270 mg of the HCl salt, respectively) or until an MSD is reached. Doses of nalbuphine solution are not to exceed 486 mg (ie, 3-fold the therapeutic dose). Dose reductions and intermediate doses may also be considered based on the results obtained in previous cohort(s). The rationale for the dosing cohorts planned is provided in Section 5.4, Selection of Doses.

Safety, PK, and PD (ie, pupillometry) assessments will be conducted for up to 24 hours after dosing or longer, at the discretion of the investigator or designee. Subjects will remain in the CRU until approximately 24 hours after administration of the study drug and after all final assessments are completed (or longer, at the discretion of the investigator or designee).

Following completion of each cohort, safety data will be unblinded and reviewed by the Data Review Committee (DRC). PK and PD data may be unblinded for review if it is available in a timely manner, but will not serve as the basis for determining dose escalation. Dose escalation will only occur if an MSD has not been identified and the previous dose level was deemed to be

safe and well tolerated. Escalation to the next dose level will continue until the MSD is identified. If the DRC observes a plateau in the incidence and severity of AEs, which do not meet the stopping criteria described in Section 4.9, then the PK data may be reviewed to determine if there is a plateau in the exposure of nalbuphine despite dose escalation.

Additional cohorts of 8 subjects per cohort may be added if a given dose level is repeated to provide additional data or if a dose level, intermediate to those proposed, is considered necessary for safety or tolerability reasons, or a dose higher than those planned is required to be tested, based on supporting safety and tolerability data. Dose escalation or reduction decisions by the DRC and the rationale in support of each dose selection will be documented. Dose escalation procedures, stopping criteria, and details about the DRC are provided in Section 4.9.

3.1.3 Qualification Phase (Part B)

Within 30 days of screening, a sufficient number of eligible subjects will participate in the Qualification Phase in order to randomize an estimated 56 subjects in the Treatment Phase. The Qualification Phase will include 1) a naloxone challenge to confirm that subjects are not opioid dependent, and 2) a drug discrimination test to ensure that subjects can distinguish between the active control (hydromorphone) and placebo.

The same procedures used for the naloxone challenge in Part A will performed in Part B: subjects will receive 0.2 mg of naloxone via an IV bolus followed by 0.6 mg naloxone IV if no withdrawal signs are observed, as described in Section 4.4. Subjects with a COWS score of <5 will be eligible to continue with the drug discrimination test. For those subjects who successfully complete the naloxone challenge in Part A and elect to participate in Part B, a naloxone re-challenge will only be required if more than 60 days has passed between the first challenge and admission to the Qualification Phase in Part B.

During the drug discrimination test, doses will be administered in a randomized, double-blind, single-dummy, crossover manner following a fasting period of at least 8 hours. Subjects will receive a single oral dose of 12 mg hydromorphone HCl solution and placebo solution on consecutive days (Days 1 and 2), approximately 24 hours apart, to ensure that they are able to discriminate the positive drug effects of the active comparator. Each subject will drink approximately 200 mL of solution on each day. The 12 mg dose of hydromorphone HCl (6 mL of 2 mg/mL) will be added to a flavored beverage (approximately 144 mL) to prepare the 150 mL dosing solution. The placebo solution will consist of a flavored beverage administered to subjects in a volume of 150 mL. After subjects drink the 150 mL dosing solution, an additional 50 mL flavored beverage will be added to the dosing container as a rinse and then administered to the subjects. Study drug administration is described in Section 5.1.2.

Pharmacodynamic and safety assessments will be conducted prior to dosing and until at least 8 hours after dosing. Data will be reviewed to determine subject eligibility, as described in Section 4.5.

3.1.4 Treatment Phase (Part B)

An estimated 56 eligible subjects will be randomized in the Treatment Phase. The last drug administration in the Qualification Phase and the first drug administration in the Treatment Phase

will be separated by a washout interval of at least 72 hours (exceeding 5 times the expected half-life of hydromorphone). During the 7 treatment periods, subjects will receive single oral doses of each treatment in a randomized, double-blind, double-dummy fashion, as described in Section 5.1.3. Each treatment will consist of a dosing solution of 150 mL of oral solution (nalbuphine, hydromorphone, or placebo [flavored beverage]) and one intact tablet (nalbuphine ER or matching placebo). After subjects drink the 150 mL dosing solution, an additional 50 mL flavored beverage will be added to the dosing container as a rinse and then administered to the subjects.

The selection of the low, intermediate, and high doses of nalbuphine solution planned for the Treatment Phase will be determined ("TBD") based on the results obtained in Part A, as described in Section 4.9. However, the total volume of dosing solution to be administered in each treatment period will be identical (ie, 150 mL dosing solution comprised of an appropriate amount of active drug and/or flavored beverage) in order to maintain the blind.

The following treatments will be administered:

- **Treatment A: Placebo**
  150 mL flavored beverage +
  1 × nalbuphine matching placebo tablet
- **Treatment B: Hydromorphone HCl 8 mg solution**
  4 mL × 2 mg/mL hydromorphone HCl + 146 mL flavored beverage +
  1 × nalbuphine matching placebo tablet
- **Treatment C: Hydromorphone HCl 16 mg solution**
  8 mL × 2 mg/mL hydromorphone HCl + 142 mL flavored beverage +
  1 × nalbuphine matching placebo tablet
- **Treatment D: Nalbuphine HCl *low dose* solution**
  low dose nalbuphine HCl solution + TBD mL flavored beverage +
  1 × nalbuphine matching placebo tablet
- **Treatment E: Nalbuphine HCl *intermediate dose* solution**
  Intermediate dose nalbuphine HCl solution + TBD mL flavored beverage +
  1 × nalbuphine matching placebo tablet
- **Treatment F: Nalbuphine HCl *high dose* solution**
  high dose nalbuphine HCl solution + TBD mL flavored beverage +
  1 × nalbuphine matching placebo tablet
- **Treatment G: Nalbuphine 162 mg ER intact tablet**
  150 mL flavored beverage +
  1 × 162 mg nalbuphine ER tablet

Drug administration will occur on Day 1 of each treatment period, followed by PD, PK, and safety assessments for up to 24 hours post-dose. Subjects will be discharged on Day 2, approximately 24 hours after dosing, at the discretion of the investigator or designee to ensure subject safety. Each treatment will be separated by a washout interval of at least 4 days.

3.1.5 Follow-up Visit (Part B)

Subjects will return for an end-of-study safety follow-up visit approximately 7 to 14 days following the last drug administration in the Treatment Phase, or at the time of early withdrawal.

3.1.6 Study Duration

Subjects who enroll in Part A will participate in the study for a maximum of 4.5 weeks. This includes up to 30 days for the Screening visit and 3 days in the Dose Selection Phase.

Subjects who enroll in Part B will participate in the study for up to 14 weeks. This includes up to 30 days for the Screening visit, up to 3 days in the Qualification Phase followed by at least a 72-hour washout, 42 days in the Treatment Phase (assuming up to a 7-day washout between each dose of study drug), and up to 14 days for the Follow-up visit.

Subjects who participate in both Part A and Part B of the study may participate for a maximum duration of approximately 19 weeks.

3.1.7 Study Schematic and Time and Events Schedules

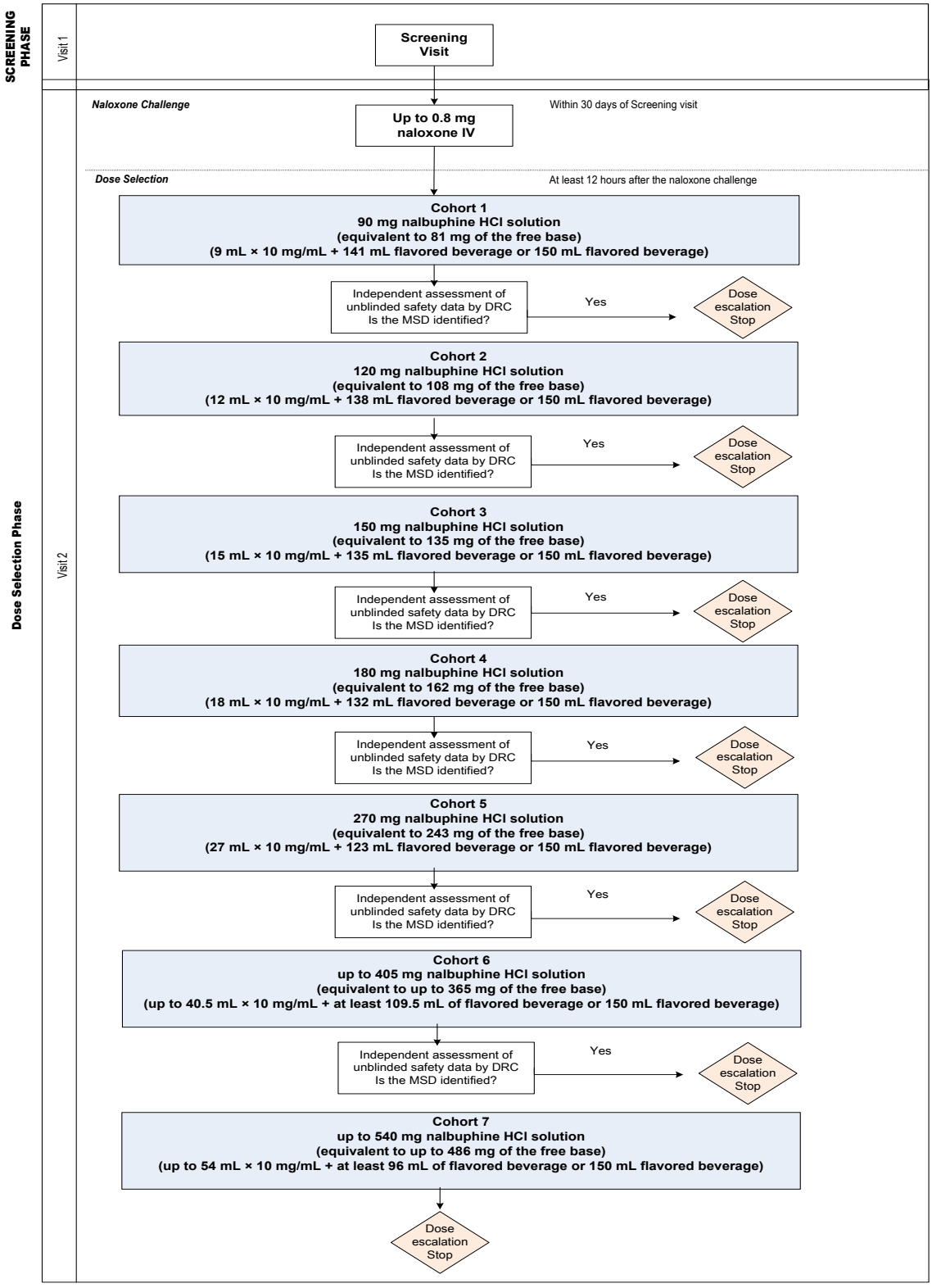
Study schematics are presented in Figure 1 (Part A) and Figure 2 (Part B). Study assessments will be performed at the visits and time points outlined in the Time and Events Schedules, as follows:

Table 1 Part A: Screening and Dose Selection Phase

Table 2 Part B: Screening and Qualification Phase

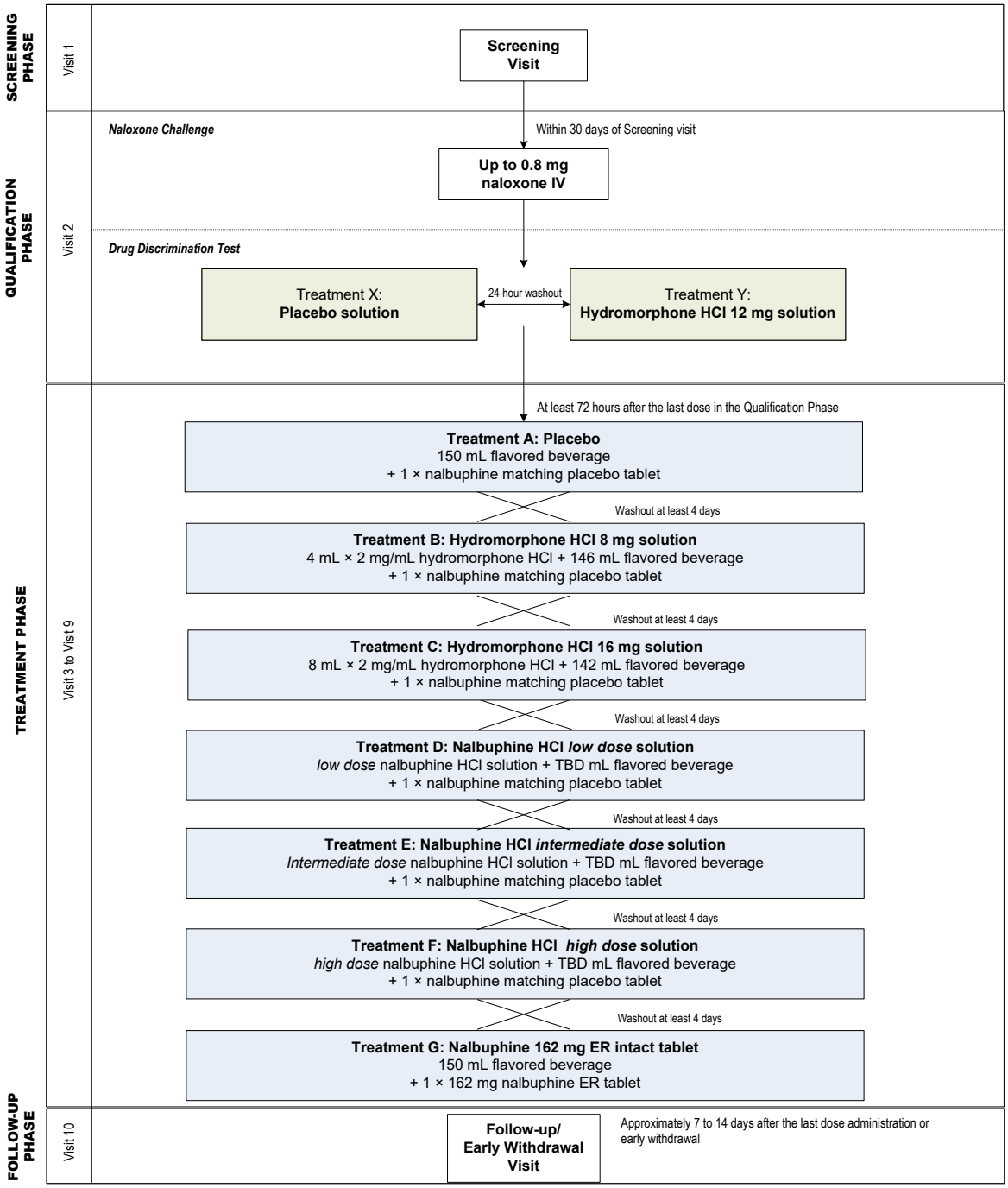
Table 3 Part B: Treatment Phase and Follow-up

Figure 1 Study Schematic for Part A (Dose Selection Study)



Footnotes Figure 1:
DRC=data review committee; ER=extended release; HCl=hydrochloride; IV=intravenous; MSD=maximum safe dose.
At each dosing of active drug, the dose will be added to a flavored beverage to prepare a dosing volume of 150 mL. An additional 50 mL of a flavored beverage will be added as a rinse to the empty dosing container that contained the 150 mL solution and then administered to the subjects.
At least 12 hours after completing the naloxone challenge, eligible subjects will receive a single oral dose of nalbuphine HCl solution or placebo solution in a randomized, double-blind manner. Each cohort will comprise 8 unique subjects who will be randomized to nalbuphine HCl (n=6) or placebo (n=2).
Following completion of each cohort, safety data will be unblinded and reviewed by the DRC. Escalation to the next dose level will continue until the MSD is identified. Dose reductions and intermediate doses may be considered based on the results obtained in previous cohort(s). Additional cohorts of subjects may be added until the MSD is identified, or if additional data are required at a given dose level or at a dose intermediate to those specified, or a dose higher than those planned is required to be tested, based on supportive safety data. If a dose higher than planned will be tested, the dose to be administered will be up to 50% greater than the dose administered in the previous cohort, based on supporting safety data.

Figure 2 Study Schematic for Part B (Main Study)



ER=extended release; HCl=hydrochloride; IR=immediate release; IV=intravenous; TBD=to be determined.

At each dosing of active drug, the dose will be added to a flavored beverage to prepare a dosing volume of 150 mL. An additional 50 mL of a flavored beverage will be added as a rinse to the empty dosing container that contained the 150 mL solution and then administered to the subjects.

In the *Qualification Phase*, the drug discrimination test will be administered to eligible subjects at least 12 hours after the naloxone challenge. Each treatment will be administered orally in a randomized, double-blind manner and separated by a 24-hour washout interval. Placebo solution will comprise 150 mL flavored beverage and hydromorphone HCl solution will comprise 6 mL x 2 mg/mL hydromorphone HCl + 144 mL flavored beverage.

In the *Treatment Phase*, each treatment will be administered orally in a randomized, double-blind, double-dummy manner and doses will be separated by at least a 4-day washout interval. Low, intermediate, and high doses of nalbuphine HCl solution will be determined in Part A.

Table 1 Part A - Time and Events Schedule: Screening and Dose Selection Phase

	Screening Visit	Dose Selection Phase																					
		Naloxone Challenge	Dose Selection Cohorts																				
Visit:	**1**	**2**																					
Day:	**–30 to –2**	**–1**	**1**																				**2**
			Assessment time points relative to dosing (hours)																				
Subject Review																							
Informed Consent	X																						
Medical History	X	X[a]																					
Medication and Recreational Drug and Alcohol Use History	X																						
Inclusion/Exclusion	X																						
Inclusion/Exclusion Eligibility		X																					
Study Restrictions Review		X																					
Demographics	X																						
DSM-IV-TR	X																						
C-SSRS (Baseline version)	X																						
Safety																							
Physical Examination	X	X[b]																					X[b]
Height, Weight, BMI	X																						
Serum Pregnancy	X	X																					
Urine Pregnancy		X																					
FSH (postmenopausal women)	X																						
HIV, Hepatitis B, Hepatitis C	X																						
Vital Signs[c]	X	X[d]	Pre				1		2		3	4	5	6		7	8	10	12	24			

[a] Focusing on any changes since the last visit.
[b] Symptom-directed physical examination
[c] Vital signs will include blood pressure, heart rate, and respiratory rate. Vital signs will also include measurements of oxygen saturation after continuous pulse oximetry monitoring is complete.
[d] Pre-naloxone challenge and at 10 minutes and 1 hour post-naloxone challenge, as indicated in Section 4.4.

	Screening Visit	Dose Selection Phase																				
		Naloxone Challenge	Dose Selection Cohorts																			
Visit:	**1**	**2**																				
Day:	**–30 to –2**	**–1**	**1**																			**2**
			Assessment time points relative to dosing (hours)																			
Oral Temperature	X	X																				24
Electrocardiogram	X	X																				24
Urine Drug Screen	X	X																				
Breath Alcohol	X	X																				
Continuous Pulse Oximetry[e]			Predose until at least 6 hours post-dose																			
Clinical Laboratory Tests	X																					24
Concomitant Medications			< -- recorded throughout -- >																			
Adverse Event Monitoring[f]	X	X	< -- recorded throughout -- >																			
COWS		X																				
Pharmacokinetics																						
Nalbuphine			Pre		0.25	0.5	1	1.5	2	2.5	3	4	5	6			8	10	12	24		
Pharmacodynamics																						
Pupillometry			Pre		0.25	0.5	1	1.5	2	2.5	3	4	5	6			8	10	12	24		
Study Administration																						
Naloxone Administration		X[g]																				
Randomization			pre[h]																			
Admission		X																				
Study Drug Administration				0																		
Discharge[i]																						X

AE=adverse event; BMI=body mass index; COWS=Clinical Opiate Withdrawal Scale; C-SSRS=Columbia-Suicide Severity Rating Scale; DSM-IV-TR=Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition – Text Revision; ECG=electrocardiogram; FSH=follicle-stimulating hormone; HIV=human immunodeficiency virus; pre=pre-dose

[e] Oxygen saturation will be monitored continuously via telemetry for at least 6 hours post-dose or longer, if deemed necessary by the investigator or designee to ensure subject safety.
[f] Spontaneous AE reporting is continuous throughout the study; however, AE questioning may be performed using a non-leading question at discretion of the clinical staff.
[g] Naloxone challenge procedures are described in Section 4.4. For female subjects, the results of the urine pregnancy test are required prior to the naloxone challenge; results of the serum pregnancy test will not be required prior to the naloxone challenge.
[h] Day 1 only.
[i] Subjects will be discharged after assessments on Day 2 are complete and at the discretion of the investigator or designee to ensure subject safety.

Table 2 Part B - Time and Events Schedule: Screening and Qualification Phase

	Screening Visit[a]	Qualification Phase		
		Naloxone Challenge[b]	Drug Discrimination Test	
Visit:	1	2		
Day:	–30 to –2	–1	1 and 2	3[c]
			Assessment time points relative to dosing (hours)	
Subject Review				
Informed Consent	X			
Medical History	X	X[d]		
Medication and Recreational Drug and Alcohol Use History	X			
Inclusion/Exclusion	X			
Inclusion/Exclusion Eligibility		X		
Study Restrictions Review		X		
Demographics	X			
DSM-IV-TR	X			
C-SSRS (Baseline version)	X			
Safety				
Physical Examination	X	X[e]		
Height, Weight, BMI	X			
Serum Pregnancy	X	X		
Urine Pregnancy		X		
FSH (postmenopausal women)	X			
HIV, Hepatitis B, Hepatitis C	X			

[a] For subjects who completed screening assessments in Part A, abbreviated screening assessments may be performed as described in Section 6.3.10.
[b] For subjects who successfully completed the naloxone challenge in Part A, a naloxone re-challenge will only be required if more than 60 days has passed between the first challenge and admission to the Qualification Phase in Part B.
[c] Day 3 assessments are performed approximately 24 hours post last dose
[d] Focusing on any changes since the last visit
[e] Symptom-directed physical examination performed

	Screening Visit[a]	Qualification Phase												
		Naloxone Challenge[b]	Drug Discrimination Test											
Visit:	1	2												
Day:	–30 to –2	–1	1 and 2											3[c]
			Assessment time points relative to dosing (hours)											
Vital Signs[f]	X	X[g]	pre			1		2	3		6	8		X
Oral Temperature	X	X												
COWS		X[h]												
Electrocardiogram	X	X												
Urine Drug Screen	X	X												
Breath Alcohol	X	X												
Continuous Pulse Oximetry			From pre-dose until at least 4 hours post-dose											
Clinical Laboratory Tests	X													
Concomitant Medications	X	X	< -- recorded throughout -- >											X
Adverse Event Monitoring[i]	X	X	< -- recorded throughout -- >											X
Pharmacodynamics														
Training/Practice[j]		X												
Drug-Specific VAS[k]					0.5	1	1.5	2	3	4	6	8		
Other VAS[l]			pre		0.5	1	1.5	2	3	4	6	8		
ODL, TDA VAS												8		
Study Administration														
Naloxone Challenge		X[m]												
Randomization			pre[n]											
Admission		X												

[f] Vital signs will include blood pressure, heart rate, and respiratory rate. Oxygen saturation will be measured after continuous pulse oximetry monitoring is complete.
[g] Pre-naloxone challenge and at 10 minutes and 1 hour post-naloxone challenge, as indicated in Section 4.4.
[h] COWS will be done at admission (prior to the naloxone challenge) and during the naloxone challenge.
[i] Spontaneous AE reporting is continuous throughout the study; however, AE questioning may be performed using a non-leading question at discretion of the clinical staff.
[j] Complete training and practice session
[k] Drug Liking VAS, Good Drug Effects VAS, and Bad Drug Effects VAS
[l] High and Drowsiness/Alertness VAS
[m] Naloxone challenge procedures are described in Section 4.4. For female subjects, the results of the urine pregnancy test are required prior to the naloxone challenge; results of the serum pregnancy test will not be required prior to the naloxone challenge.
[n] Day 1 only.

	Screening Visit[a]	Qualification Phase		
		Naloxone Challenge[b]	Drug Discrimination Test	
Visit:	1	2		
Day:	–30 to –2	–1	1 and 2	3[c]
			Assessment time points relative to dosing (hours)	
Study Drug Administration			0	
Dispense Subject ID Card				X
Discharge[o]				X

AE=adverse event; BMI=body mass index; COWS=Clinical Opiate Withdrawal Scale; C-SSRS=Columbia-Suicide Severity Rating Scale; DSM-IV-TR=Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition – Text Revision; ECG=electrocardiogram; FSH=follicle-stimulating hormone; HIV=human immunodeficiency virus; ID=identification; ODL=Overall Drug Liking; pre=pre-dose; TDA=Take Drug Again; VAS=visual analog scale

[o] Subjects will be discharged after assessments on Day 3 are complete and at the discretion of the investigator or designee to ensure subject safety.

Table 3 Part B - Time and Events Schedule: Treatment Phase and Follow-Up

	TREATMENT PHASE																		FU or EW
	Treatment Periods 1 to 7																		
Visit:	3 to 9																		10
Day:	–1	1																2	—
		Assessment time points (hours)																	
Subject Review																			
Study Restrictions Review	X																		X
Medical History	X[a]																		X[a]
C-SSRS (Since Last Visit)	X																		X
Safety																			
Physical Examination	X[b]																		X[b]
Serum Pregnancy	X[c]																		X
Urine Pregnancy	X[c]																		
Vital Signs[d]	X	pre			0.5	1	1.5	2	3	4	5		6		7	8	10	12	24	X
Oral Temperature	X																		X
ECG	X																		X
COWS[e]	X[f]																		
Urine Drug Screen	X[f]																		
Breath Alcohol	X																		X

[a] Focusing on any changes since the last visit
[b] Symptom-directed physical examination performed
[c] Serum pregnancy at Treatment periods 1 and 7 only; urine pregnancy at Treatment periods 2, 3, 4, 5, and 6
[d] Vital signs will include blood pressure, heart rate, and respiratory rate. Oxygen saturation will be measured after continuous pulse oximetry monitoring is complete.
[e] COWS may be administered adhoc during the Treatment phase, at the investigator's discretion, based on any observed or reported AEs that may indicate signs or symptoms of withdrawal.
[f] Subjects must have both a negative UDS result and a COWS score < 5 to continue the study. Subjects who have a positive UDS result and score < 5 on the COWS may be rescheduled at the discretion of the investigator. Subjects who have a COWS score ≥ 5, with or without a positive UDS result, will be discontinued from the study and receive appropriate medical care for at least 4 hours or longer until the investigator determines that the subject can be safely discharged from the clinical unit.

	TREATMENT PHASE																			FU or EW
	Treatment Periods 1 to 7																			
Visit:	3 to 9																			10
Day:	–1	1																	2	—
	Assessment time points (hours)																			
Continuous Pulse Oximetry	From pre-dose until at least 6 hours post-dose																			
Clinical Laboratory	X[g]																			X
Concomitant Medications[h]	X	<---------- Recorded throughout ---------->																		X
AE Monitoring[i]	X	<---------- Recorded throughout ---------->																		X
Pharmacodynamics																				
Training/Practice	X[j]	X[k]																		
Drug-Specific VAS[l]					0.5	1	1.5	2	3	4	5	5.5	6	6.5	7	8	9	12	24	
Other VAS[m]		pre			0.5	1	1.5	2	3	4	5	5.5	6	6.5	7	8	9	12	24	
ODL, TDA VAS																		12	24	
Drug Similarity VAS																		12		
DAT, DSST, SSTM		pre			0.5	1	1.5	2	3	4	5	5.5	6	6.5	7	8	9	12	24	
Pupillometry		pre			0.5	1	1.5	2	3	4	5	5.5	6	6.5	7	8	9	12	24	
Pharmacokinetics																				
Nalbuphine		pre		0.25	0.5	1	1.5	2	3	4	5	5.5	6	6.5	7		9	12	24	

[g] Hematology, clinical chemistry, and urinalysis
[h] Concomitant medications will be recorded throughout the study; however, specific questioning will be performed at admission(s) and Follow-up
[i] Spontaneous AE reporting is continuous throughout the study; however, AE questioning may be performed using a non-leading question at discretion of the clinical staff.
[j] Pharmacodynamic training and practice session
[k] Pharmacodynamic refresher session for DAT, DSST, and SSTM
[l] Drug Liking VAS, Good Drug Effects VAS, Bad Drug Effects VAS, Any Drug Effects VAS
[m] High, Drowsiness/Alertness, Hallucination, Bowdle VAS

	TREATMENT PHASE																			FU or EW
	Treatment Periods 1 to 7																			
Visit:	3 to 9																			10
Day:	–1	1																	2	—
		Assessment time points (hours)																		
Study Administration																				
Randomization		pre[n]																		
Admission	X																			
Drug Administration			0[o]																	
Discharge[p]																			X	

AE=adverse event; COWS=Clinical Opiate Withdrawal Scale; C-SSRS=Columbia-Suicide Severity Rating Scale; DAT=Divided Attention Test; DSST= Digit Symbol Substitution Test; ECG=electrocardiogram; EW=early withdrawal; FU=follow up; ODL=Overall Drug Liking; pre=pre-dose; SSTM= Sternberg Short-Term Memory; TDA=Take Drug Again; VAS=visual analog scale

[n] Treatment period 1 only
[o] Day 1 of each Treatment period; each drug administration will be separated by at least 4 days
[p] Approximately 24 hours post-dose in each treatment period (unless subject has a COWS score ≥ 5; see footnote f above), after the completion of assessments, at the discretion of the investigator or designee

3.2 Discussion of Study Design

The overall study design is consistent with guidelines for the assessment of abuse potential in humans.[8,9] In accordance with these guidelines, subjects will be healthy individuals who are non-dependent recreational opioid users.

For this study, nalbuphine will be compared to hydromorphone and placebo. Details for the rationale for selecting the positive control can be found in Section 3.2.1 and the rationale for the specific doses selected can be found in Section 5.4.

Due to inter-individual variability in subjective responses, human abuse potential studies are typically conducted using a double-blind crossover design, where each subject receives several doses of comparator and the investigational drug, as well as placebo. Thus, each subject acts as his/her own control. Subjects will be healthy individuals, with previous non-therapeutic (recreational) experience with opioids. These subjects are the most face-valid population to study because they represent the population at greatest risk for abuse of a novel compound with abuse potential, and they can provide meaningful ratings of the drug experiences with a lower risk of false negative results. In an abuse potential study, a negative result with a non-drug-using population can be considered inconclusive, since these subjects often do not like the effects of drugs that are readily abused by substance users.

In addition to the requirement that subjects be “history qualified” (ie, have a history of recreational opioid use), this study uses a pharmacologic qualification to ensure that subjects who meet the drug use history criteria can also distinguish and like the subjective effects of the positive control drugs. In previous qualifications performed at the investigational site, approximately 40% to 60% of history-qualified subjects could not adequately distinguish or report positive drug effects of the test drug. Therefore, the pharmacologic qualification procedure provides more objective confirmation of drug use history and ensures that subjects can respond appropriately in a research clinic setting.

Randomization will be used to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

A placebo control is used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active treatment as well as to minimize subject and investigator bias. Blinded treatment, including the use of double-blind and double-dummy procedures, will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

Assessing abuse potential requires a relative comparison to an active drug with known abuse potential and one that does not (placebo). The positive control should have measurable abuse potential previously established through experimental studies and epidemiological data, and should be a drug of abuse in the same pharmacological class as the test drug.

3.2.1 Selection of Hydromorphone Positive Control

Hydromorphone is a C-II scheduled opioid with known abuse potential[10] following both oral and IV administration and was selected as the active control for this study.

The abuse potential of hydromorphone has been demonstrated through experimental studies and epidemiological data, and is a drug of abuse in the same pharmacological class as the test drug, nalbuphine. From an abuse potential perspective, opioids (eg, hydromorphone, hydrocodone, oxycodone, and morphine) are expected to produce significant effects in recreational drug users and hydromorphone is a potent opioid that is expected produce significant effects when appropriate doses are selected for the recreational, non-dependent population.[10,11,12] Therefore the type of opioid may be less relevant as an active control as compared to the selection of appropriate doses.

In this study, hydromorphone is included in the drug discrimination test in the Qualification Phase and in the Treatment Phase. Justification of the hydromorphone doses is provided in Section 5.4, Selection of Doses. In the Qualification Phase, subjects will be qualified on 12 mg hydromorphone HCl solution, to ensure that subjects can both tolerate and are able to differentiate the pharmacological effects of hydromorphone relative to placebo during the Main Study (Part B). For hydromorphone (12 mg dose), a minimum 15-point difference (minimum score $\geq$ 65) will be required on the measure of Drug Liking in the Qualification Phase, in accordance with the FDA guidance.[13] In the Treatment Phase, 2 doses (8 mg and 16 mg) of hydromorphone will be administered to qualified subjects. A minimum 11-point difference will be required on the measure of Drug Liking between hydromorphone and placebo (including E_{max} to validate the study) because a 15-point difference may not be detected at the lower 8 mg dose of hydromorphone but would still be clinically important. An 11-point difference will also be used for the analysis of Drug Liking between nalbuphine and placebo. Of note, a 10-point difference on a VAS scale has been previously cited as being clinically relevant as a suitable threshold in terms of abuse potential.[14] The requirements for drug discrimination are outlined in Section 4.5. Since hydromorphone is the primary control for this study and has high abuse potential, study validity will be confirmed for hydromorphone.

The doses of hydromorphone HCl in this study, ranging from 8 mg to 16 mg can be safely administered to screen non-dependent, recreational opioid users and are expected to produce significant effects on PD measures related to abuse potential. The most frequently observed adverse effects associated with hydromorphone are similar to those of other opioids and include constipation, lightheadedness, dizziness, sedation, nausea, vomiting, and sweating.[15]

Except for the significantly faster oral elimination half-life (2.6 hours), compared to nalbuphine, hydromorphone has comparable bioavailability (~20% versus 16% for nalbuphine) with a marked first-pass hepatic and no pharmacologically active metabolites. T_{max} following oral administration of an oral solution is 0.7 hours for hydromorphone compared to 0.5 hours for nalbuphine solution.

3.2.2 Nalbuphine Treatment

It is recommended that human abuse potential studies examine several doses of an investigational drug, ranging from minimally effective to supratherapeutic, provided that the

safety is known and precautions are taken to address safety concerns.[8] The safety and tolerability of nalbuphine ER tablets at single doses greater than 162 mg or daily doses greater than 162 mg BID has not been established in a healthy population.[1] Notable adverse effects such as vomiting and nausea are observed when doses of nalbuphine are escalated up to 162 mg in healthy volunteers. Therefore, the Dose Selection Phase in Part A of this study is designed to evaluate escalating doses of nalbuphine using a solution formulation, with the intent to identify a low, intermediate, and high (eg, supratherapeutic) doses that are considered safe to administer in Part B. Nalbuphine will be administered orally as a solution in order to maximize peak concentrations (C_{max}), without the confounder of an ER mechanism, and evaluate the abuse potential of nalbuphine at peak exposure levels that are determined to be safe in the recreational opioid user population.

Based on the safety data summarized in Section 5.4, dose selection of nalbuphine HCl in Part A will begin at 81 mg (equivalent to 90 mg of the HCl salt) and range until an MSD is determined. Sequential dosing cohorts of 8 unique non-dependent, recreational opioid users will be randomized so that subjects will receive either a single dose of nalbuphine (n=6) or placebo (n=2) in order to identify an MSD. Safety measures are included in the design to ensure that subjects are adequately monitored during the Dose Selection Phase. This will include the unblinding of the safety data following completion of dosing of each cohort and review by the DRC (see Section 4.9.1 Data Review Committee). Dose escalation for the active arm subjects in the next cohort will only occur if an MSD has not been identified and the previous nalbuphine dose level was deemed safe and well tolerated. In addition, subjects will not be discharged from the CRU until they are no longer impaired by drugs administered during the study, at the discretion of the investigator or designee.

The median T_{max} of nalbuphine is expected to occur between 0.5 and 1.5 hours post-dose after oral administration of nalbuphine solution, while the median T_{max} is expected to occur between 3 and 6 hours post-dose after nalbuphine ER tablets.[1] The PK sampling in the Treatment Phase was developed to capture the expected T_{max} of nalbuphine of both nalbuphine formulations. The mean T_{max} for orally-administered hydromorphone HCl solution is expected to occur at approximately 0.7 hours.[16] In addition, the $t_{1/2}$ of nalbuphine ranges from 6.6-9.6 hours, whereas the $t_{1/2}$ for hydromorphone is approximately 2.3 hours. Based on this, a 24-hour assessment period and 24-hour post-dose discharge for each treatment visit is considered safe for the subjects, and at this time the PD measures are expected to return to approximately baseline. A minimum 4-day washout between each dose in the Treatment Phase is considered acceptable based on the $t_{1/2}$ of the active agents to be used in this study, as it is a duration that is longer that five times the maximum $t_{1/2}$ of the longest acting drug in the study, as recommended in the FDA guidance.[8]

4. STUDY POPULATION

4.1 Number of Subjects

In Part A, approximately 5 cohorts of approximately 8 unique subjects per cohort is planned or until the MSD is identified. Additional cohorts may be added, at the sponsor's and investigator's discretion, if additional data at a dose level are needed or if a dose level, intermediate to those

proposed, needs to be considered for safety or tolerability reasons, or a dose higher than those planned is required to be tested, based on supporting safety data.

In Part B, a sufficient number of subjects will participate in the Qualification Phase in order to randomize an estimated 56 subjects into the Treatment Phase, with the intent to complete approximately 42 subjects. Replacement subjects may be added at the sponsor's and investigator's discretion to ensure that sufficient data are collected to meet the main study objectives.

4.2 Inclusion Criteria

Subjects will be considered eligible to participate in this study, for either Part A or Part B, if each one of the following inclusion criteria is satisfied at Screening:

1. Healthy male or female subjects 18 to 55 years of age, inclusive.
2. Body mass index (BMI) within the range of 18.0 to 33.0 kg/m^2, inclusive, and a minimum weight of 50.0 kg.
3. Current opioid users who have used opioids for recreational (non-therapeutic) purposes (ie, for psychoactive effects) at least 10 times in the past year and used opioids at least once in the 8 weeks before Screening.
4. Female subjects of childbearing potential with male sexual partners must be using and willing to continue using medically acceptable contraception (as specified in Section 4.6.2) for at least 1 month prior to Screening (at least 3 months for oral and transdermal contraceptives) and for at least 1 month after last study drug administration.

   Female subjects of non-childbearing potential must meet the criteria specified in Section 4.6.2.

   Male subjects with female sexual partners of childbearing potential must be using and willing to continue using medically acceptable contraception (as specified in Section 4.6.2) from Screening and for at least 1 month after the last study drug administration.
5. Must provide written informed consent prior to the initiation of any protocol-specific procedures.

4.3 Exclusion Criteria

Subjects will not be considered eligible to participate in this study, for either Part A or Part B, if any one of the following exclusion criteria is satisfied at Screening:

1. Self-reported substance or alcohol dependence (excluding nicotine and caffeine) within the past 2 years, as defined by the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition – Text Revision (DSM-IV-TR), and/or has ever participated or plans to participate in a substance or alcohol rehabilitation program to treat their substance or alcohol dependence.

2. Heavy smoker (≥ 20 cigarettes per day) and/or who is unable to abstain from smoking for at least 8 hours during the in-clinic periods. Unable to abstain from using other nicotine-containing products (eg, gum, patch, e-cigarettes) during the in-clinic periods.
3. History or presence of clinically significant abnormality as assessed by physical examination, medical history, ECGs, vital signs, or laboratory values, which in the opinion of the investigator would jeopardize the safety of the subject or the validity of the study results.
4. History or presence of any clinically significant illness (eg, cardiovascular, pulmonary, hepatic, renal, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, oncologic, musculoskeletal, psychiatric) or any condition, which, in the opinion of the investigator or designee, would jeopardize the safety of the subject or the validity of the study results.
5. History of major mental illness that in the opinion of the investigator may affect the ability of the subject to participate in the study. Institutionalized subjects will not be eligible for participation.
6. Clinically significant infection/injury/illness within 1 month prior to Screening, as assessed by the investigator or designee.
7. Positive for hepatitis B, hepatitis C, or HIV.
8. Donation or loss of more than 500 mL whole blood within 30 days preceding entry into the Treatment Phase.
9. Difficulty with venous access or unsuitable or unwilling to undergo catheter insertion.
10. Female subjects who are currently pregnant (have a positive pregnancy test) or lactating or who are planning to become pregnant within 30 days of last study drug administration.
11. History of severe allergic reaction (including anaphylaxis) to any substance, or previous status asthmaticus, or food allergies/intolerances/restrictions, or special dietary needs which, in the judgment of the investigator, contraindicates the subject's participation in the study.
12. History of allergy or hypersensitivity to hydromorphone, nalbuphine, or related drugs (eg, other opioids) or naltrexone or related drugs (eg, other antagonists) or to any known excipients (eg, lactose).
13. Subjects with any lifetime history of suicidal ideation or suicidal behavior, as assessed by the C-SSRS (baseline version).
14. Documented history of, or currently active, seizure disorder or history of clinically significant head injury (including surgery) or syncope of unknown origin.
15. Use of a prohibited medication, as specified in Section 4.6.1.
16. Treatment with an investigational drug within 5 times the elimination $t_{1/2}$, if known (eg, a marketed product) or within 30 days (if the elimination $t_{1/2}$ is unknown) prior to first drug administration or is concurrently enrolled in any research, judged not to be scientifically or medically compatible with this study (exclusion is not applicable to subjects who participate in Part B after they have participated and received study drug in Part A of this study).

17. An employee of the sponsor or research site personnel directly affiliated with this study or their immediate family member defined as a spouse, parent, child or sibling, whether biological or legally adopted.
18. A subject who, in the opinion of the investigator or designee, is considered unsuitable or unlikely to comply with the study protocol for any reason.
19. Subject has current pending legal charges or is currently on probation based on self-report at Screening.

4.4 Naloxone Challenge (Part A and Part B)

Eligible subjects who meet Screening criteria will undergo a naloxone challenge test at least 12 hours prior to study drug administration in the Dose Selection Phase in Part A and prior to the first drug administration in the Drug Discrimination Test in Part B. For female subjects, results of the urine pregnancy test will be required prior to the naloxone challenge; results of the serum pregnancy test will not be required prior to the naloxone challenge. For those subjects who successfully complete the naloxone challenge in Part A and elect to participate in Part B, a naloxone re-challenge will only be required if more than 60 days has passed between the first challenge and admission to the Qualification Phase in Part B.

Baseline vital signs and the COWS[17] will be assessed before administration of the first naloxone dose. The naloxone doses selected for the challenge are consistent with doses commonly administered to confirm opioid non-dependence.

The test will be administered as follows:

Step 1: Naloxone 0.2 mg will be given via IV bolus followed by a 2 mL to 3 mL saline flush. The subject will be observed for 1 minute after the bolus administration for signs and symptoms of withdrawal using the COWS.

Step 2: If the subject develops signs or symptoms of withdrawal following the first IV bolus (COWS score ≥5), the second bolus will not be administered and the subject will be medically managed.

If there is no evidence of withdrawal after 1 minute (COWS score <5), a second IV bolus of naloxone 0.6 mg will be given within 5 minutes of the first administration, followed by a 2 mL to 3 mL saline flush. The subject will be observed and an additional COWS assessment will be conducted at 5 minutes after the second naloxone dose. Vital signs will be assessed at 10 minutes (± 5 minutes) and 60 minutes (± 10 minutes) following the second naloxone dose. Additional COWS and/or vital sign assessments may be conducted if medically necessary.

A sample form of the COWS is presented in Appendix 11.3.

Subjects who present with signs or symptoms of withdrawal following administration of the naloxone challenge (ie, COWS score ≥5) will be excluded from the study and will not be eligible to participate in the Drug Discrimination Test. Subjects who develop signs or symptoms of

withdrawal will be medically managed for at least 4 hours and will be discharged at the discretion of the investigator or medically qualified designee.

Refer to Section 6.3.9 for COWS assessments to be performed during the Treatment Phase in Part B.

4.5 Qualification Criteria (Part B)

Subjects must meet the following qualification criteria to be eligible to enter the Treatment Phase:

1. Peak score (E_{max}) of ≥65 on the Drug Liking VAS and greater than that of placebo by at least 15 points in response to 12 mg hydromorphone.
2. Drug Liking VAS scores over time that are consistent with the known pharmacology of 12 mg hydromorphone.
3. Acceptable placebo response on Drug Liking VAS (score between 40 and 60, inclusive).
4. Ability to complete the PD assessments and have acceptable overall responses for placebo and hydromorphone based on all other measures that are consistent with the known pharmacology of the drugs administered, as judged by the investigator or designee.
5. Able to tolerate 12 mg hydromorphone, as judged by the investigator or designee based on available safety and PD data (eg, no episodes of vomiting within the first 4 hours post-dose).
6. General behavior suggests that the subject could successfully complete the study, as judged by the research site staff.

4.6 Study Restrictions

4.6.1 Prohibited Medications

Subjects will be required to avoid using non-prescription medication (except nicotine-containing substances and acetaminophen up to 2000 mg per day) within 7 days prior to first drug administration and throughout the study, unless in the opinion of the medical monitor, in consultation with the investigator or designee, the product will not interfere with the study procedures or data integrity or compromise the safety of the subject.

Subjects will be required to avoid using prescription medications or natural health products (except vitamin or mineral supplements, acceptable forms of birth control, and hormone replacement) within 14 days prior to first drug administration and throughout the study, unless in the opinion of the investigator or designee, the product will not interfere with the study procedures or data integrity or compromise the safety of the subject.

Concomitant medications are prohibited in this study unless prescribed by the investigator to treat clinical events or exempted by the investigator on a case-by-case basis because they would be unlikely to affect the study results or subject safety (eg, topical medications). All medications taken by subjects after Screening until the completion of the Follow-up visit will be documented

as concomitant medications. The reported medications will be reviewed and evaluated by the investigator to determine if they affect a subject's eligibility or continued participation in the study.

4.6.2 Contraceptive Precautions

For women of childbearing potential with male sexual partners, examples of medically acceptable forms of contraception are provided in Table 4. Subjects must agree to use medically acceptable contraception for at least 1 month prior to screening (at least 3 months for oral and transdermal contraceptives) and for at least 1 month after last study drug administration. Women must also abstain from ovum donation from screening and for at least 1 month after last study drug administration.

Women of childbearing potential without male sexual partners must be willing to maintain their sexual status (including abstinence) throughout the study.

Women who are not of childbearing potential must be surgically sterile (hysterectomy and/or bilateral oophorectomy/salpingo-oophorectomy, as determined by subject medical history) or congenitally sterile, or must be post-menopausal. Post-menopausal is defined as being amenorrheic for at least 1 year without another cause and a follicle-stimulating hormone (FSH) level ≥26 IU/L.

Table 4 Medically Acceptable Forms of Contraception and Duration of Use for Females of Childbearing Potential with Male Partners

Medically Acceptable Forms of Contraception	Prior to Screening	During the Study
Combined oral pill Patch Vaginal ring	3 months	Throughout the study. Subjects will be advised to continue using acceptable contraception for at least 1 month after the last study drug administration.
True abstinence Intrauterine device or system Progestin implant or injection Bilateral tubal ligation Double-barrier methods (ie, male condom in addition to a diaphragm, cervical cap, or contraceptive sponge)	1 month	

For male subjects with female sexual partners of childbearing potential, examples of medically acceptable forms of contraception include true abstinence, vasectomy, or male condom for subjects plus an additional method of contraception for their female partners.

4.6.3 Dietary and Other Restrictions

In addition to the inclusion and exclusion criteria listed in Section 4.2 and Section 4.3, the subject must agree to abide by each of the following restrictions for the specified time:

- Subjects will be asked to abstain from alcohol for 24 hours prior to each study visit.
- Subjects will be asked to abstain from recreational drug use throughout the study, from Screening until after the last treatment visit.
- Subjects in both Part A and Part B will be required to abstain from smoking for at least 2 hours prior to dosing and at least 15 minutes before each breath alcohol measurement. Subjects in Part A will also be required to abstain from smoking for at least 6 hours after dosing in the Dose Selection Phase.

  Subjects in Part B will also be required to abstain from smoking for at least 4 hours after dosing in the drug discrimination test and for at least 6 hours after dosing in each Treatment period. Smoking will be permitted at short breaks, at the discretion of the research site staff, at times other than the restricted time intervals described above.
  The use of other nicotine-containing substances (eg, gum, patch, e-cigarettes) is not permitted during inpatient stays at the CRU.
- Subjects in both Part A and Part B will be required to fast (abstain from food) for at least 8 hours prior to dosing and for at least 4 hours post-dosing during the Dose Selection Phase in Part A and during the drug discrimination test and Treatment Phase in Part B. Water will be permitted *ad libitum* except for at least 1 hour prior to dosing and for at least 1 hour post-dosing, with the exception of any liquids administered as part of dosing procedures.
- Subjects will be asked to abstain from the following foods from 1 week prior to the Dose Selection Phase in Part A and Qualification Phase in Part B until after the last treatment visit:
  - grapefruit, pomegranate, pomelo, and star fruit and their juices/products;
  - poppy seeds and Seville oranges and foods containing them (eg, orange marmalade);
  - leafy green portion from vegetables of the mustard green family (eg, kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard greens); however, lettuce and white cabbage are allowed in limited quantities;
  - drinks/foods containing quinine (ie, tonic water).
- Subjects will be asked not to consume more than 450 mg of caffeine per day (eg, approximately 5 cups of tea or 3 cups of regular coffee or 8 cans of cola or 2 energy drinks) from 1 week prior to the Dose Selection Phase in Part A and Qualification Phase in Part B until after the last treatment visit. Subjects will not be permitted to consume caffeine-containing beverages while housed at the research site.
- Subjects will be asked to refrain from driving, operating machinery, or engaging in hazardous activities until they and the investigator are sure the study drug is not impairing their judgment and/or ability to perform skilled tasks. Subjects will be informed that driving under the influence is a criminal offense and that if they are caught driving under the influence, they may be prosecuted to the fullest extent of the law.

- Subjects will be asked to abstain from strenuous physical activity for 48 hours prior to each study visit. Subjects will not be permitted to engage in strenuous exercise during inpatient stays at the research site.
- Subjects will be required to abstain from blood donation during the study and for 30 days after the Follow-up visit.
- Subjects will be required to follow the informed consent form (ICF) and the clinic code of conduct.

4.7 Rescue Medication

Subjects will receive all standard medical treatment, including administration of rescue medication, should subjects experience severe (Grade 3 or higher) AEs. Standard safety medication (eg, IV naloxone, antihistamine [eg, Benadryl®], epinephrine, solumedrol, ranitidine, advanced cardiac life support [ACLS] rescue medication, etc.) will be administered, if required. If a subject requires treatment for nausea and vomiting, antiemetic medications (eg, ondansetron 4 to 8 mg q8h PO and dimenhydrinate 25 to 75 mg q4-6h PO) may be administered, if not medically contraindicated for the subject.

The principal investigator or designee will be on site during all dosing until at least the continuous oxygen monitoring period is complete (at least 6 hours post-dose in Part A, and at least 4 hours post-dose during the drug discrimination test and at least 6 hours post-dose during each Treatment period in Part B). The investigator or designee will be on-call or on-site thereafter. Dedicated ACLS nurses or paramedics will be assigned to the study during drug administration to monitor AEs and perform safety measures (ie, vital signs).

Subjects will be supervised by staff nurses and paramedics for the duration of the study. In case of emergency or SAEs that require emergency care, the study site is equipped with fully-stocked crash carts, oxygen, suction, and defibrillator. If needed, subjects will be transported to the nearest emergency room to receive more intensive or continuing treatment.

4.8 Subject Discontinuation/Stopping Criteria

Any subject who voluntarily withdraws consent or is discontinued (eg, because of an AE) from the study prior to completion will be considered as withdrawn from the study. Subjects may be discontinued from the study under any of the following circumstances:

- Occurrence of intolerable AE, as assessed by the investigator or designee
- Clinically significant abnormality on vital signs, ECG, clinical laboratory, or physical examination assessments, as assessed by the investigator or designee
- Withdrawal of consent
- Lost to follow-up
- Administrative reasons (eg, sponsor decision)
- Major violation of the protocol
- If in the opinion of the qualified investigator, it is in the best interest of the subject

- Pregnancy
- Non-compliance with study requirements and restrictions
- Use of a concomitant medication that, in the opinion of the investigator or designee, could interfere with the study procedures or data integrity or compromise the safety of the subject
- Positive urine drug screen at
    - Admission to the Dose Selection Phase in Part A or Qualification Phase in Part B: If a subject presents with a positive urine drug screen at any visit, the urine drug screen may be repeated and/or the subject may be rescheduled at the discretion of the investigator or designee. If benzodiazepines or THC are positive, inclusion will be at the discretion of the investigator, for example, if drug levels are stable at low concentrations or decreasing due to the long half-lives of parent compounds and/or metabolites. THC levels that have increased from the time of the last visit may be acceptable, at the discretion of the investigator or designee, provided that there are no visible signs of impairment and/or intoxication due to THC exposure (eg, euphoria, dry mouth, slowed reflexes, excessive drowsiness, increased appetite, red eyes, paranoia, anxiety, hallucinations, tachycardia, emitting odor of marijuana).
    - Admission to any Treatment Period in Part B: Subjects who have a positive urine drug screen and a COWS score < 5 may be rescheduled at the discretion of the investigator or designee. If benzodiazepines or THC are positive, inclusion will be at the discretion of the investigator, for example, if drug levels are stable at low concentrations or decreasing due to the long half-lives of parent compounds and/or metabolites. THC levels that have increased from the time of the last visit may be acceptable, at the discretion of the investigator or designee, provided that there are no visible signs of impairment and/or intoxication due to THC exposure (eg, euphoria, dry mouth, slowed reflexes, excessive drowsiness, increased appetite, red eyes, paranoia, anxiety, hallucinations, tachycardia, emitting odor of marijuana).
- COWS score ≥ 5. Subjects will be medically managed for at least 4 hours or longer until the investigator determines that the subject can be safety discharged from the CRU.
- Positive breath alcohol test at admission to the Dose Selection Phase in Part A or Qualification Phase or any Treatment Period in Part B. Subjects with a positive result at Screening or admission to any visit may be rescheduled at the discretion of the investigator or designee.
- Termination of the study
- Subject did not meet the qualification criteria outlined in Section 4.5.
- Dose escalation (Part A) has been stopped according to the criteria outlined in Section 4.9.

When an event such as a family emergency, a transient intercurrent illness (such as a cold) unrelated to study drug, or a remediable act of non-compliance prevents a subject from participating in a scheduled visit, but the subject wishes to continue in the study, with the

permission of the sponsor/medical monitor and in consultation with the investigator the research site staff may attempt to reschedule the visit and retain the subject in the study.

If a subject is prematurely discontinued from participation in the study for any reason after study drug administration, the investigator or designee must make every effort to perform the assessments scheduled for the Follow-up visit. The reason for withdrawal will be recorded in the case report form (CRF) and the subject's source medical record.

Replacement subjects may be added at the sponsor's discretion, in agreement with the principal investigator. Each replacement subject will be assigned to the same treatment sequence as the subject who is replaced.

4.9 Dose Escalation Procedures and Stopping Criteria (Part A)

4.9.1 Data Review Committee

During the Dose Selection Phase in Part A, the safety data and, if available, PK data will be unblinded after completion of each dose cohort and reviewed by the DRC. The DRC will comprise, at a minimum, the sponsor representative, medical monitor (drug safety representative), and the investigator (or designee). Other representatives may be involved in data review and dose selection, as appropriate.

Dose escalation for the next cohort will proceed if the dose administered in the previous cohort was deemed to be safe and well tolerated by the DRC. The PK data will be unblinded and evaluated if available in a timely manner, but will not be required for dose escalation decisions. In addition, the results from the Dose Selection Phase will be reviewed and considered by the DRC for dose selection in the Treatment Phase in Part B.

4.9.2 Dose Escalation and Stopping Rules

Dose escalation may proceed when the DRC have reviewed the available safety data for a cohort (and all preceding cohorts, as applicable) and agree that the safety profile supports proceeding with the evaluation of the next higher dose level. Escalation to the next dose level will continue until the MSD is identified (doses of nalbuphine solution will not exceed 486 mg, which corresponds to 3-fold the therapeutic dose) and only if it is supported by the safety data review by the DRC.

Dose escalation will be stopped if the following is observed in 3 or more subjects who received nalbuphine solution in a cohort experience the following AEs within 4 hours of dosing:

- Grade 3 or higher nausea or,
- Any episode of vomiting or,
- Grade 3 or higher somnolence

Furthermore, dose escalation will be stopped if any of the following is observed in at least 1 subject in a cohort who received nalbuphine solution:

- Sustained (~30 seconds) respiratory depression that results in SpO_2 reduction below 92% that requires significant intervention (eg, naloxone administration).
- QTc prolongation (>500 ms or >60 ms above the baseline).
- Any Grade 3 or higher AE or an SAE that is considered by the investigator to be related to nalbuphine and clinically significant, or, any AE deemed by the investigator to be dose-limiting.

If the DRC observe a plateau in the incidence and severity of AEs, which do not meet the stopping criteria described above, then the PK data may be reviewed to determine if there is a plateau in the exposure of nalbuphine despite dose escalation. If a plateau is observed in the PK data, the MSD will be identified based on the available safety and PK exposure data.

5. STUDY DRUG INFORMATION

5.1 Study Drug Administration

Nalbuphine solution and ER tablets are manufactured using nalbuphine HCl salt. The dose strength of the ER tablet refers to the content of the free base active moiety rather than the nalbuphine salt. For the nalbuphine HCl ER tablet, 162 mg is equivalent to 180 mg nalbuphine HCl salt and 1 mL of 10 mg/mL nalbuphine HCl is equivalent to 9 mg nalbuphine free base.

Flavored beverage: The doses of study drug will be administered with a flavored, low caloric, artificially sweetened, non-carbonated beverage (eg, diet cranberry cocktail).

5.1.1 Dose Selection Phase (Part A)

During the Dose Selection Phase, subjects in each cohort will receive a single oral dose of nalbuphine HCl solution or matching placebo in a randomized, double-blind fashion (Table 5) after at least an 8-hour fast. The actual doses administered in each cohort may be adjusted (increased, decreased, or repeated) based on the evaluation of safety data obtained in previous cohorts. Additional cohorts of subjects may be added to those planned in Table 5 until the MSD is identified. Higher doses can be up to 50% greater (but not to exceed 486 mg (3-fold the therapeutic dose) than the dose administered in the previous cohort based on supporting safety data.

The dosing solution (150 mL) will be administered in a dark bottle. After subjects drink the dosing solution, an additional 50 mL of flavored beverage will be added to the dosing container as a rinse and then administered to the subjects. The start of dosing will be considered time zero and subjects will be informed that the duration allocated for dosing will be 5 minutes. All dosing administration procedures will be outlined in the study specific procedures.

All subjects within a cohort will receive the same dose of nalbuphine HCl solution if randomized to the active drug. Dose escalation procedures are described in Section 4.9.

Table 5 Planned Oral Doses of Nalbuphine Hydrochloride Solution in the Dose Selection Phase

Cohort (n=8)	Nalbuphine Free Base Dose Level	Nalbuphine HCl Equivalent Dose	Nalbuphine HCl Solution (n=6)	Placebo Solution (n=2)
1	81 mg	90 mg	9 mL × 10 mg/mL + 141 mL flavored beverage	150 mL flavored beverage
2	108 mg	120 mg	12 mL × 10 mg/mL + 138 mL flavored beverage	150 mL flavored beverage
3	135 mg	150 mg	15 mL × 10 mg/mL + 135 mL flavored beverage	150 mL flavored beverage
4	162 mg	180 mg	18 mL × 10 mg/mL + 132 mL flavored beverage	150 mL flavored beverage
5	243 mg	270 mg	27 mL × 10 mg/mL + 123 mL flavored beverage	150 mL flavored beverage
6[a]	up to 365 mg	up to 405 mg	up to 40.5 mL × 10 mg/mL + 109.5 mL or required volume of flavored beverage for a total volume of 150 mL solution	150 mL flavored beverage
7[a]	up to 486 mg	up to 540 mg	up to 54 mL × 10 mg/mL + 96 mL or required volume of flavored beverage for a total volume of 150 mL solution	150 mL flavored beverage

HCl=hydrochloride.

[a] The dose of nalbuphine free base in Cohorts 6 and 7 may increase up to a 50% increase from the preceding dose but not to exceed 486 mg (3-fold the therapeutic dose) based on the evaluation of safety data in the previous cohorts.

For the nalbuphine solution, the dose will be added to a flavored beverage to prepare a dosing solution of 150 mL.

For both nalbuphine and placebo treatments, after subjects drink the 150 mL dosing solution, an additional 50 mL of flavored beverage will be added to the dosing container as a rinse and then administered to the subjects. Dosing procedures will be specified in study specific procedures.

Actual doses may be adjusted according to the evaluation of safety data from Part A. Dose reductions, intermediate doses, or higher doses up to 50% greater than the dose administered in the previous cohort may be considered based on the safety results obtained in previous cohorts. Additional cohorts of subjects may be added until the MSD is identified or until lack of linearity is observed in the nalbuphine plasma PK profile (see Section 4.9 for details).

5.1.2 Qualification Phase (Part B)

During the Qualification Phase, hydromorphone HCl and placebo solution (Table 6) will be administered orally in a randomized, double-blind fashion after at least an 8-hour fast. Each treatment will be separated by a washout of approximately 24 hours.

The dosing solution (150 mL) will be administered in a dark bottle. After subjects drink the dosing solution, an additional 50 mL of flavored beverage will be added to the dosing container as a rinse and then administered to the subjects. The start of dosing will be considered time zero and subjects will be informed that the duration allocated for dosing will be 5 minutes. All dosing administration procedures will be outlined in the study specific procedures.

Table 6 Double-blind Treatments Administered in the Drug Discrimination Test

Treatment	Hydromorphone HCl Solution	Placebo Solution
Treatment X: Placebo Solution	—	150 mL flavored beverage
Treatment Y: Hydromorphone HCl 12 mg Solution	6 mL × 2 mg/mL + 144 mL flavored beverage	—

HCl=hydrochloride

For the hydromorphone solution, the dose will be added to a flavored beverage to prepare a dosing volume of 150 mL. For both hydromorphone and placebo treatments, after subjects drink the 150 mL dosing solution, an additional 50 mL of flavored beverage will be added to the dosing container as a rinse and then administered to the subjects. Dosing procedures will be specified in study specific procedures.

5.1.3 Treatment Phase (Part B)

Treatments A through G are described in Table 7. During the Treatment Phase, subjects will receive single oral doses of each treatment in a randomized, double-blind, double-dummy fashion after at least an 8-hour fast. Each treatment administered in the Treatment Phase will consist of 150 mL oral dosing solution (containing nalbuphine, hydromorphone or placebo [flavored beverage]) and 1 tablet (containing nalbuphine or placebo).

For the nalbuphine solution, the low, intermediate, and high doses will be determined by the DRC based on the results obtained from the Dose Selection Phase in Part A, as described in Section 4.9. However, the total volume of solution to be administered in each treatment period will be identical (ie, 150 mL solution comprised of an appropriate amount of active drug and/or flavored beverage) in order to maintain the blind.

Table 7 Double-Blind Administration of Doses During the Treatment Phase

Tx	Placebo Solution	Hydromorphone HCl Solution	Nalbuphine HCl Solution *Low Dose*	Nalbuphine HCl Solution *Intermediate Dose*	Nalbuphine HCl Solution *High Dose*	Nalbuphine ER Intact Tablet	Nalbuphine ER Matching Placebo Tablet
A	150 mL flavored beverage	—	—	—	—	—	1 tablet
B	—	4 mL × 2 mg/mL + 146 mL flavored beverage	—	—	—	—	1 tablet
C	—	8 mL × 2 mg/mL + 142 mL flavored beverage					1 tablet
D	—	—	TBD	—	—	—	1 tablet
E	—	—	—	TBD	—	—	1 tablet
F	—	—	—	—	TBD	—	1 tablet
G	150 mL flavored beverage	—	—	—	—	1 × 162 mg tablet	—

DRC=data review committee; ER=extended release; HCl=hydrochloride; TBD=to be determined; Tx=treatment
Treatment A: Placebo
Treatment B: Hydromorphone HCl 8 mg solution
Treatment C: Hydromorphone HCl 16 mg solution
Treatment D: Nalbuphine HCl low dose solution
Treatment E: Nalbuphine HCl intermediate dose solution
Treatment F: Nalbuphine HCl high dose solution
Treatment G: Nalbuphine ER tablet 162 mg
The selection of the low, intermediate, and high doses of nalbuphine HCl will be determined by the DRC based on the results obtained from the Dose Selection Phase in Part A.
For the nalbuphine and hydromorphone solution, the dose will be added to a flavored beverage to prepare a dosing volume of 150 mL. For all treatments, after subjects drink the 150 mL dosing solution, an additional 50 mL of flavored beverage will be added to the dosing container as a rinse and then administered to the subjects. Dosing procedures will be specified in study specific procedures.

The dosing solution will be administered in a dark bottle. For each treatment, subjects will be instructed to ingest the tablet with the 150 mL of solution. After subjects drink the dosing solution, an additional 50 mL of flavored beverage will be added to the dosing container as a rinse and then administered to the subjects. The start of dosing will be considered time zero and subjects will be informed that the duration allocated for dosing will be 5 minutes. All dosing administration procedures will be outlined in the study specific procedures.

5.2 Study Drug Identification

5.2.1 Nalbuphine

Nalbuphine HCl solution

Each 1 mL contains 10 mg nalbuphine HCl (equivalent to 9 mg of the free base), 2 mg sodium chloride, 9.41 mg sodium citrate dihydrate, 12.62 mg citric acid, and water for injection; pH adjusted with hydrochloric acid. Nalbuphine HCl solution (10 mg/mL) will be provided by the CRU.

Nalbuphine ER Tablets

Nalbuphine ER tablets 162 mg will be provided by the sponsor.

5.2.2 Hydromorphone Hydrochloride

Each 1 mL contains hydromorphone HCl 2 mg, citric acid 2 mg, sodium citrate 2 mg, sodium chloride 7.48 mg, hydrochloric acid and/or sodium hydroxide to adjust pH, and water for injection.[15]

Hydromorphone HCl (2 mg/mL) will be provided by the CRU.

5.2.3 Placebo

Matching nalbuphine placebo tablets will be provided by the sponsor.

Placebo solution will consist of a flavored beverage provided by the CRU.

5.2.4 Naloxone Hydrochloride (Naloxone Challenge Test - Qualification Phase)

Naloxone HCl will be supplied in concentration of 0.4 mg/mL, and 1 mL vials/ampoules (sourced by the clinical site). Each box will be labeled with a label containing information in compliance with regulatory and safety requirements.

Naloxone will be provided by the CRU.

5.2.5 Packaging and Labeling

Nalbuphine HCl solution is available in 1 mL ampoules.

Nalbuphine ER tablets and matching placebo will be packaged in HDPE bottles with induction seal child-resistant closures containing 70 tablets each. Tablets should be stored at 20°C-25°C (68°F-77°F) with excursions permitted between 15°C and 30°C (between 59°F and 86°F).

Each container of study drug will be clearly labeled with study-specific information meeting all the applicable regulatory requirements.

Clinical trial drug supply labels will bear the following information:

a) a statement indicating that the drug is an investigational drug to be used only by a qualified investigator;
b) the name, number, or identifying mark of the drug and quantity of drug in each unit;
c) the expiration date of the drug;
d) the recommended storage conditions of the drug;
e) the lot number of the drug;
f) the name and address of the sponsor;
g) the protocol code or study identification; and
h) the quantity of drug per package.

Clinical study drug supplies will be labeled in both French and English.

5.2.6 Handling, Storage, and Accountability

All study drugs will be transported, received, stored, and handled strictly in accordance with the container or product label. The investigator will ensure that the study drug is stored and dispensed in accordance with ICH QE6(R1) (Guideline for Good Clinical Practice), the instructions supplied to the research site and its designated pharmacy, and the *Guidelines for Temperature Control of Drug Products during Storage and Transportation, (GUIDE-0069*). Appropriate storage temperature and transportation conditions will be maintained for the study drug from the point of manufacture up to delivery of the study drug.

Upon receipt by the study site, the research pharmacy staff will examine the shipment and temperature monitoring devices (if applicable) to verify the study drugs were received in acceptable condition. Once inspected, the study drugs will be promptly transferred to the appropriate environmentally-controlled storage area. Study drugs will be stored in a restricted access, secured area, with access limited to authorized research site staff, under physical conditions consistent with investigational product's specific requirements.

The research site's pharmacist or delegate is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The investigator is ultimately responsible for ensuring that the site and/or Pharmacy maintain accurate records of the receipt of all study drug shipped to the site including, but not limited to: the date received, lot number, expiration date, quantity received, and the disposition of all investigational product(s).

Current dispensing records will be maintained for each subject, including but not limited to, the date and quantity of drug dispensed.

All original containers, whether empty or containing study drug will be returned to the pharmacy. Returned study drugs will be neither dispensed again (even to the same subject) nor relabeled or reassigned for use by other subjects. Study drugs returned by study subjects will be stored and disposed of according to the sponsor's instructions. Contents of the study drug containers will not be combined. Unused study drugs and study drugs returned by the subjects will be available for verification by the sponsor's site monitor.

5.2.7 Dispensing

The study drug will be dispensed or administered according to applicable regulations and protocol instructions. Details regarding the preparation and administration of the study drugs will be outlined in study-specific procedures. Only eligible subjects participating in the study will receive the study drug. Only authorized research site staff may supply or administer the study drugs.

During the Dose Selection Phase in Part A and Qualification Phase in Part B, the solution will be swallowed by the subjects under the supervision of study personnel.

During the Treatment Phase, subjects will ingest the solution and tablet under the supervision of study personnel.

5.3 Method of Assigning Subjects to Treatment Groups

Randomization will be used to avoid bias in the assignment of subjects to treatment sequences, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

Each potential subject will be assigned a unique number (Subject Number) in the screening process. This number will be used to identify the subject throughout the study. Subjects who enter the Treatment Phase will be assigned a unique Randomization Number to identify their sequence of study treatments. Once any subject number is assigned, it cannot be reassigned to any other subject.

All randomization codes will be generated by the sponsor/designated unblinded statistician(s) at INC Research before the start of the study. Sealed code break envelopes will be provided before the start of the study.

5.3.1 Qualification Phase Treatment Sequences (Part B)

Subjects who enter the Qualification Phase will be assigned, in ascending order, a qualification randomization number to identify the sequence of their treatments (Table 8).

Table 8 Treatment Sequences in the Qualification Phase

Treatment Sequence	Day 1	Day 2
XY	X	Y
YX	Y	X

HCl=hydrochloride
Treatment X: Placebo
Treatment Y: Hydromorphone HCl 12 mg solution

5.3.2 Treatment Phase Treatment Sequences (Part B)

For the treatment phase, qualified subjects will be randomized to 1 of 14 treatment sequences based on a computer-generated randomization schedule. The study drug will be prepared for each subject based on their randomization code. Subjects will receive all 7 treatments in the order specified by the treatment sequence according to a two 7×7 Williams square design (Table 9).

Table 9 Treatment Sequences in the Treatment Phase

Treatment Sequence	Period 1	Period 2	Period 3	Period 4	Period 5	Period 6	Period 7
ABGCFDE	A	B	G	C	F	D	E
BCADGEF	B	C	A	D	G	E	F
CDBEAFG	C	D	B	E	A	F	G
DECFBGA	D	E	C	F	B	G	A
EFDGCAB	E	F	D	G	C	A	B
FGEADBC	F	G	E	A	D	B	C
GAFBECD	G	A	F	B	E	C	D
EDFCGBA	E	D	F	C	G	B	A
FEGDACB	F	E	G	D	A	C	B
GFAEBDC	G	F	A	E	B	D	C
AGBFCED	A	G	B	F	C	E	D
BACGDFE	B	A	C	G	D	F	E
CBDAEGF	C	B	D	A	E	G	F
DCEBFAG	D	C	E	B	F	A	G

ER=extended release; HCl=hydrochloride
Treatment A: Placebo
Treatment B: Hydromorphone HCl 8 mg solution
Treatment C: Hydromorphone HCl 16 mg solution
Treatment D: Nalbuphine HCl low dose solution
Treatment E: Nalbuphine HCl intermediate dose solution
Treatment F: Nalbuphine HCl high dose solution
Treatment G: Nalbuphine 162 mg ER intact tablet

5.4 Selection of Doses

5.4.1 Nalbuphine Dose Selection

The Dose Selection Phase (Part A) is designed to evaluate escalating doses of nalbuphine solution, with the intent to identify an MSD and, in accordance with regulatory recommendations, select low, intermediate, and high doses for administration in Part B.[8] The proposed starting dose is 81 mg nalbuphine solution (equivalent to 90 mg of the HCl salt). While doses up to 162 mg have been previously studied in healthy subjects as a solid dosage form, adverse effects following escalating nalbuphine single doses administered as an oral solution has not been investigated beyond the 54 mg dose level.

The solution formulation was selected for administration of nalbuphine as it provides flexibility in dose strength selection. Furthermore, the solution will maximize C_{max}, while maintaining the same AUC exposure as following an nalbuphine ER tablet. Food effect on exposure is also relatively lower compared with the ER tablet (Section 1.2).

The incidence of nausea and vomiting was observed, respectively, in single doses of 54 mg solution (5.9% nausea/5.9% vomiting) and 108 mg intact tablets (30% nausea/25% vomiting). All AEs were mild and both doses were well tolerated. None of the subjects administered the 54 mg dose of nalbuphine (equivalent to 60 mg of the HCl salt) as a solution reported somnolence. Therefore, considering that this dose was well tolerated in healthy subjects, and that the opioid-experienced population tend to be more tolerant of opioid-related AEs, the starting dose of 81 mg (equivalent to 90 mg of the HCl salt) was selected in Part A. Sequential dosing of cohorts of non-dependent, recreational opioid users will be administered a single dose of nalbuphine solution ranging from 81 mg (equivalent to 90 mg of the HCl salt) up to an MSD (if the dose levels are determined to be safe by the DRC) or placebo in order to identify an MSD (Section 4.9). The proposed doses may be reduced or escalated by 27 mg increments (equivalent to 30 mg increments of the HCl salt) or up to 50% greater than the dose administered in the previous cohort as described in Section 5.1.1.

To support the objectives of the main study and given that nausea and vomiting may limit the signals of abuse potential (eg, drug liking), a dose range (low dose, intermediate dose, and high dose) of nalbuphine solution will be selected based on the safety results obtained in Part A. Dose selection in Part A is designed to adequately evaluate doses that can be well tolerated and are expected to minimize the influence of negative drug effects on subjective scales.

A dose of 162 mg nalbuphine ER administered orally as an intact tablet will be included in the Treatment Phase (Part B) to evaluate the PD effects of nalbuphine under conditions of intended drug product administration. Nalbuphine ER 162 mg tablet is the highest to be marketed tablet strength.

5.4.2 Hydromorphone Dose Selection

Hydromorphone doses of 8 mg and 16 mg are expected to produce significant effects on Drug Liking and other measures related to abuse potential, while not being at a level where tolerability may become a limitation. Doses of hydromorphone immediate-release formulations between 8 mg and 25 mg have been shown to produce sufficient responses on subjective drug measures,

including Drug Liking.[11,14] Based on experience at the CRU and data in the literature,[18] doses of hydromorphone less than 8 mg (ie, 4 mg and 6 mg) did not differentiate sufficiently from placebo on subjective PD measures. In addition, ceiling effects have been observed for the objective measure pupillometry at the 17.5 mg dose. [14] Hence, the doses of 8 mg and 16 mg hydromorphone selected in this study are within the range expected to produce significant drug effects and minimize negative effects that could potentially decrease subjective scores. Opioids such as hydromorphone are characterized by a dose-response profile that results in greater subjective effects (eg, drug liking) with greater doses, until they are no longer tolerated due to dose-related increases in adverse effects.

For the Qualification Phase, the dose of hydromorphone (ie, 12 mg) will be an intermediate dose of those used in the main study (ie, 8 mg and 16 mg), to ensure both appropriate responses compared with placebo and tolerability of the higher dose. This will ensure that subjects can tolerate doses and have an increased likelihood to have appropriate PD responses to the doses selected for analysis.

5.5 Blinding and Unblinding Procedures

5.5.1 Dose Selection Phase (Part A)

For each dosing cohort, an unblinded statistician from INC Research, not otherwise involved in the study, will prepare a list of subject randomization numbers. These randomization numbers will be used to prepare individual subject doses. Sealed qualification code break envelopes will be available for each subject in case of emergency.

Upon completion of each cohort of subjects, the randomization codes for the completed subjects will be unblinded by the CRU pharmacy. After unblinding, the safety data will be reviewed to determine if dosing can proceed for the next planned dosing cohort, as described in Section 4.9.

5.5.2 Qualification Phase (Part B)

For each qualification group, an unblinded statistician from INC Research, not otherwise involved in the study, will prepare a list of subject randomization numbers. These randomization numbers will be used to prepare individual subject doses. Sealed qualification code break envelopes will be available for each subject in case of emergency.

Upon completion of each group of subjects, the randomization codes for the completed subjects will be unblinded by the CRU pharmacy, and the eligibility of subjects to participate in the Treatment Phase will be assessed as described in Section 4.5.

5.5.3 Treatment Phase (Part B)

The only persons with access to the blinding schema during the Treatment Phase will be the designated pharmacy personnel who are responsible for the dispensing of study drug, the compliance auditor(s) who verify conformity to study procedures, and the unblinded statisticians who generate the code. Under normal circumstances, the blind will not be broken until all subjects have completed all treatments. During the Treatment Phase, blinded dosing information

will be broken only in an emergency where knowledge of dosing information could impact further treatment decisions or aid in the emergency treatment of a subject. Individual blinded dosing information can be broken by opening a subject's sealed code break envelope, thereby, not compromising the blind for the remaining subjects. Individual code breaks by the investigator or designee will result in the withdrawal of the subject from the study. The date, time, and reason for the unblinding will be documented in the appropriate section of the CRF and in the source documents.

5.6 Treatment Compliance

Study drugs will be administered under the supervision of study personnel and treatment compliance will be verified according to protocol requirements.

6. STUDY PROCEDURES AND ASSESSMENTS

All study assessments will be performed at the visits and time points outlined in the Time and Events Schedule (Section 3.1.7). Study drug administration will be considered as time zero. Other logistical considerations (eg, sequence of events, assessment windows) will be outlined in study-specific procedures.

6.1 Pharmacodynamic Assessments

All subjects will undergo a training and practice regimen prior to completion of the computerized subjective measures. Subjects will also receive PD refresher sessions prior to dosing in the Treatment Phase. Measures will be administered and data will be captured electronically using proprietary computerized software (PsychometRx®; INC Research Toronto, Inc.).

Testing conditions for PD assessments should remain as consistent as possible for each treatment period. Subjects will be monitored carefully to ensure that they are completing the assessments appropriately. See Section 9.4 for details regarding the anonymity of subject information.

6.1.1 Visual Analog Scale

Table 10 shows the VAS items administered in this study. Each VAS is scored as an integer from 0 to 100. The use of a unipolar or bipolar scale is determined by the nature of the subjective effect being measured. Unipolar VASs (eg, High, Good Drug Effects, Bad Drug Effects, Any Drug Effects, and Hallucinations) are presented with anchors such as "Not at all" (score = 0) to "Extremely" (score = 100), where the neutral point equals 0. Note that scales that refer specifically to drug (eg, Good Drug Effects, Bad Drug Effects, Any Drug Effects) are not administered pre-dose. When appropriate, VASs will be administered as bipolar measures, meaning that the neutral point equals 50 (eg, Drug Liking, Overall Drug Liking, Take drug Again, and Drowsiness/Alertness VAS). The neutral point will also be labeled with an anchor, such as "neither like nor dislike".

Eligible subjects who appear to have difficulty differentiating between bipolar and unipolar scales (eg, making errors such as selecting 50 as neutral for a unipolar scale) during the

Qualification Phase will undergo additional practice training on the difference between the scale types.

Table 10 Description of Subjective Effects Visual Analog Scales

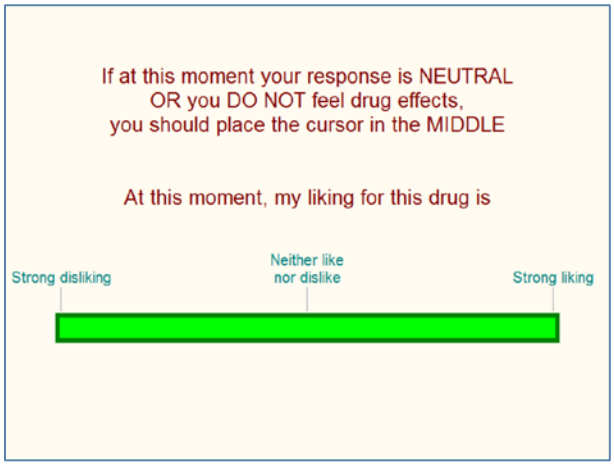
Scale Interpretation	Exclude Pre-dose	Description	Question Text	Response Anchors
Balance	Yes	Drug Liking	At this moment, my liking for this drug is	0: Strong disliking 50: Neither like nor dislike 100: Strong liking
Global	Yes	Overall Drug Liking	Overall, my liking for this drug is	
Global	Yes	Take Drug Again	I would take this drug again	0: Definitely not 50: Neutral 100: Definitely so
Positive	Yes	Good Drug Effects	At this moment, I feel good drug effects	0: Not at all 100: Extremely
Positive	No	High	At this moment, I feel high	
Negative	Yes	Bad Drug Effects	At this moment, I feel bad drug effects	
Other effects	No	Hallucinations	I am experiencing hallucinations	
Other effects	Yes	Any Drug Effects	At this moment, I feel any drug effect	
Other effects	No	Drowsiness/Alertness	At this moment, my mental state is	0: Very drowsy 50: Neither drowsy nor alert 100: Very alert

Scales have 5 possible interpretations: (1) “Positive” subjective effects, (2) “Negative” subjective effects, (3) the “Balance” between positive and negative effects, (4) “Other effects” (ie, pharmacologic effects that indicate an active substance, which may be perceived as either positive or negative depending on the context), and (5) "Global" (ie, end-of-day assessment or next day overall assessment).

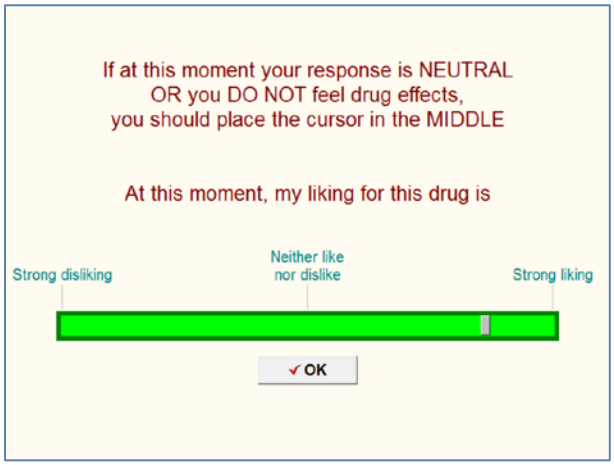
The overall appearance of all VAS items is similar to the screen images below. Figure 3A presents the display for a typical question. Using a mouse, the subject must position the cursor over the small vertical box (a “slider”) and click on it to move it left or right. To register the response, the subject must then press the “OK” button that appears below the horizontal line (Figure 3B). This multi-step procedure was designed to reduce the possibility of either accidental or automatic responding to such scales. The questions and anchors will be modified appropriately to reflect study-specific questions.

Figure 3 Sample Screen Images for Visual Analog Scale Presentation

A.



B.



6.1.1.1 Drug Similarity VAS

The Drug Similarity VASs provide an estimate of the drug class with which drug users identify the test drug. The same VAS procedures used to assess subjective drug responses will be used to assess perceived drug similarity. Subjects will be asked to compare the drug they received to a comparison drug on a scale ranging from "Not at all similar" to "Very similar" (Table 11). Each scale is scored as an integer from 0 to 100, where the position of the subject's response on the scale represents a defined integer. Drugs that a subject has not personally experienced often enough to use as a standard of comparison (based on the screening assessment) will not be included in his or her questionnaire.

Table 11 Description of Drug Similarity Visual Analog Scales

Description	Question Text	Response Anchors
Drug similarity	How similar is the drug you most recently received to ***[drug name]***?	0: Not at all similar 100: Very similar
*where the question will be repeated for each **[drug name]** in the following list:*		
Phencyclidine (PCP) Caffeine Cocaine (including crack) Codeine, morphine, oxycodone, hydrocodone, hydromorphone Ecstasy (MDMA) Heroin	LSD Methadone Nicotine Placebo D-amphetamine ("Speed") or methamphetamine	Pseudoephedrine (Sudafed) Halcion, Xanax, or Valium Ketamine ("Special K") THC (marijuana, cannabis, hash)
At the conclusion of the list of specific drugs, a general question will appear:		
Overall Familiarity	How familiar was the effect of the drug you most recently received?	0: Very unfamiliar 100: Very familiar

6.1.1.2 Bowdle VAS

The Bowdle VAS[19] consists of 13 items for which the subject is asked to rate his or her current feelings. An adapted computerized version of Bowdle VAS will be administered with 11 items examining internal and external perception sub-scales. Each VAS will be scored from 0 to 100, with 0 reflecting "Not at all" and 100 reflecting "Extremely." Lower individual and overall scores indicate fewer psychedelic effects.

The individual items of the questionnaire are listed below:

1. My body or body parts seemed to change their shape or position (BODY)
2. My surroundings seemed to change in size, depth, or shape (SURROUNDINGS)
3. The passing of time was altered (TIME)
4. I had feelings of unreality (REALITY)
5. It was difficult to control my thoughts (THOUGHTS)
6. The intensity of colors changed (COLORS)
7. The intensity of sound changed (SOUND)
8. I heard voices or sounds that were not real (VOICES)
9. I had the idea that events, objects, or other people had particular meaning that was specific for me (MEANING)
10. I had suspicious ideas or the belief that others were against me (SUSPICIOUS)
11. I felt anxious (ANXIOUS)

Items 1, 2, 3, 5, 6, and 7 are combined to assess the derived variable "subjective external perception." Items 4, 8, 9, 10, and 11 are combined to assess the derived variable "subjective internal perception."

If one of the items is missing, the related score will not be calculated.

6.1.2 Divided Attention Test

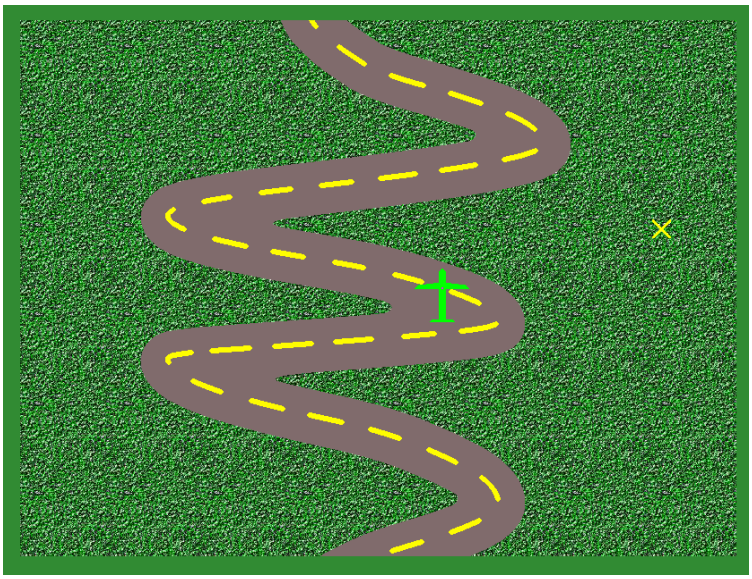
The Divided Attention Test (DAT) is a manual-tracking test with a simultaneous visual target detection component. The subject is provided with a joystick with a trigger to execute this measure. During testing, the subject is presented with the image of an airplane and a randomly curving road (Figure 4). As the road moves down the screen, the subject is to try and position the image of the airplane over the center of the road.[20] At random times during this process, a visual target will briefly present itself at random positions on the screen and immediately disappear. The subject is to respond to the visual target as fast as possible by pressing a button on the joystick. There are 16 targets presented during each trial. Each test consists of three 1-minute trials over different road courses. Performance is measured based on the subject's ability to keep the image of the airplane over the road, and the subject's ability to respond to the visual target.

The following outcome measures will be used to assess performance on this task:

- Root mean square (RMS) distance: the RMS distance from the center of the road (pixels)
- Greatest distance: the maximum distance from the center of the road (pixels)

- Response latency of correct responses (msec)
- Average number of false alarms
- Percentage over road: percentage of time over the road (%)
- Percentage of target hits (%)

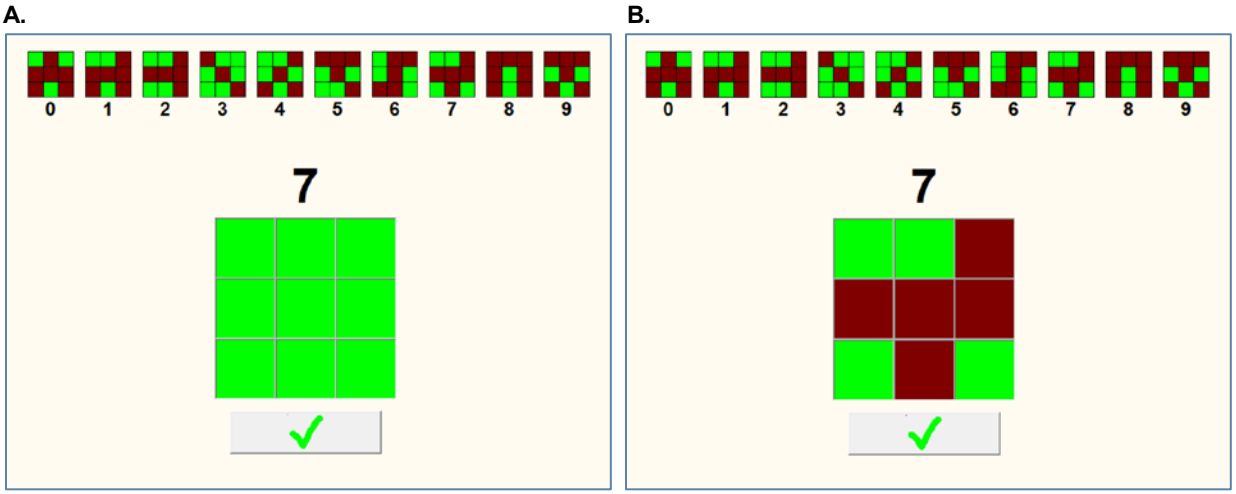
Figure 4 Sample Screen Image for the Divided Attention Test



6.1.3 Digit Symbol Substitution Test

The Digit Symbol Substitution Test (DSST) (modified) is a test of processing speed and visual-motor coordination. Subjects are presented with a legend or key at the top of the screen, which shows 10 digits displayed with 10 different associated symbols (Figure 5A). Just below the center of the screen, a single digit appears with a 3 × 3 grid of 9 squares presented below. Inside the grid, subjects must draw the symbol associated with the digit displayed on the screen (Figure 5B). When they have drawn the appropriate symbol, a new single digit and workspace appear. The goal is for the subject to complete as many symbols correctly as they can in the amount of time determined in the measure configuration (typically 90 seconds). Each time subjects perform this task, the same 10 symbols will be used, but the order of the symbols across the top of the screen and the corresponding digit will change. The task is scored for the number of symbols completed and the number of errors (symbols completed incorrectly).

Figure 5 Sample Screen Image for the Digit Symbol Substitution Test



6.1.4 Sternberg Short-Term Memory

The Sternberg Short-Term Memory (SSTM) task[21] is a measure of immediate memory in which subjects are asked to remember a series of digits that are rapidly presented on a computer screen.

The SSTM task involves rapid presentation of target lists of 2, 4, and 6 stimulus digits (1.2 seconds/digit). Two seconds after presentation of each list of digits, a series of 24 probe digits is presented. The subject is to identify as quickly as possible whether or not each probe appeared in the target list by pressing buttons on a response box meaning “YES” or “NO.” Probes that appeared on the target list are called “positive”, while probes that did not appear on the target list are called “negative.”

The test consists of 3 trials with digit sequence size lengths of 2, 4, and 6. Performance is assessed by measures of response latency and accuracy.

6.1.5 Pupillometry

Pupillometry will be used as an objective physiological PD measure as it is a sensitive measure of central opioid/stimulant action and appears to be resistant to tolerance development with repeated administration. An electronic pupillometer (NeuroOptics) will be used to measure pupil diameter. Data from a series of frames will be used in the calculation, and the final display will show the weighted average and standard deviation (SD) of the pupil size. Measurements will be collected under mesopic lighting conditions. For each subject, every effort will be made to use the same eye for all assessments throughout the study.

6.2 Pharmacokinetic Assessments

In Part A and Part B, venous blood samples (2 mL) will be collected to determine the plasma concentrations of nalbuphine following oral administration of nalbuphine solution and nalbuphine ER tablet. Samples will be collected, processed, and shipped according to the

instructions provided in the laboratory manual and instructions from the sponsor or bioanalytical laboratory.

The PK sample collection timepoints are included in Table 1 for Part A and Table 3 for Part B. Blood volumes required for PK sampling are available in Appendix 11.1 (Part A) and in Appendix 11.2 (Part B).

The plasma samples will be analyzed for nalbuphine and metabolites by Covance using validated methods.

Plasma samples will be shipped frozen on dry ice from the research site to Covance at the address provided in the laboratory manual. Samples will not be shipped without prior arrangement with the bioanalytical laboratory and notification to the sponsor.

Drug concentration information that may unblind the study will not be reported to the study site or blinded personnel until the study has been unblinded.

6.3 Safety Assessments

Safety will be determined by an ongoing evaluation of the following:

- AEs
- Vital sign measurements
- ECGs
- Clinical laboratory tests
- Physical Examination
- COWS

6.3.1 Medical History

Medical histories will be obtained during screening (Part A and Part B) and will include demographic data (date of birth, sex, race, and ethnicity); histories of acute, chronic, and infectious disease; contraception use, surgical and oncologic histories; and any reported conditions affecting major body systems. All findings on medical history will be evaluated by the investigator for clinical significance.

The DSM-IV-TR modules will be used to screen for alcohol and substance dependence.

6.3.2 Medication History and Recreational Drug and Alcohol Use

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

A history of all drugs used for recreational/non-medicinal purposes (ie, psychoactive effects) and alcohol use will also be collected during the screening visit(s).

6.3.3 Physical Examination

A complete physical examination, assessing the subject's overall health and physical condition, will be performed at the Screening visit including height, weight, and BMI. Subsequent physical examinations will be performed per the Schedule of Events and may be performed by physicians or mid-level providers, such as advanced practice nurses and physician assistants, if they are appropriately licensed and credentialed to perform these examinations in accordance with local requirements and/or regulations.

Any clinically significant worsening after the start of study drug will be reported as an AE. Clinically significant findings observed prior to start of Study Drug treatment will be recorded as part of the medical history.

6.3.4 Electrocardiograms

12-Lead ECGs will be performed by the site and interpreted by the investigator or other appropriately credentialed designee. The ECGs will be performed with the electrodes positioned on the torso after the subject has been resting in a supine or semi-supine position for at least 3 minutes. The ECG will electronically measure and calculate ventricular heart rate and the PR, QRS, QT, QTcB, and QTcF intervals. The QTcF will be used for clinical evaluations.

6.3.5 Vital Signs

Vital signs will be measured after subjects have been at rest for approximately 3 minutes at the time points specified in the Schedule of Events. Vital signs will consist of systolic and diastolic blood pressure (mmHg), heart rate (bpm), and respiratory rate (breaths/min). Oral temperature (°C) will also be taken at some time points. In addition, pulse oximetry measurements will be taken with the vital signs monitoring system (eg, Dinamap) at designated time points and recorded after the continuous monitoring period (Section 6.3.6).

6.3.6 Continuous Pulse Oximetry

Continuous pulse oximetry will be performed by telemetry from pre-dose until at least 4 hours post-dose during the Qualification Phase in Part B and at least 6 hours post-dose during the Dose Selection Phase in Part A and the Treatment Phase in Part B, or longer, based on the discretion of the investigator or designee.

Continuous monitoring will include real-time measurements of SpO_2. Oxygen saturation readings will be recorded at designated time points. After the continuous monitoring period, pulse oximetry measurements will be taken with the vital signs monitoring system (eg, Dinamap) at designated time points and recorded.

6.3.7 Columbia-Suicide Severity Rating Scale

The C-SSRS is a unique, simple, and short method of assessing both behavior and ideation that tracks all suicidal events, and provides a summary of suicidal ideation and behavior. It assesses the lethality of attempts and other features of ideation (frequency, duration, controllability, reasons for ideation, and deterrents), all of which are significantly predictive of completed suicide.

Two versions of the C-SSRS will be used in this study: the Baseline version assesses lifetime suicidal ideation and behavior, and the Since Last Visit version assesses suicidal thoughts or behaviors the subject may have had since the last time the C-SSRS was administered.

Occurrence of *suicidal ideation* after baseline is defined as having answered "yes" to at least 1 of the 5 suicidal ideation subcategories (ie, wish to be dead; non-specific active suicidal thoughts; active suicidal ideation with any methods [no plan] without intent to act; active suicidal ideation with some intent to act [without specific plan]; and active suicidal ideation with specific plan and intent) at any post-baseline evaluation. Occurrence of *suicidal behavior* after baseline is defined as having answered "yes" to at least 1 of the 4 suicidal behavior subcategories (ie, actual attempt, interrupted attempt, aborted attempt, and preparatory acts or behavior) at any post-baseline evaluation.

A trained rater will record the clinical observations on the scale, which will be used as the source document.

6.3.8 Clinical Laboratory Assessments

Blood and urine samples will be collected, processed, and shipped according to the instructions provided in the laboratory manual. All laboratory safety data will be reviewed by the investigator or designee for clinical significance. See Section 9.4 for details regarding the anonymity of subject information.

Blood volumes required per laboratory test and study period/phase are provided in Appendix 11.1 (Part A) and in Appendix 11.2 (Part B).

Clinical Chemistry: Quantitative analysis will be performed for the following analytes: alkaline phosphatase, calcium, chloride, creatinine, random glucose, potassium, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase, sodium, total bilirubin, and urea.

Hematology: A peripheral blood smear will be performed to assess blood cell morphology. Quantitative analysis will be performed for at least the following analytes: hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count, WBC differential (absolute counts), and numerical platelet count.

Urinalysis: Qualitative or quantitative analysis will be performed for the following analytes, as appropriate: specific gravity, pH, ketones, random glucose, nitrite, blood, leukocyte esterase, protein, urobilinogen, and bilirubin. If nitrite, blood, or protein tests are positive, a microscopic examination will be performed.

Pregnancy: Pregnancy tests for female subjects will test for the presence of β-Human Chorionic Gonadotropin (HCG) in blood serum or urine. Results of blood serum and urine pregnancy tests will be reported and determined to be negative prior to study continuation and/or dosing.

FSH: Post-menopausal status for female subjects, as applicable, will be confirmed by FSH testing at Screening.

Viral Screen: Serology will screen for hepatitis B, hepatitis C, and HIV. Only subjects with negative viral serology tests will be eligible for the study. Positive results will be managed according to local regulatory requirements.

Breath Alcohol: Breath alcohol testing will be performed. If there is any doubt or concern regarding alcohol use, research site staff may request a breath alcohol test at any time during the study.

Drugs of Abuse Screen: The urine drug screen will test for the following drugs of abuse: THC, oxycodone, other opiates (ie, the opiate panel will test for the presence of codeine, hydrocodone, hydromorphone, morphine, and oxymorphone), amphetamines (ie, amphetamine and methamphetamine), cocaine, and benzodiazepines. Refer to Section 4.8 for subject discontinuation rules in the event of a positive urine drug screen.

6.3.9 Clinical Opioid Withdrawal Scale

A sample form of the COWS is presented in Appendix 11.3.

6.3.9.1 Treatment Phase Admission

At each admission to a Treatment period (Periods 1 through 7), subjects will undergo an assessment for signs or symptoms of withdrawal based on the COWS:

- Subjects with a COWS score < 5 will be allowed to continue participating in the study period.
- Subjects with a COWS score ≥ 5) will be discontinued from the study and medically managed for at least 4 hours or longer until the investigator determines that the subject can be safely discharged from the CRU.

6.3.9.2 Adhoc Assessments

The COWS may be administered adhoc during the Treatment Phase, at the investigator's discretion, based on any observed or reported AEs that may indicate signs or symptoms of withdrawal.

Subjects with an adhoc COWS score < 5 will be allowed to continue participating in the study.

Subjects with an adhoc COWS score ≥ 5 will be discontinued from the study and medically managed for at least 4 hours or longer until the investigator determines that the subject can be safely discharged from the CRU.

6.3.10 Screening Assessments for Subjects who Participate in both Part A and Part B

Eligible subjects who participate in Part A may also participate in Part B (after informed consent to participate in Part B is obtained) and will only require re-screening (ie, completion of all screening assessments) if a duration of 60 days or greater has passed between the screening visit in Part A and the first visit (admission to the Qualification Phase) in Part B.

If a duration of at least 4 days but less than 60 days has passed from the screening visit in Part A and the first visit (admission to the Qualification Phase) in Part B, the following assessments will be performed for the subject:

- Blood samples will be collected for evaluation of hemoglobin, hematocrit, and liver enzymes (ie, ALT and AST) levels.
- Blood samples will be collected for HIV, hepatitis B and hepatitis C tests.
- Serum pregnancy test (females only).

6.4 Appropriateness of Measures

The selected PD measures will assess positive and negative subjective drug effects associated with the abuse potential of a drug, as well as objective measures evaluating the cognitive and opiate effects. A number of concurrent measures will be used in this study to assess the abuse potential of nalbuphine relative to hydromorphone and placebo. These measures are grouped as follows:

- Measures of balance of effects (eg, rating of "at the moment" drug liking)
- Measures of global effects (eg, willingness to take the drug again)
- Measures of positive effects (eg, good effects, high)
- Measures of negative effects (eg, bad effects)
- Measures of stimulant and sedative effects (eg, drowsiness/alertness)
- Measures of perceptual disturbances (eg, hallucinations, Bowdle VAS)
- Measures of cognitive effects (eg, DAT, DSST, SSTM)
- Measure of opiate effect (eg, pupil size)

The selection of subjective abuse potential measures in this study, including the use of a bipolar Drug Liking VAS as the primary endpoint, is consistent with regulatory and literature guidelines.[8,22,23] The assessment of drug liking has been chosen as the primary measure in the current study because the degree of subject liking is considered one of the most sensitive indices of abuse liability.[12] The Drug Liking VAS and the Overall Drug Liking VAS assess slightly different aspects of drug liking. Drug Liking VAS assesses the subject's liking of the drug at the moment the question is asked, may be less subject to recall bias, and is useful for understanding the time-course of the effects. The Overall Drug Liking VAS is thought to assess 'global' drug effects (ie, subjective effects over the whole course of the experience including any carry-over effects), and has the additional advantage that the subject is generally sober by the time of the assessment (ie, end of day and/or next day). Other VAS items will measure positive, negative, and other subjective effects to assess the pharmacologic response to the study drugs. The Take Drug Again VAS will provide a global measure of drug effects and indicate the subject's willingness to take the drug again.

Pupillometry will be used as an objective physiological PD measure as it is a sensitive measure of central opioid action and appears to be resistant to tolerance development with repeated administration. Impairing effects will be evaluated on various measures of cognition evaluating divided attention, visual spatial processing speed, and short-term memory.

PK samples will be evaluated for plasma concentrations of nalbuphine. Standard safety assessments, such as AE reporting, vital signs (including oxygen saturation monitoring), physical examination, and ECGs will be included in this study.

7. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The investigator or designee and research site staff are responsible for the detection, documentation, classification, reporting, and follow-up of events meeting the definition of an AE or SAE.

Spontaneously reported or observed AEs will be recorded throughout the study, beginning at the time the subject gives informed consent. Subjects will be monitored throughout confinement for AEs and AEs may be elicited using a non-leading question at the discretion of the clinical staff. Regardless of seriousness, intensity, or presumed relationship to study drug, all AEs will be recorded in the source documentation from the time of first contact with the subject (eg, Screening) until the end of the Follow-up period of the study. AEs that occur after screening and prior to administration of the first dose of study drug will be recorded in the source documentation as baseline signs and symptoms. All measures required for management of AEs will be recorded in the source documentation.

7.1 Definitions

7.1.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and may not necessarily have a causal relationship with the administered treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant laboratory abnormality, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. During the study, an AE can also occur outside the time that the investigational product(s) was given (eg, during a washout period).

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE. Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures are not AEs.

Pre-existing conditions, diseases, or disorders are not considered AEs unless there is a change in intensity, frequency, or quality.

7.1.2 Serious Adverse Events and Serious Unexpected Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening (at the time of the event),

- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

A serious and unexpected AE is an SAE that is not identified in nature, intensity, or frequency in the risk information set out in the IB or on the label of the drug.

7.1.3 Clinical Laboratory Abnormalities and Other Abnormal Assessments

Abnormal laboratory findings (eg, from clinical chemistry, hematology, or urinalysis) and other abnormal assessments (eg, from vital signs or ECGs) judged as clinically significant by the investigator or designee will be recorded as AEs or SAEs if they meet the definitions provided in Section 7.1.1 and Section 7.1.2. Furthermore, abnormal laboratory findings and other abnormal assessments present at baseline that significantly worsen following the start of the study (ie, become clinically significant) will be reported as AEs or SAEs. However, abnormal laboratory findings present at the start of the study that do not worsen will not be reported as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

7.2 Evaluation of Adverse Events and Serious Adverse Events

The investigator or designee is responsible for making an assessment as to the seriousness, intensity, causality, and outcome of an AE.

7.2.1 Classification of Adverse Event Intensity

For each recorded AE or SAE, the investigator or designee must make an assessment of intensity based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (Table 12). If there is insufficient information to determine intensity, the AE must still be reported.

Table 12 Classification of Adverse Event Intensity

Classification	Definition
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death.

Source: National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03) available for download at: https://evs.nci.nih.gov/ftp1/CTCAE/About.html.

7.2.2 Classification of Adverse Event Causality

For each recorded AE or SAE, the investigator or designee must make an assessment of causality based on the criteria in Table 13 to determine the relationship between the AE and the study drug.

Table 13 Classification of Adverse Event Causality

Classification	Definition
Unrelated	The AE or SAE is judged to be *clearly and incontrovertibly due only to extraneous causes* (eg, disease, environment) and does not meet the criteria for study drug relationship listed under probable, possible, or unlikely.
Unlikely	The AE or SAE is *unlikely* related to the study drug, when the AE or SAE ▪ does not follow a reasonable temporal sequence from administration of the study drug ▪ may readily have been produced by the subject's clinical state, environmental, or toxic factors, or other modes of therapy administered to the subject ▪ does not follow a known pattern of response to the study drug ▪ does not reappear or worsen when the study drug is re-administered
Possible	The AE or SAE is *possibly related* to the study drug, when the connection to the study drug appears unlikely but cannot be ruled out with certainty. This causal relationship is assigned when the AE or SAE ▪ follows a reasonable temporal sequence from administration of the study drug ▪ may have been produced by the subject's clinical state, environmental, or toxic factors, or other modes of therapy administered to the subject ▪ follows a pattern of response to the suspected study drug
Probable	The AE or SAE is *probably related* to the study drug, when the connection to study drug can be made with a high degree of certainty. This causal relationship is assigned when the AE or SAE ▪ follows a reasonable temporal sequence from administration of the study drug ▪ cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental, or toxic factors, or other modes of therapy administered to the subject ▪ disappears or decreases upon cessation or reduction in dose (note that there are important exceptions when an AE or SAE does not disappear upon discontinuation of the study drug, yet drug relatedness clearly exists, eg, bone marrow depression or tardive dyskinesias) ▪ follows a known pattern of response to the suspected study drug ▪ reappears upon re-challenge

7.2.3 Classification of Adverse Event Outcome

For each recorded AE or SAE, the investigator or designee must make an assessment of outcome at the time of last observation. The outcome of AEs or SAEs will be documented as outlined in Table 14.

Table 14 Classifications for Adverse Event Outcomes

Classification	Definition
Fatal	The subject died.
Resolved	The AE or SAE has ended.
Resolved with Sequelae	The AE or SAE has ended but changes are noted from baseline.
Unresolved	The AE has not ended. An AE outcome can only be categorized as unresolved, if the AE is ▪ *ongoing* at the end of the reporting period (ie, 14 days after the final Follow-up visit) and the investigator deems that further follow-up is not medically required ▪ *lost to follow-up* after repeated unsuccessful attempts to contact the subject ▪ *ongoing and referred* to the subject's physician or a specialist

7.3 Reporting Procedures

7.3.1 Serious Adverse Events and Serious Unexpected Adverse Events

Any SAE—expected or unexpected, irrespective of relationship to study treatments, including death due to any cause—experienced by a study subject will be reported to INC Research Safety and Pharmacovigilance by the investigator or designee within 24 hours of learning of the event.

The contact information for the INC Research Safety and Pharmacovigilance is as follows:

Name	INC Research Safety and Pharmacovigilance
Email	INCDrugSafety@incresearch.com
Fax	1-877-464-7787

Any SAEs occurring during the trial will be reported in an expedited manner to the regulatory authorities. INC Research assumes responsibility for appropriate reporting of SAEs to the regulatory authorities (eg, Health Canada). Information regarding the SAE, and all follow-up evaluations, will be transmitted to Trevi Therapeutics, Inc. by email (hard copy of documents to be scanned and attached to the email).

Contact information for the Medical Monitor in this study is as follows:

Name	Thomas Sciascia, M.D.
Telephone	203-903-9894
Fax	203-562-0266
Email	Thomas.Sciascia@trevitherapeutics.com

INC Research assumes responsibility for appropriate reporting of AEs to the regulatory authorities (eg, Health Canada).

Trevi Therapeutics, Inc. will report to the investigator all SAEs that are unlisted and associated with the use of the study drug. The investigator must report these events to the appropriate Institutional Review Board (IRB) that approved the protocol (unless otherwise required and documented by the IRB).

All additional follow-up evaluations for SAEs will be reported to Trevi Therapeutics, Inc.

7.3.2 Any Adverse Event

Regardless of seriousness, intensity, or presumed relationship to study drug, all AEs will be recorded in the source documentation. Whenever possible, diagnoses will be recorded, when signs and symptoms are due to a common etiology. In addition, the investigator must record his or her opinion as to the intensity of the AE and whether the AE is related to study drug. All measures required for management of the AE will be recorded in the source documentation.

7.3.3 Pregnancy

In the event of a subject pregnancy, research site staff will report the pregnancy to INC Research Safety and Pharmacovigilance within **24 hours** of learning of the event. Any subject who becomes pregnant during the study will be immediately withdrawn.

Follow-up information regarding the course and outcome of the pregnancy, including any post-natal sequelae in the infant, will be obtained where possible (ie, with the consent of the subject or subject's partner).

7.4 Follow-up of Adverse Events and Serious Adverse Events

All unresolved AEs, that were reported by the investigator to have a "probable" causal relationship to study drug, will be followed for a minimum of *14 days* after the subject's final study visit, the events are resolved, the patient is lost to follow-up, or the AE has stabilized, unless the investigator's judgment dictates otherwise, the event has resolved or stabilized before the 14-day period, or the subject is lost to follow-up.

All AEs and SAEs that result in discontinuation will be followed until one of the following occurs:

- The event resolves

- The event stabilizes
- The event returns to a baseline value, if a baseline value is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct

When it becomes unlikely that any additional information can be obtained (eg, subject or health care practitioner fails to provide additional information, the subject is lost to follow-up), the investigator or designee will ensure that the follow-up includes any pertinent supplemental investigations (eg, laboratory tests or investigations, histopathological examinations or consultation with other health care professionals) to elucidate the nature and/or causality of the AE or SAE.

Investigators are not obligated to actively seek AEs or SAEs in former study subjects that occur following the follow-up period.

8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

8.1 Statistical and Analytical Plans

8.1.1 Analysis Populations

8.1.1.1 Dose Selection Phase (Part A)

The following analysis populations will be used for Part A:

- *Dose Selection Randomized Population*: All subjects who are assigned a randomization number in the Dose Selection Phase.
- *Dose Selection Safety Population*: All subjects in the Dose Selection Randomized Population who receive any Dose Selection treatment. These subjects will be included in the safety analysis for this phase.
- *Dose Selection PK Population*: All subjects in the Dose Selection Randomized population who received a dose of nalbuphine and have evaluable PK data. These subjects will be used in the PK analysis for this phase.

8.1.1.2 Qualification and Treatment Phase (Part B)

- *Qualification Safety Population*: All subjects who receive at least one dose of study medication during the Qualification Phase.
- *Randomized Population*: All subjects who are assigned a randomization number in the Treatment Phase.
- *Safety Population*: All randomized subjects who receive any study treatment in the Treatment Phase.

- *Completers Population*: All subjects in the Safety population who receive all study treatments and complete all treatment periods in the Treatment Phase regardless whether they have protocol deviations. Subjects must have at least one response on Drug Liking VAS within 2 hours of T_{max} for each treatment in the study.
- *PK Population*: All subjects in the Randomized population who receive at least 1 dose of nalbuphine from whom at least 1 PK sample is obtained after dosing, and who have no protocol deviations or other circumstances that would exclude the subjects from analysis.

Details of subject evaluability criteria will be determined prior to study unblinding.

8.1.2 General Statistical Considerations

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

The PK analyses will be performed by INC Research using Phoenix WinNonlin (release 6.4 or higher) and other statistical analyses will be performed using SAS® (release 9.3 or higher).

8.1.3 Planned Analyses of Primary and Secondary Pharmacodynamic Assessments (Part B)

PD data will be analyzed for the Completers population. The primary endpoint is Drug Liking VAS E_{max}, and the key secondary endpoints are Overall Drug Liking VAS E_{max}, and Take Drug Again VAS E_{max}.

For the Qualification Phase, Drug Liking VAS E_{max} will be summarized by treatment and paired difference for the Completers population using descriptive statistics.

For the Treatment Phase, PD data at each time point will be summarized by descriptive statistics including mean, standard error (SE), minimum, first quartile (Q1), median, third quartile (Q3) and maximum. PD data will be presented graphically (where appropriate) for the Completers population. Derived endpoints will be summarized by treatment and paired difference using descriptive statistics. PD endpoints will be provided in both tables and figures (as applicable). Outliers will be listed by measure and parameter.

PD endpoints for the Treatment Phase (E_{max}, E_{min}, and TA_AUE, as appropriate) will be analyzed using a mixed-effect model if the distribution of the residuals is normally distributed. The model will include treatment, period, sequence and first-order carryover effect (where applicable) as fixed effects, baseline (pre-dose) measurement as a covariate (where applicable), and subject nested within treatment sequence as random effect. First, the residuals from each mixed-effect model, excluding carryover effects, will be investigated for normality using the Shapiro-Wilk W-test. Parameters will be analyzed under the assumption of a normal distribution if the *P* value of the test is ≥ 0.01. [24] The null and alternative hypotheses for this analysis are shown below:

H_0: The distribution of residuals is normal versus H_a: The distribution of residuals is not normal

If the normality assumption of a model is satisfied, it will be determined if carryover effects should be included. When conducting drug abuse potential studies, Chen and Tsong (2007)[25] have recommended the inclusion of first-order carryover as a fixed effect in the mixed-effects model. The adoption of this conservative approach would address possible effects associated with the subjective nature of these studies. Carryover effects are defined as the treatment administered in the previous treatment period; for Treatment Period 1, placebo (Treatment A) will be used. If the carryover effect is found to be non-significant at alpha=0.25, then the term will be dropped from the analysis model.

If the normality assumption of the model is satisfied, least square means, SE, and 95% confidence intervals (CIs) for treatments and treatment differences will be derived from the mixed-effects model. *P* values will be provided for the effects and the contrasts. CIs and *P* values will be one-sided for the primary endpoint and key secondary endpoints. CIs and *P* values will be two-sided for all other secondary PD parameters.

If the normality assumption of the model is not satisfied, the distribution of the paired difference for each contrast will be examined. Each paired difference will be investigated for normality using the Shapiro-Wilk W-test. If the *P* value for the distribution of the paired difference is ≥ 0.01 or the distribution is quite symmetric (skewness = −1 to 1), a paired t-test will be used. Means, SE, and 95% CIs for paired treatment differences will be presented. Otherwise, the sign test will be used. The median, first quantile and third quantile, 95% CI and *P* value for the paired difference will be presented.

The primary objective of a human abuse potential (HAP) study is to provide information on the relative abuse potential of a test drug in humans. The statistical analysis of a HAP study should address the following questions:

1. Does the known drug of abuse (positive control) produce reliable abuse-related responses compared to placebo (study validity)?
2. Does the test drug produce abuse-related responses that are smaller than those of the positive control?
3. Does the test drug produce abuse-related responses that are similar to placebo?

To address these issues, the following hypotheses must be tested:

1. Validation test of the sensitivity and integrity of the study: Does the positive control (C) produce mean responses that show greater abuse potential compared to placebo (P)? This question may be expressed using the following hypothesis:

$$H_0: \mu_C - \mu_P \leq \delta_1 \text{ versus } H_a: \mu_C - \mu_P > \delta_1 \text{ where } \delta_1 > 0$$

2. Does the test drug (T) produce mean responses that show less abuse potential compared to positive control (C)?

$$H_0: \mu_C - \mu_T \leq \delta_2 \text{ versus } H_a: \mu_C - \mu_T > \delta_2 \text{ where } \delta_2 \geq 0$$

3. Does the test drug (T) produce mean responses that show similar abuse potential compared to placebo (P)?

$$H_0: \mu_T - \mu_P \geq \delta_3 \text{ versus } H_a: \mu_T - \mu_P < \delta_3 \text{ where } \delta_3 > 0$$

These hypotheses will be applied to the primary and key secondary endpoints. A 10-point difference was reported to be clinically meaningful for Drug Liking[26] and High VAS,[27] however these differences have not been validated.[27] Nalbuphine has not been previously evaluated in HAP studies, and therefore, its effect size on the primary measure of Drug Liking and other study measures is unknown. Appropriate and clinically significant margins for nalbuphine have not been previously defined. The evaluation of nalbuphine in this study is exploratory and considered a safety study. Nalbuphine is a new chemical entity (NCE); the statistical methods proposed herein are novel based on the newly issued guidance[8], and clinically meaningful point differences have not be established for the other VAS scales being measured. A minimum 15-point difference between hydromorphone 12 mg and placebo is required in the Qualification Phase. However, hydromorphone 8 mg will be administered in the Treatment Phase. As a 15-point difference may not be detected in the lower dose of hydromorphone, δ_1, will be set to 11. Due to the exploratory nature of this study, δ_2 will be set to 0 for comparisons of nalbuphine with hydromorphone; δ_3 will be set to 11.[28]

For study validity purposes, the primary endpoint, E_{max} for Drug Liking VAS, will be compared for the positive controls, hydromorphone 8 and 16 mg, and placebo. The comparison will assess the null hypothesis that the mean difference in Drug Liking E_{max} between hydromorphone and placebo is less than or equal to 11 against the alternative hypothesis that the mean difference in Drug Liking E_{max} between hydromorphone and placebo is greater than 11. If statistically significant, it will confirm the sensitivity of the study and allow for the comparison of the other pairwise comparisons shown below. The hypotheses can be expressed as follows:

$$H_0: \mu_C - \mu_P \leq 11 \text{ versus } H_a: \mu_C - \mu_P > 11$$

where μ_C is the mean for the positive controls, hydromorphone 8 and 16 mg, and μ_P is the mean for placebo and will be applied to the following contrasts:

- Treatment B: Hydromorphone 8 mg versus Treatment A: Placebo
- Treatment C: Hydromorphone 16 mg versus Treatment A: Placebo

The primary hypothesis for the comparison will assess the null hypothesis that the mean difference in Drug Liking E_{max} between hydromorphone and nalbuphine is less than or equal to 0 against the alternative hypothesis that the mean difference in Drug Liking E_{max} between hydromorphone and nalbuphine is greater than 0.

Comparison between the test drug, nalbuphine, and the positive control, hydromorphone 8 and 16 mg, will be:

$$H_0: \mu_C - \mu_T \leq 0 \text{ versus } H_a: \mu_C - \mu_T > 0$$

where μ_C is the mean for the positive control, hydromorphone, and μ_T is the mean for nalbuphine and will be applied to the following contrasts:

- Treatment B: Hydromorphone 8 mg versus Treatment D: Nalbuphine *low dose*
- Treatment B: Hydromorphone 8 mg versus Treatment E: Nalbuphine *intermediate dose*
- Treatment B: Hydromorphone 8 mg versus Treatment F: Nalbuphine *high dose*

- Treatment B: Hydromorphone 8 mg versus Treatment G: Nalbuphine 162 mg ER intact
- Treatment C: Hydromorphone 16 mg versus Treatment D: Nalbuphine *low dose*
- Treatment C: Hydromorphone 16 mg versus Treatment E: Nalbuphine *intermediate dose*
- Treatment C: Hydromorphone 16 mg versus Treatment F: Nalbuphine *high dose*
- Treatment C: Hydromorphone 16 mg versus Treatment G: Nalbuphine 162 mg ER intact

For VAS scales, the hypothesis for the comparison between nalbuphine and placebo will be:

$$H_o: \mu_T - \mu_P \geq 11 \text{ versus } H_a: \mu_T - \mu_P < 11$$

where, μ_T is the mean for nalbuphine and μ_P is the mean for placebo and will be applied to the following contrasts:

- Treatment D: Nalbuphine *low dose* versus Treatment A: Placebo
- Treatment E: Nalbuphine *intermediate dose* versus Treatment A: Placebo
- Treatment F: Nalbuphine *high dose* versus Treatment A: Placebo
- Treatment G: Nalbuphine 162 mg ER intact versus Treatment A: Placebo

No clinically meaningful differences have been defined for any of the other PD measures and thus, assigning a δ margin is not applicable. Furthermore, changes observed on measures of cognition or performance do not inherently imply that the drug has abuse potential, but rather provide important information related to the drug's CNS pharmacology.[8] For PD endpoints that have not been defined as primary or key secondary, the following 3 hypotheses will be used to provide information on the relative abuse potential of the test drug in humans:

1. $H_0: \mu_C - \mu_P = 0$ versus $H_a: \mu_C - \mu_P \neq 0$
2. $H_0: \mu_C - \mu_T = 0$ versus $H_a: \mu_C - \mu_T \neq 0$
3. $H_0: \mu_T - \mu_P = 0$ versus $H_a: \mu_T - \mu_P \neq 0$

A significance level of 0.05 will be used for all individual one-sided and two-sided hypothesis tests. Multiple comparison adjustments will not be made.

The abuse potential of nalbuphine will be assessed through evaluation and integrative interpretation of the pattern of results across the various types of measures: measures of positive response (ie, measures most predictive of the drug's abuse potential and reinforcing properties), measures of negative response (ie, measures that potentially mitigate against abuse potential), measures of stimulant effects, measures of other effects and measures of cognitive and psychomotor effects. The treatment comparisons will support evaluation of the importance of the steepness of the dose-response curves and the similarity of responses to nalbuphine, as compared to the responses to hydromorphone and placebo.

Sensitivity Analysis

Inclusion criteria for Part B of the Qualification Phase include having a peak score (E_{max}) on the Drug Liking VAS greater than that of placebo by at least 15 points in response to 12 mg hydromorphone. In order to assess the robustness of this 15-point difference, a sensitivity

analysis will be conducted in the Treatment Phase to assess the null hypothesis that the mean difference in Drug Liking VAS E_{max} between the positive controls, hydromorphone 8 and 16 mg, and placebo is less than or equal to 15 against the alternative hypothesis that the mean difference in Drug Liking VAS E_{max} between hydromorphone and placebo is greater than 15. The hypothesis can be expressed as:

$$H_0: \mu_c - \mu_P \leq 15 \text{ versus } H_a: \mu_c - \mu_P > 15$$

8.1.4 Analysis of Pharmacokinetics

Pharmacokinetic analyses will be performed using the Dose Selection PK population in Part A and the PK population in Part B.

The PK parameters for plasma nalbuphine and (Part A only) its metabolites will be calculated using non-compartmental analysis and will be summarized by dose level in Part A and by treatment in Part B. Graphs of the concentration (original and log transformed) versus time will be generated. Descriptive statistics, including n, mean, SD, coefficient of variation (CV), minimum, median, and maximum will be calculated by dose level (Part A) and treatment (Part B) and time point for each study drug. Concentrations below the limit of quantification (BLQ) will be set to zero for the generation of summary statistics for concentrations and the generation of mean concentration-time plots.

For the calculation of the PK parameters, concentration-time data will be treated as follows: BLQ concentrations before the first quantifiable concentration will be set to zero; BLQ concentrations after the first quantifiable concentration will be treated as missing; and pre-dose sampling times relative to dosing will be set to zero. Descriptive statistics, including n, mean, SD, geometric mean, geometric CV, minimum, median, and maximum, will be calculated by dose level and treatment group for all PK parameters except T_{max} , $t_{½}$, and kel. Time to maximum observed plasma concentration data will be summarized with minimum, median, maximum, Q1 and Q3. The $t_{½}$ and kel data will be summarized with n, mean, SD, CV, minimum, median, and maximum.

PK profiles will be analyzed for all subjects, even if some PK sampling time points are missed. The PK parameters will be subject to quality control criteria. If quality control criteria are met, the PK parameters will be used in analyses and models. Quality control criteria for PK will be sufficient to eliminate unreliable data. Details will be provided in the SAP.

The PK parameters summary will be presented separately for a subset (if applicable) of subjects who do not vomit within 12 hours of dosing in Part A and Part B of the study.

8.1.5 Analysis of Safety Assessments

For Part A, the analysis of safety assessments will be performed using the Dose Selection Safety population. For Part B, the analysis of safety assessments will be performed using the Safety population.

Assessment of safety will be based on the incidence of AEs, AEs resulting in discontinuation, and SAEs by treatment. AE summaries will be provided showing the number and percentage of subjects who experienced at least one AE. AEs will also be tabulated by maximum severity and

by maximum relationship to study drug. These summaries will be presented by body system and preferred term (Medical Dictionary for Regulatory Activities [MedDRA] 20.0 or higher). SAEs and AEs resulting in discontinuation will be summarized separately. Adverse event data from the Qualification Phase will be listed by subject for the Randomized population but not summarized further.

Clinical laboratory data collected during the Treatment Phase will be summarized by the type of laboratory test and visit. Descriptive statistics (mean, SD, minimum, median and maximum) and the number of subjects with laboratory test results below, within, and above normal ranges will be tabulated by visit. Abnormal findings in laboratory data will be listed.

Treatment Phase vital signs (blood pressure, respiratory rate, heart rate, SpO_2) will be analyzed as minimum, maximum, and final post-dose values, since the analyses of these extremes are more meaningful than analyses of individual time points.

The ECG data (absolute values in heart rate and the PR, QRS, QT, QTcB and QTcF intervals) will be summarized using descriptive statistics for data collected in the Treatment Phase.

Physical examination abnormal results will be listed by subject and visit. Baseline and since last visit C-SSRS results will be listed. No summaries will be provided.

8.1.6 Interim Analyses

No interim analyses are planned for this study; however, based on a review of the results from cohorts in the Dose Selection Phase in Part A, low, intermediate, and high doses of nalbuphine will be selected by the DRC for the Treatment Phase in Part B. Therefore, dose selection decisions and conclusions made by the DRC will be documented and included in the appendix of the CSR.

8.1.7 Missing Data

For PD and PK analyses, missing data for subjects who are administered all scheduled study treatments for all the treatment sessions will be considered as random non-informative missing for analysis purposes. Missing values will be examined on a case-by-case basis. Further details on missing values imputation for descriptive statistics and endpoints derivations will be provided in the SAP.

8.1.8 Demographics and Other Baseline Characteristics

For Part A and Part B, demographics and baseline characteristics (age, sex, race, ethnicity, recreational drug and alcohol use history, body weight, height, and BMI) will be summarized using descriptive statistics (number of subjects, mean, SD, minimum, median and maximum for continuous variables, and the proportion of subjects for categorical variables) for the Randomized population. No formal statistical comparison between the groups will be performed.

Medical history will be listed by subject. Medical history will be coded into the most recent version of MedDRA available (version 20.0 or later).

Prior and concomitant medications will be coded using the most recent version of the World Health Organization drug codes available (WHO Drug). Prior and concomitant medications will be listed by subject. The incidence of concomitant antiemetic medication use in will be tabulated by cohort (ie, dose level) and treatment (active drug or placebo) for Part A and by treatment for Part B.

The number of subjects in each treatment group will be presented, in addition to the number of subjects who complete each visit. The reasons for all post-randomization discontinuations will be tabulated and grouped by treatment and major reason. All deviations related to study inclusion or exclusion criteria, conduct of the trial, subject management, or subject assessment will be described.

8.2 Determination of Sample Size

In Part A, cohorts of 8 subjects in a ratio of 6:2 nalbuphine:placebo will be considered a sufficient sample size for the Dose Selection Phase based on dose escalation paradigms used historically for HAP studies. The proposed single doses of nalbuphine solution for the first cohort will be 81 mg (equivalent to 90 mg of the HCl salt). Dose escalation will only occur for each subsequent cohort if an MSD has not been identified and the previous dose level was deemed to be safe and well tolerated. Escalation to the next dose level will continue until the maximum safe dose is identified or the highest proposed dose level of nalbuphine is achieved. Additional cohorts of 8 subjects may be added if a given dose level will be repeated to provide additional data or if a dose level, intermediate to those proposed, needs to be considered for safety or tolerability reasons.

In Part B, 56 healthy male and female subjects with a history of recreational opioid drug use will be enrolled in the Treatment Phase, with the intent to complete 42 subjects.

The sample size calculation was conducted based on unpublished Drug Liking VAS E_{max} (bipolar scale) data collected at the investigational site, which included hydromorphone 8 mg as the investigational positive control. Based on this data, the mean paired difference between hydromorphone and placebo was 24.6. Within-group SDs were 18.4 for hydromorphone and 18.0 for placebo. As determined by a published algorithm,[29] adjusting for 7 periods and 14 sequences, with a 1-sided significance level of 0.05 and $\delta_1 = 11$, a sample size of 42 subjects will have at least 90% power to detect a difference in Drug Liking VAS E_{max} (bipolar scale). Assuming an approximate 25% dropout rate, 56 subjects (4 subjects per sequence) will be randomized into the Treatment Phase, with the intention to complete approximately 42 subjects (3 subjects per sequence).

9. STUDY ADMINISTRATION

9.1 Study Identification Card

Eligible subjects will be given a study identification card during the Qualification Phase (Part B) that confirms they are participants in a research trial with hydromorphone, nalbuphine solution, and an investigational drug.

Subjects will be provided with immediate medical care contact information that can be used during out-patient days between treatments. The card should contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. Subjects should be instructed to carry the card with them at all times until the end of their participation in the study.

9.2 Data Collection and Electronic Data Capture

The investigator or designee will record all required subject data using the specified data collection method agreed upon by INC Research Toronto, Inc. and Trevi Therapeutics, Inc. (ie, paper source and/or the electronic data capture [EDC] system).

The study site will use a validated EDC system to enter subject data onto electronic case report forms (eCRFs). Data will be collected using the EDC system and entered into a quality controlled clinical database. Prior to the commencement of the study, items to be included in the clinical database will be determined and suitable paper source documents will be created to ensure the appropriate collection of all required data. Clinical staff conducting the study will enter the required data onto source documents and generally different staff (who have been trained to do so) will enter the data from source documents into the clinical database, although there may be some staff overlap. All entries, corrections, and alterations will be made by the investigator or other authorized study personnel, and all data entries will be verified for accuracy and correctness. The EDC system is optimized for manual keying and review (including review by independent monitors) and maintains a full audit trail.

For subjects who do not qualify for the Treatment Phase of the study, demographic data collected during the Screening and Qualification visits will be entered into the clinical database.

Clinical laboratory and/or PK data will be transmitted electronically from external vendors to INC Research Data Management and reconciled against the clinical database. PsychometRx™ data will be captured electronically and imported into the clinical database.

The study file and all source data will be retained at the clinical site until notification is given by the sponsor for destruction.

9.3 Regulatory and Ethical Considerations

9.3.1 Ethical Conduct of the Study

The investigator will conduct the study in accordance with Good Clinical Practice (GCP) and all applicable regulations, including, where applicable, the Declaration of Helsinki. The study will also be carried out in keeping with applicable national and local laws and regulations. This may include an inspection by the sponsor's representatives and/or regulatory authority's representatives at any time.

9.3.2 Regulatory Authority Approval

In accordance with applicable local regulations, the sponsor or designee will obtain approval from the appropriate regulatory agency prior to a site initiating the study in that country or jurisdiction.

9.3.3 Ethics Approval

The investigator will ensure that this protocol is reviewed and approved by the appropriate IRB.

The IRB will also review and approve the site's ICFs (Part A and Part B) and any other written information provided to the subject, including any advertisements used for subject recruitment. Prior to the enrollment of subjects, the investigator or designee will forward copies of the IRB approval and approved study documentation to the sponsor for their records.

If, during the study, it is necessary to amend study documentation (eg, protocol, ICF), the investigator or designee will be responsible for ensuring that the IRB reviews and approves these amended documents. IRB approval of an amended ICF must be obtained before new subjects consent to take part in the study using the amended form. Copies of the IRB approval of the amended study documentation and the approved materials will be forwarded to the sponsor as soon as available.

9.3.4 Subject Informed Consent

The investigator or designee will inform the subject or, where applicable, the subject's legally authorized representative (eg, parent, guardian, next of kin, other individual, other body with appropriate jurisdiction) of all aspects pertaining to the subject's participation in the study.

The process for obtaining subject informed consent will be in accordance with all applicable regulatory requirements. The investigator or designee and the subject or the subject's legally acceptable representative will both sign and date the ICF before the subject can participate in the study. Informed consent will be obtained from each subject before entry into each part of the study (ie, subjects will sign and date an ICF for Part A and an ICF for Part B).

In the ICF for Part B, subjects will be blinded on how they will receive the study drugs (hydromorphone and placebo) in the drug discrimination test. Subjects will not know whether they will be receiving one of these study drugs on 2 occasions or each drug on 1 occasion during the 2-day test period of the Qualification Phase. This will mitigate subject expectations of drug-related effects.

The subject or subject's legally acceptable representative will receive a copy of the consent form(s), and the original form(s) will be retained in the site study records. The subject's decision regarding participation in the study will be entirely voluntary. The investigator or designee will emphasize to the subject or the subject's legally acceptable representative that consent regarding study participation may be withdrawn at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

If the ICF is amended during the study, the investigator will follow all applicable regulatory requirements pertaining to the implementation and use of the amended ICF, including use for previously consented subjects.

9.3.5 Principal Investigator Reporting Requirements

In accordance with applicable local regulatory requirements, the investigator may be obligated to provide periodic safety updates on the conduct of the study at his or her research site and notification of study closure to the IRB. Such periodic safety updates and notifications are the responsibility of the investigator and not of the sponsor. The sponsor will be provided with copies of all notifications sent to the IRB.

9.4 Privacy

9.4.1 Subject Identifiers

To ensure subject anonymity and to limit disclosure, subjects will be assigned a unique subject identifier at their first assessment. This subject identifier will be cross-referenced in the subject's chart. The subject identifier will not contain any potentially identifiable information. A subject identifier log will be maintained, by the investigator, linking each subject's name to the corresponding subject identifier.

9.4.2 Purpose of Collecting Personal Information and Use

The purpose of collecting personal information from subjects (including health and medical information) during this study is for scientific research and/or as supportive evidence for drug-related submissions to regulatory authorities, in compliance with legal or regulatory requirements.

By signing the study protocol, the investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals by Trevi Therapeutics. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement.

9.4.3 Access and Disclosure of Personal Information

The knowledge gained through this study is the property of Trevi Therapeutics, Inc.. The sponsor, representatives and affiliated companies of the sponsor, the IRB, Health Canada, and other regulatory agencies (such as the United States Food and Drug Administration) may inspect subject medical records related to the study to check the validity and accuracy of the data

gathered in this study. Subject names will not be supplied to the Sponsor. Only the subject number and subject initials will be recorded in the CRF (unless not allowed by local regulations), and if the subject name appears on any other document (eg, laboratory report), it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The subject will be told that representatives of the sponsor, IRB/IEC, or regulatory authorities may inspect their medical records to verify the information collected and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

With the agreement of the subject, the investigator may inform the subject's primary care physician about his or her participation in the study and will forward any clinically significant findings from clinical tests such as ECGs and laboratory tests. The primary care physician may contact the investigator for any further information regarding the subject's participation in the study. The subject has the right to request access to and request corrections of his or her medical record.

9.4.4 Release of Subject Information

The results of this study will be reported in such a manner that subjects will not be identifiable in any way. Published reports or presentations will refer to grouped data or coded individual data and not to any identifiable individuals. Study reports sent to the sponsor or drug regulatory agencies (eg, Health Canada) will not include subject names.

9.4.5 Consent for Collection, Access, Use and Disclosure of Subject Information

By signing the ICF, the subject consents to the collection, access, use, and disclosure of his or her information as described in the ICF document. If a subject withdraws consent, some of the subject's information may still be collected, used, and disclosed by those involved in this study per applicable laws.

9.5 Study Monitoring

9.5.1 Study Monitoring by Sponsor and/or Third Party Monitor

The study will be monitored by Trevi Therapeutics or its designee. Monitoring and auditing procedures will be conducted in accordance with applicable regulations, GCP guidelines, the study monitoring plan, and sponsor procedures.

In addition, the investigator will permit inspection of the study files by authorized representatives of Trevi Therapeutics or the regulatory agencies. Domestic and foreign regulatory authorities, the IRB/IEC, and an auditor authorized by the sponsor may request access to all source documents, CRFs, 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. Medical records and other study documents may be copied during audit or inspection provided that patient names are obliterated on the copies to ensure confidentiality.

Throughout the course of the study, the study monitor will make frequent contact with the investigator. This will include telephone calls and on-site visits. The investigator or designee will ensure that the study monitor has access to the on-site study documentation and medical records for the duration of the study.

During the on-site visits, the CRF will be reviewed for completeness and adherence to the protocol. The study monitor will also perform drug accountability checks and perform a review of the regulatory records to ensure completeness of documentation.

Activities to be completed during the monitoring visits include, but are not limited to, the following:

- Check and assess the progress of the study
- Review study data collected
- Conduct source document verification
- Identify any issues and address their resolution

This will be done in order to verify that

- The data are authentic, accurate, and complete;
- The safety and rights of subjects are being protected; and
- The study is conducted in accordance with the currently approved protocol (and any amendments), GCP, and all applicable regulatory requirements.

The investigator agrees to allow the monitor direct access to all relevant documents and to allocate the investigator's time and/or time of research site staff to the monitor to discuss findings and any relevant issues.

In addition to contact during the study, the monitor will also contact the site prior to the start of the study to discuss the protocol and data collection procedures with research site personnel.

At study closure, monitors will also conduct all activities as indicated in Section 9.8, Study and Site Closure.

9.6 Principal Investigator's Data Responsibility

The completed CRFs will be reviewed against source documents by the monitor at each monitoring visit. If any data, signatures, or forms are missing or incorrect, the investigator or designee will be informed and corrections will be made. Case report forms will be collected from the study site at the termination of the study after all monitoring visits and data queries are completed.

9.7 Data Quality Assurance

Actions to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study center; the review of protocol procedures with the investigator and associated study personnel prior to study start; the use of suitable source

documents, as well as periodic site monitoring by the sponsor. Written instructions will be provided for the collection, preparation, and shipment of blood, plasma, and urine samples. The sponsor or designee will review source documents for accuracy and completeness during on-site monitoring visits and after their return to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. The data will be entered into the clinical study database and any queries will be resolved by site staff.

9.8 Study and Site Closure

Upon completion of the study, the following activities, when applicable, will be conducted by the study monitor, in conjunction with the investigator or designee, as appropriate:

- Return of all study data to the sponsor
- Data clarifications or resolutions
- Accounting, reconciliation, and final disposition of used and unused study drugs and emergency code break envelopes
- Review of site study records for completeness
- Return of treatment codes to the sponsor

In addition, the sponsor reserves the right to temporarily suspend or prematurely discontinue this study at any time and for any reason. If such action is taken, the sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. The sponsor will promptly inform any other investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons and will inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator will promptly inform the IRB and provide the study subjects with the reason for the suspension or termination.

If the study is prematurely discontinued, all study data will be returned to the sponsor. In addition, the site will conduct final disposition of all unused study drugs in accordance with the sponsor's procedures for the study.

9.9 Records Retention

Following closure of the study, the investigator will maintain a copy of all site study records in their original format in a safe and secure location in accordance with applicable regulatory requirements (for 25 years in Canada).

Essential documents include:

- Signed informed consent documents for all subjects
- Subject identification code list, screening log (if applicable), and enrollment log
- Record of all communications between the investigator and the IRB
- Copies of CRFs and of documentation of corrections for all subjects
- Investigational product accountability records

- All other source documents (subject medical records, hospital records, laboratory records, etc.)
- All other documents as listed in Section 8 of the ICH E6 Guideline for Good Clinical Practice (Essential Documents for the Conduct of a Clinical Trial)

Normally, these records will be held in the investigator's archives. If the investigator is unable to meet this obligation, he or she will ask the sponsor for permission to make alternative arrangements. Details of these arrangements will be documented.

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11. APPENDICES

11.1 Amount of Blood Drawn per Study Visit: Dose Selection Study (Part A)

	Pharmacokinetic Sampling	Safety			Total
		Clinical Chemistry	Hematology	Serology	
	Blood Volume (mL) [Number of Samples]				
Approximate volume per sample (mL)	*2 mL*	*5 mL*	*4 mL*	*5 mL*	
Screening		5 [1]	4 [1]	5 [1]	14 [3]
Dose Selection Phase					
Males	2 [15]	5 [1]	4 [1]		39 [17]
Females	2 [15]	10 [2]	4 [1]		44 [18]
Total					
Males	**30 [15]**	**10 [2]**	**8 [2]**	**5 [1]**	**53 [20]**
Females	**30 [15]**	**15 [3]**	**8 [2]**	**5 [1]**	**58 [21]**

Blood volumes shown in the table are approximate. Additional blood samples may be taken if needed to follow-up on individual subject safety.

11.2 Amount of Blood Drawn per Study Visit: Main Study (Part B)

	Pharmacokinetic Sampling	Safety			Total
		Clinical Chemistry	Hematology	Serology	
	Blood Volume (mL) [Number of Samples]				
Approximate volume per sample (mL)	*2 mL*	*5 mL*	*4 mL*	*5 mL*	
Screening		5 [1]	4 [1]	5 [1]	14 [3]
Qualification Phase					
Day -1 (Females only)		5 [1]			5 [1]
Treatment Period					
1	2 [16]	5 [1]	4 [1]		41 [18]
2	2 [16]	5 [1]	4 [1]		41 [18]
3	2 [16]	5 [1]	4 [1]		41 [18]
4	2 [16]	5 [1]	4 [1]		41 [18]
5	2 [16]	5 [1]	4 [1]		41 [18]
6	2 [16]	5 [1]	4 [1]		41 [18]
7	2 [16]	5 [1]	4 [1]		41 [18]
Follow-up		5 [1]	4 [1]		9 [2]
Total					
Males	**224 [112]**	**45 [9]**	**36 [9]**	**5 [1]**	**310 [131]**
Females	**224 [112]**	**50 [10]**	**36 [9]**	**5 [1]**	**315 [132]**

Blood volumes are approximate. Additional blood samples may be taken if needed to follow-up on subject safety.

11.3 Clinical Opiate Withdrawal Scale

The COWS will be used to record the signs and symptoms of withdrawal observed in Step 1 and Step 2 of the naloxone challenge test (Section 4.4).

The scores for each item are added to obtain the total score.

Subject Number:		**Date/Time:**
INSTRUCTIONS: For each item, circle the number that best describes the subject's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. Add the numbers for each item to obtain the total score.		
	Signs	**Measures**
1	Resting Pulse Rate: _____ beats/min	*Measured after subject is sitting or lying for 1 minute* **0** pulse rate 80 or below **1** pulse rate 81–100 **2** pulse rate 101–120 **4** pulse rate greater than 120
2	Sweating	*Over past ½ hour not accounted for by room temperature or subject activity* **0** no report of chills or flushing **1** subjective report of chills or flushing **2** flushed or observable moistness on face **3** beads of sweat on brow or face **4** sweat streaming off face
3	Restlessness	*Observation during assessment* **0** able to sit still **1** reports difficulty sitting still, but is able to do so **3** frequent shifting or extraneous movements of legs/arms **5** unable to sit still for more than a few seconds
4	Pupil size	**0** pupils pinned or normal size for room light **1** pupils possibly larger than normal for room light **2** pupils moderately dilated **5** pupils so dilated that only the rim of the iris is visible
5	Bone or joint aches	*If subject was having pain previously, only the additional component attributed to opiates withdrawal is scored* **0** not present **1** mild diffuse discomfort **2** subject reports severe diffuse aching of joints/muscles **4** subject is rubbing joints or muscles and is unable to sit still because of discomfort
6	Runny nose or tearing	*Not accounted for by cold symptoms or allergies* **0** not present **1** nasal stuffiness or unusually moist eyes **2** nose running or tearing **4** nose constantly running or tears streaming down cheeks
7	GI upset	*Over ½ hour*

Subject Number: **Date/Time:**

INSTRUCTIONS: For each item, circle the number that best describes the subject's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. Add the numbers for each item to obtain the total score.

	Signs	Measures	
		0	no GI symptoms
		1	stomach cramps
		2	nausea or loose stool
		3	vomiting or diarrhoea
		5	multiple episodes of diarrhoea or vomiting
8	Tremor	*Observation of outstretched hands*	
		0	no tremor
		1	tremor can be felt, but not observed
		2	slight tremor observable
		4	gross tremor or muscle twitching
9	Yawning	*Observation during assessment*	
		0	no yawning
		1	yawning once or twice during assessment
		2	yawning three or more times during assessment
		4	yawning several times/minute
10	Anxiety or irritability	**0**	none
		1	subject reports increasing irritability or anxiousness
		2	subject obviously irritable or anxious
		4	subject so irritable or anxious that participation in the assessment is difficult
11	Gooseflesh skin	**0**	skin is smooth
		3	piloerection of skin can be felt or hairs standing up on arms
		5	prominent piloerection

Total Score:

Initials of individual completing assessment:

12. PROTOCOL AMENDMENTS

12.1 Protocol Amendment 1

The protocol was amended based on feedback from Health Canada to include contraception use for male subjects and modify the dose escalation stopping rule for QTc prolongation criteria compared to baseline. Minor clarifications were also incorporated into the protocol.

Details of all changes following feedback from Health Canada and the rationale are provided below:

- Section 4.2, Inclusion Criterion #4: added paragraph for contraception use by male subjects. Subjects must be using and willing to continue using medically acceptable contraception from Screening and for at least 1 month after the last study drug administration.
- Section 4.6.2 Contraception Precautions: added examples of medically acceptable forms of contraception to include true abstinence, vasectomy, or male condom for subjects plus an additional method of contraception for their female partners.
- Section 4.8, Subject Discontinuation/Stopping Rules: bullet for QTc prolongation criterion was modified from >70 ms above the baseline to >60 ms above the baseline as suggested in the ICH E14 guideline as a commonly used threshold.

Details of the minor clarifications incorporated into the protocol and the rationale are provided below:

- Section 3.1.7, Table 3 Part B Time and Events Schedule: Treatment Phase and Follow-Up: Corrected footnote “c” to include urine pregnancy test at admission to Treatment Period 6 and add serum pregnancy test to Treatment Period 7. Revised footnote text: “serum pregnancy at Treatment periods 1 and 7 only; urine pregnancy at Treatment periods 2, 3, 4, 5, and 6.”
- Section 4.8, Subject Discontinuation/Stopping Rules: clarified the timing of positive breath alcohol test results in which a subject may be rescheduled at the discretion of the investigator or designee. The following text “at Screening or admission to any visit” was added to the sentence: “Subjects with a positive result at Screening or admission to any visit may be rescheduled at the discretion of the investigator or designee.”
- Section 5.2.5, Packaging and Labeling: corrected the number of tablets that will be packaged in HDPE bottles from 60 to 70 tablets. Updated protocol text: Nalbuphine ER tablets and matching placebo will be packaged in HDPE bottles with induction seal child-resistant closures containing 70 tablets each.

12.2 Protocol Amendment 2

The dose escalation scheme in Part A was amended to allow an incremental increase in the dose of nalbuphine based on a percentage of up to 50% from the last dose (rather than an absolute 27 mg dose increase), if supported by the safety data of the preceding cohorts.

The amendment is proposed based on the safety results of the first 4 cohorts indicating a lower than expected incidence of AEs and severity up to the 162 mg nalbuphine. Data indicated that - unlike healthy subjects- nalbuphine is much better tolerated in the non-dependent recreational opioid population and that the dose-AE response was flat over the selected dose range. At the 162 mg therapeutic dose (Cohort 4) only one Grade 2 AE was observed out of a total of 14 AEs. Subjects dosed at 81 mg had very mild AEs (2 out of 6 subjects had Grade 1 somnolence) with no nausea or vomiting compared to 5.9% in healthy subjects. Grade 1 vomiting and nausea were observed in one subject out of 6 at 135 mg while doubling the dose from 81 mg to 162 mg resulted in a single AE of Grade 2 nausea reported in one out of 6 drug treated subjects. This is in contrast to the observed incidence of vomiting (32%), nausea (41%) AEs in healthy subjects at the 162 mg dose. There was no effect on oxygen saturation ($spO_2 > 95\%$), ECG parameters, or any other vital signs over 24 hours post-dose in any individual subject up to 162 mg dose.

In view of the "flat" dose-response observed in this subject population, the protocol was amended to allow an incremental increase in the dose of nalbuphine based on a percentage of up to 50% from the previous dose (rather than an absolute 27 mg dose increase). The 50% increase was selected to ensure a sufficient differentiation between the doses while keeping in perspective the potential safety of the subjects as the doses are escalated to the higher doses. Given the high inter-subject variability of 54% in nalbuphine plasma C_{max} and 46% in AUC, a 50% increase seemed further justified.

In addition, an option to use both PK and safety data to identify the MSD was included to reduce the potential unnecessary exposure to escalating doses of study drug in the study population. Nalbuphine exposure increases with increasing dose in a proportional fashion over the 27 mg to 162 mg doses, the highest tested dose in healthy subjects. On the other hand, PK in the uremic pruritus subjects on hemodialysis indicated a plateau in exposure when the dose was increased from 162 mg to 216 mg (mean C_{max} = 83 ng/mL and AUC=761 h·ng/mL compared to 80 ng/mL and 770 h·ng/mL, respectively) (Study TR01). Therefore it would be reasonable to assume that as doses of nalbuphine increase, the exposure in the current otherwise healthy subjects would also start to deviate from proportionality and/or plateau at doses higher than 162 mg. If this were to be the case, then further increases in doses would not be expected to have a significant impact on the safety or tolerability of the drug.

Thus the option to review the PK data to determine if a plateau in the exposure of nalbuphine is reached despite dose escalation was added in Section 4.9.2. Dose Escalation and Stopping Rules. If a plateau is observed in the PK data, the MSD will be identified based on the available safety and PK exposure data. This option is intended to reduce the potential unnecessary exposure to escalating doses of study drug in the study population.

The proposed amendment for the dose escalation will involve at least a Cohort 5 at a dose of 243 mg dose (1.5 × 162 mg). As per the amended protocol, the option to dose additional cohorts may be considered proposed if the stopping rules in Section 4.9.2 are not met in Cohort 5.

Typically, human abuse liability studies evaluate the highest proposed therapeutic dose of the test drug as well as doses that are multiples of the highest proposed therapeutic dose (usually 2-3 times greater, if this can be done safely) in comparison to a positive control(s) and placebo. Our intent is to increase the dose until a 2- to 3-fold the therapeutic dose is reached assuming the dose stopping rules are not met. Doses are not to exceed 486 mg (3-fold the therapeutic dose). Figure 1 and Table 5 have been updated accordingly in the protocol to clarify the planned dose escalation scheme**.**

Additional protocol clarifications were also added regarding urine drug screens, the statistical analyses of the PD data in Part B, and data listings of the C-SSRS.

Details of all changes to the protocol and the rationale are provided below:

- Section 3.1.2, Dose Selection Study (Part A), modified text to indicate that at least 5 cohorts are planned and doses may escalate in an amount up to 50% of the dose administered in the previous cohort, as deemed appropriate by the safety and tolerability data. Additional cohorts may be added if a dose higher than those planned is required to be tested based on supportive safety data. Added that the doses of nalbuphine solution tested are not to exceed 486 mg (ie, 3-fold the therapeutic dose). If the DRC observes a plateau in the incidence and severity of AEs, which do not meet the stopping criteria described in Section 4.9, then the PK data may be reviewed to determine if there is a plateau in the exposure of nalbuphine despite dose escalation. The changes in dose escalation procedures were added based on the preliminary safety data observed in the initial cohorts enrolled in Part A.
- Figure 1, Study Schematic for Part A (Dose Selection Study), footnote, indicated that a dose higher than planned may be required to be tested based on supportive safety data. The higher dose selected may be up to 50% greater than the dose administered in the previous cohort based on supportive safety data.
- Section 4.1, Number of Subjects, indicated that additional cohorts may be added in Part A if a dose higher than those planned is also required to be tested based on supportive safety data.
- Section 4.8, Subject Discontinuation/Stopping Criteria, urine drug screen results exclusions were modified to current standards at the CRU for the recreational drug user population as described in the note-to-file entitled Urine Drug Testing and Positive THC - Directive for Interpretation and Eligibility Considerations for Non-Dependent Recreational Drug Users dated 17-Jul-2018.
- Section 4.9.2, Dose Escalation and Stopping Rules, modified the criterion for vomiting from “Grade 2 or higher” to “any episode” of vomiting within the 4-hour post-dose interval. The change was implemented to indicate that any vomiting episode will be considered as a signal of possible intolerance during the safety data review by the DRC.

  In addition, added an option to use both PK and safety data to identify the MSD. If the DRC observe a plateau in the incidence and severity of AEs, which do not meet the stopping criteria described in this section, then the PK data may be reviewed to determine if there is a plateau in the exposure of nalbuphine despite dose escalation. If a plateau is observed in the PK data, the MSD will be identified based on the available safety and PK

exposure data. This option is intended to reduce the potential unnecessary exposure to escalating doses of study drug in the study population.

Specified that the doses of nalbuphine solution will not exceed 486 mg, which corresponds to 3-fold the therapeutic dose

- Section 5.1.1, Dose Selection Phase (Part A), clarified in the text and the footnote of Table 5 that the actual doses administered in each cohort may be adjusted (increased, decreased, or repeated) based on the evaluation of safety data obtained in previous cohorts. Additional cohorts of subjects may be added to those planned (Table 5) until the MSD is identified. Higher doses can be up to 50% greater (but not to exceed 486 mg) than the dose administered in the previous cohort based on supporting safety data.
- Section 5.4.1, Nalbuphine Dose Selection, clarified that the proposed doses may be reduced or escalated by 27 mg increments (equivalent to 30 mg increments of the HCl salt) or up to 50% greater than the dose administered in the previous cohort as described in Section 5.1.1.
- Section 8.1.3, Planned Analyses of the Primary and Secondary Pharmacodynamic Assessments (Part B), parameters will be analyzed under the assumption of a normal distribution if the *P* value of the test is ≥ 0.01 (modified from *P* value ≥ 0.05). In cases where the normality of the distribution of the residuals is not satisfied and the Shapiro-Wilk W-test is applied, a paired t-test will be used if the *P* value is ≥ 0.01 (modified from *P* value ≥ 0.05) and the skewness = -1 to 1 (modified from -0.5 to 0.5). The change reflects current standards established at the CRU based on scientific conferences attended by the FDA. In addition, in the second-to-last paragraph, the first sentence had been included in error and was corrected to indicate that a *P* value of 0.05 will be used to denote statistical significance for both one-sided and two-sided hypothesis tests.

  Inclusion criteria for Part B of the Qualification Phase include having a peak score (E_{max}) on the Drug Liking VAS greater than that of placebo by at least 15 points in response to 12 mg hydromorphone. In order to assess the robustness of this 15-point difference, a sensitivity analysis was added to the planned analysis for the Treatment Phase to assess the null hypothesis that the mean difference in Drug Liking VAS E_{max} between the positive controls, hydromorphone 8 and 16 mg, and placebo is less than or equal to 15 against the alternative hypothesis that the mean difference in Drug Liking VAS E_{max} between hydromorphone and placebo is greater than 15.

- Section 8.1.5, Analysis of Safety Assessments, clarified that the results from both the since last visit and baseline versions of the C-SSRS will be included in the data listings.

On Page 2, the sponsor address zip code was corrected from 06150 to 06510. Minor formatting changes are not described.