Sponsor Name:	**Trevi Therapeutics, Inc.**
Protocol Number and Title:	**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**
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I confirm that I have reviewed this document and agree with the content.

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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC_{inf}	Area Under the Plasma Concentration versus -Time Curve from Time 0 Extrapolated to Infinity
AUC_{last}	Area Under the Plasma Concentration versus -Time Curve from Time 0 to the last measurable concentration
AUE	Area Under the Effect curve
BLQ	Below Limit of Quantification
BMI	Body Mass Index
CI	Confidence Interval
CL/F	Apparent Clearance
CM	Concomitant Medication
C_{max}	Maximum Observed Plasma Concentration
COWS	Clinical Opiate Withdrawal Scale
CRF or eCRF	Case Report Form or electronic Case Report Form
CRU	Clinical Research Unit
C-SSRS	Columbia-Suicide Severity Rating Scale
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
E_{max}	Maximum (peak) Effect
E_{min}	Minimum (peak) Effect
ER	Extended-Release
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone

Abbreviation	Description
HAP	Human Abuse Potential
HCl	Hydrochloride
HIV	Human Immunodeficiency Virus
ICH	International Council for Harmonisation
IQR	Inter-Quartile Range
IV	Intravenous
k_{el}	First-Order Elimination Rate Constant Associated with the Terminal (Log-Linear) Portion of the Curve
LNH	Low/Normal/High (classification)
LLOQ	Lower Limit of Quantification
LSM	Least Square Mean
MSD	Maximum Safe Dose
MedDRA	Medical Dictionary for Regulatory Activities
MPC	Maximum Pupil Constriction
NA	Not Applicable
NCE	New Chemical Entity
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PT	Preferred Term
Q1	1st Quartile or 25th Percentile
Q3	3rd Quartile or 75th Percentile
QTcB	QT Interval Corrected by Bazett Formula
QTcF	QT Interval Corrected by Fridericia Formula
RBC	Red Blood Cell
RMS	Root Mean Square
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System
SD	Standard Deviation
SE	Standard Error

Abbreviation	Description
SI	Standard International System of Units
SOC	System Organ Class
SOP	Standard Operating Procedure
SpO_2	Oxygen Saturation
SSTM	Sternberg Short-Term Memory Test
$t_{1/2}$	Terminal Elimination Half Life
TBD	To Be Determined
t_{max}	Time to Maximum Observed Plasma Concentration
TA_AUE	Time-Averaged Area Under the Effect Curve
TA_PAOC	Time-Averaged Pupillometry Area Over the Curve
TEAE	Treatment-Emergent Adverse Event
TE_{max}	Time to Maximum Effect
TE_{min}	Time to Minimum Effect
TLF	Table, Listing and Figure
TMPC	Time to MPC
VAS	Visual Analogue Scale
Vd/F	Apparent Volume of Distribution
WBC	White Blood Cell (count)
WHO-DD	World Health Organization- Drug Dictionary

2. PURPOSE

The purpose of this Statistical Analysis Plan (SAP) is to ensure that the data listings, summary tables and figures that will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. RESPONSIBILITIES

The Syneos Health biostatistics team will perform the statistical analyses and is responsible for developing the randomization plan, randomization schedule, and statistical analysis plan (SAP) including table, listing and figure (TLF) shells, quality control plan as well as the production and quality control of all TLFs, including results for the safety, pharmacodynamics (PD) and pharmacokinetics (PK) endpoints.

Due to the unexpected closure of the investigational site following completion of Part A, but before commencement of Part B, the scope of this analysis plan is limited to Part A only (see Section 5). While the study Protocol provides full documentation of the plan for Part B undertaking, no reference to Part B in this SAP will be included. In addition, any exclusion to specific reference to Part A implies that the proposed methods are applicable to Part A, i.e., specifically referring to Part A hereon in is redundant. In addition, the use of the term “Dose Selection Phase” and “Part A” are interchangeable.

2.2. TIMINGS OF ANALYSES

The primary analysis of safety, PD and PK will be conducted after all subjects complete the final study visit or terminate early from the study and after the database is locked.

No interim analysis is planned for this study.

3. STUDY OBJECTIVES

3.1. EXPLORATORY OBJECTIVES

The exploratory objectives that will be evaluated in the Dose Selection Phase (referred to as Part A in the Protocol) are the following:

- 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.

3.2. BRIEF DESCRIPTION

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

The study is limited to Part A (Dose Selection Phase) as described in the Protocol. The purpose will be to conduct an exploratory dose selection phase to identify the appropriate low, intermediate, and high doses of nalbuphine solution administered as single doses in the Treatment Phase of the eventual planned Main Study (Part B).

Part A will be a randomized, double-blind, placebo-controlled dose escalation study and will include the following:

- Screening (Visit 1)

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

Screening will be an outpatient visit during which informed consent will be obtained and screening assessments will be completed, including a review of medical history and recreational drug use history against inclusion and exclusion criteria to determine subject eligibility for the study.

The dose selection phase is a randomized, double-blind, placebo-controlled dose escalation to determine the MSD of nalbuphine. 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. 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. 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: e.g., 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 hydrochloride (HCl) salt, respectively) or until an MSD is reached. There are 5 planned unique cohorts; however, 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 if a dose higher than those planned is required to be tested, based on supporting safety data. Each cohort will enroll 8 subjects (6 active, 2 placebo). Subjects will participate in a single cohort and will receive single oral doses of nalbuphine or placebo.

PK, PD (i.e., pupillometry) and safety assessments will be conducted pre-dose and up to 24 hours post-dose or longer, at the discretion of the investigator or designee. Subjects will be discharged approximately 24 hours after drug administration, at the discretion of the investigator or designee. Following the completion of each cohort, safety data will be unblinded and reviewed by the Data Review Committee (DRC) to determine if dose escalation is required. 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.

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

Subjects will be discharged approximately 24 hours after each drug administration (following completion of all post-dose procedures), at the discretion of the investigator or designee.

The follow-up visit will be conducted approximately 7 to 14 days after the last drug administration in the treatment phase or at the time of early withdrawal from the study and will include standard safety assessments.

An overview of the study design is shown in **Error! Reference source not found.**. Study assessments will be performed at the visits and time points outlined in the Time and Events Schedule (Table 2).

3.3. SUBJECT SELECTION

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 and tolerability data.

3.3.1. Inclusion Criteria

Subjects will be considered eligible to participate in this study 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 (i.e., 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 of the Protocol) 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 of the Protocol.

5. 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 of the Protocol) from Screening and for at least 1 month after the last study drug administration.
6. Must provide written informed consent prior to the initiation of any Protocol-specific procedures.

3.3.2. Exclusion Criteria

Subjects will not be considered eligible to participate in this study 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 (e.g., gum, patch, e-cigarettes) during the in-clinic periods.

3. History or presence of clinically significant abnormality as assessed by physical examination, medical history, electrocardiograms (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 (e.g., 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 human immunodeficiency virus (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 (e.g., other opioids) or naltrexone or related drugs (e.g., other antagonists) or to any known excipients (e.g., lactose).

13. Subjects with any lifetime history of suicidal ideation or suicidal behavior, as assessed by the Columbia-Suicide Severity Rating Scale (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 of the Protocol.

16. Treatment with an investigational drug within 5 times the elimination half-life ($t_{1/2}$), if known (e.g., 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.

3.3.3. Naloxone Challenge

Eligible subjects who meet Screening criteria will undergo a naloxone challenge test at least 12 hours prior to study drug administration. 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.

Baseline vital signs and the COWS 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 of the Protocol.

Subjects who present with signs or symptoms of withdrawal following administration of the naloxone challenge (i.e., 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.

3.4. DETERMINATION OF SAMPLE SIZE

Approximately 5 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 human abuse potential (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 MSD is identified. If the DRC observes a plateau in the incidence and severity of AEs, which do not meet the stopping criteria (Section 4.9 of the Protocol), 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 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, or a dose higher than those planned is required to be tested, based on supporting safety and tolerability data.

3.5. TREATMENT ASSIGNMENT & BLINDING

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 (e.g., 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 in the screening process (subject number). 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 designated unblinded statistician(s) at Syneos Health before the start of the study. Sealed code break envelopes will be provided before the start of the study.

Each subject will participate in a naloxone challenge, by which 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. At least 12 hours after the naloxone challenge, eligible subjects will be randomized to either placebo or active treatment (allocation 6 Active: 2 Placebo) in a double-blind manner according to the randomization schedule. For each dose selection cohort, an unblinded statistician from Syneos Health, 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 dose selection 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, and the PD and safety data will be reviewed to determine if dose escalation to the next cohort should occur.

3.6. ADMINISTRATION OF STUDY MEDICATION

Subjects will be administered study drug with a flavored, low caloric, artificially sweetened, non-carbonated beverage (e.g., diet cranberry cocktail). Each subject will receive a single oral dose of either nalbuphine HCl solution or matching placebo 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 1 until the MSD is identified. Higher doses can be up to 50% greater 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.

There are 7 planned cohorts (Table 1). 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 of the Protocol.

Table 1 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	405 mg	40.5 mL × 10 mg/mL + 109.5 mL flavored beverage	150 mL flavored beverage
7[a]	Up to 486 mg	540 mg	54 mL × 10 mg/mL + 96 mL flavored beverage	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.

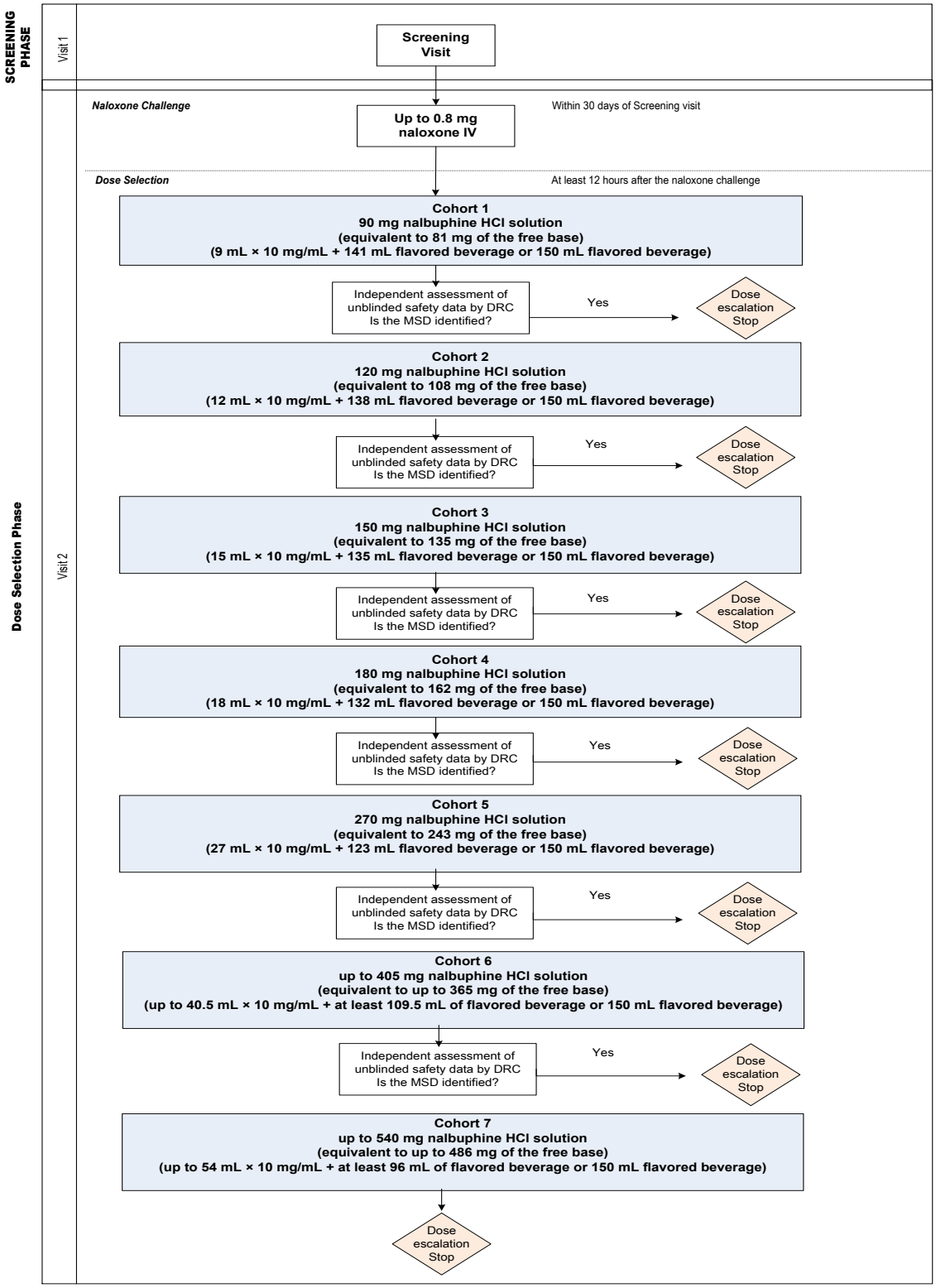
Actual doses may be adjusted according to the evaluation of safety data. Dose reductions, intermediate doses, or higher doses up to 50% greater than the dose administered in the previous cohort may be considered based on the safety results obtained in previous cohorts. Additional cohorts of subjects 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 of the Protocol for details).

3.7. STUDY PROCEDURES AND FLOWCHART

An overview of the study design is shown in Figure 1. Study assessments will be performed at the visits and time points outlined in the Time and Events Schedule (Table 2).

Figure 1 Study Schematic



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..

Table 2 Time and Events Schedule

	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			

[a] Focusing on any changes since the last visit.
[b] Symptom-directed physical examination

	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)																	
Vital Signs[c]	X	X[d]	Pre				1		2		3	4	5	6		7	8	10	12	24
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																		

[c] Vital signs will include blood pressure, heartrate, 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 of the Protocol.

[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 of the Protocol. 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.

	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)																	
Study Drug Administration				0																
Discharge[i]																				X

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[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.

4. ENDPOINTS

4.1.1. 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 versus time curve from time 0 to the 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
- k_{el}: first-order elimination rate constant associated with the terminal (log-linear) portion of the curve
- $t_{½}$: apparent first-order terminal elimination half-life will be calculated as $0.693/k_{el}$
- CL/F: apparent clearance
- Vd/F: apparent volume of distribution

4.1.2. Safety Endpoints

The safety endpoints will include the following:

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

4.1.3. Exploratory Endpoints

The exploratory endpoints for this study are:

- Identification of a 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}, k_{el}, $t_{1/2}$, CL/F and Vd/F will be calculated.
- Pupillometry (maximum pupil constriction [MPC], time to MPC [TMPC], and time-averaged pupillometry area over the curve [TA_PAOC]).

5. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

Due to the unexpected closure of the investigational site prior to the initiation of Part B of this study, only Part A was completed. Part B will be placed with a new investigation site sometime in the future. As a result, only those endpoints associated with Part A will be summarized and evaluated. Consequently, this updated SAP provides a detailed description of planned assessments for Part A only.

6. ANALYSIS POPULATIONS

The study analysis populations will consist of the following:

- Dose Selection Randomized Population
- Dose Selection Safety Population
- Dose Selection PK Population

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

6.1. DOSE SELECTION RANDOMIZED POPULATION

The Dose Selection Randomized Population will include all subjects who are assigned a randomization number in the Dose Selection Phase. Unless specified otherwise, this population will be used for subject listings and for summaries of subject disposition for this phase.

6.2. DOSE SELECTION SAFETY POPULATION

The Dose Selection Safety Population will include all subjects in the Dose Selection Randomized Population who receive any Dose Selection treatment. The Dose Selection Safety Population will be used for all analyses of safety endpoints, the listing of PK concentration data and for the analyses of PD pupillometry data in this phase.

6.3. DOSE SELECTION PK POPULATION

The Dose Selection PK Population will include all subjects in Dose Selection Randomized Population who receive a dose of nalbuphine and have evaluable PK data, and who have no protocol deviations or other circumstances that would exclude them from analysis. Details of subject inclusion in the Dose Selection PK Population will be determined prior to study unblinding. The Dose Selection PK Population will be used for all PK analyses and for the listing of derived PK parameters in this phase.

6.4. PROTOCOL DEVIATIONS

All protocol deviations related to study inclusion or exclusion criteria, conduct of the trial, subject management or subject assessment will be listed. Protocol deviations will be reviewed by the Sponsor, the principal investigator, the lead statistician and the study scientist and will be finalized before unblinding the study. All deviations will be listed.

7. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

7.1. GENERAL METHODS

Study data will be reported in subject data listings and summary tables. Descriptive statistics will be provided by cohort or treatment group and observation time (visit) of interest, as appropriate. If not specified otherwise, the standard summary statistics that will be calculated for quantitative and qualitative variables are:

Continuous:	number of subjects (N), mean, SD or standard error (SE), minimum, median, and maximum
Categorical:	number of subjects, absolute and relative frequencies per class (denominators for relative frequencies will be described in the tables)

Frequency counts of 0 will be reported as "0" with no percentage.

Data collected pre- and post-treatment during the Dose Selection Phase will be summarized by time point and cohort (PD [i.e., pupillometry], PK plasma concentrations) or as maximum, minimum and final post-dose individual values by cohort (vital signs).

Data collected at other “off-treatment” times (e.g., baseline, admission and follow-up) will be summarized by cohort. These data include demography, baseline conditions, and safety evaluations (lab, ECG).

7.2. KEY DEFINITIONS

Administration of the first dose of study drug during the Dose Selection Phase is defined as Study Day 1. Study Day -1 is the day before dosing and all assessments prior to Study Day 1, including Screening will have negative study days. Nominal Time is the scheduled measurement time relative to time 0. Time 0 is the time of dosing on Day 1. Time 0 is precisely defined for each analysis below. For data collected pre- and post-administration, baseline is the last observed measurement prior to the administration of study drug. Hence, we have one possible baseline.

For AEs and concomitant medications (CMs), time since dose will be calculated as the difference between the event or medication start date/time and the date/time of the treatment dose of each period. Time since dose will be expressed in days, hours and minutes. If onset time is in seconds, it will be expressed as “<1 min”. If time is missing, duration will be expressed in days. Methods for handling partial start date/times of AEs and CMs are described in Section 7.3.

Duration will be calculated for AEs that resolve as the difference between the resolution date/time and onset date/time and will be expressed in days, hours and minutes. If duration is in seconds, it will be express as “<1 min”. If time is missing, duration will be expressed in days. Methods for handling partial resolution and onset dates of AEs and CMs onset are described in Section 7.3.

Age is calculated based on the date of birth and date of full informed consent on the database level and this value will be used in analyses. In case date of birth was provided as year only, age is calculated as difference of 01Jan<year of birth> and date of informed consent.

A subject will be defined as "completed" if s/he completes the Follow-up Visit 10. Termination at a different time point will be considered as discontinuation. This applies only for the Treatment Phase.

Subjects will be defined as "completed" if s/he completes Visit 2. Termination at a different time point will be considered as discontinuation.

Nominal Time is the scheduled measurement time of the time point relative to the dose time.

Time since dose is the actual elapsed time from the first administration of study drug in a cohort. So, for example, if study drug is administered at 08:00 on Day 1, 10:30 on Day 1 represents a Time Since Dose of 2:30 or 2.5 hours.

7.3. MISSING DATA

For PD and PK analyses, missing data for subjects who are administered all scheduled study treatments for all the treatment periods will be considered as random non-informative missing for analysis purposes. Missing values will be examined on a case-by-case basis to confirm this. Missing values for PD assessments will not be imputed. The handling of missing PK data is detailed in Section 10.4.

AEs and medications with incomplete start dates and times will be considered as treatment-emergent or prior/concomitant, respectively, according to the following algorithm:

1. If the AE occurrence type is specified for the AE on the eCRF, it will be used to determine treatment-emergence. If the AE occurrence type is 'Treatment Period X' then the AE will be assigned as treatment-emergent. This will be verified using the algorithms below (steps 3 through 7).

2. If a medication started and stopped prior to the start of study treatment the medication will be considered prior. This will be verified using the algorithms below (steps 3 through 7).

3. Comments will be reviewed for additional information when treatment emergence is ambiguous.

4. Only the start year is reported: If the year is after or the same as the year of the first dose date, then the event will be considered treatment-emergent.

5. Only the start month and year are reported: If the month/year is after or the same as the month/year of the first dose date, then the event will be considered treatment-emergent.

6. Only the start time is missing: If the event occurred or medication was started on or after the date of the first dose date, then the event will be considered treatment-emergent and the event will be attributed to that treatment; if it occurred before the first dose in the treatment period (e.g., at admission), it will be attributed to the treatment administered in the previous period.

7. For AEs with missing or incomplete start dates, if it can be determined based on the available start date components or the stop date to which treatment group(s) the AE should be assigned to then the AE will be assigned to the appropriate treatment group. If it cannot be determined, then the AE will be assigned to all treatment groups received.

For treatment-emergent AEs (TEAEs), time since dose will be expressed in days, hours and minutes. If either time is missing, time since dose will be expressed in days.

Duration will be calculated for AEs that resolve as the difference between the resolution date and time and onset date and time and will be expressed in days, hours and minutes. If either time is missing, duration will be expressed in days.

Time since dose and duration will only be calculated when both dates are complete.

7.4. VISIT WINDOWS

7.4.1. Pharmacodynamic (PD) Assessments

PK samples will be collected after the completion of all PD assessments within the following allowable windows:

Table 3 Acceptable Collection Window for PD Assessments

Time Point (hours)	Acceptable Collection Window
Pre-dose	Within 2 hours prior to study drug administration
Post-dose time points 0.25h, 0.5h, 1h, 1.5h	±5 minutes of nominal time

7.4.2. Pharmacokinetic (PK) Sample Collection

PK samples will be collected after the completion of all PD assessments within the following allowable windows:

Table 4 Acceptable Collection Window for PK Blood Sample Collection

Time Point (hours)	Acceptable Collection Window
Pre-dose	Within 60 minutes prior to study drug administration
Post-dose time points 0.25h, 0.5h, 1h, 1.5h	Within + 2 minutes of the completion of PD assessments
Post-dose time points 2.0h, 2.5h, 3.0h, 4.0h, 5.0h, 6.0h, 8.0h, 10.0h, 12.0h	Within + 5 minutes of the completion of PD assessments
Post-dose time point 24.0h	Within + 15 minutes of the completion of PD assessments

7.5. POOLING OF CENTERS

This is a single center study, therefore pooling of centers is Not Applicable (NA).

7.6. SUBGROUPS

No subgroups will be evaluated.

8. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

8.1. SUBJECT DISPOSITION AND WITHDRAWALS

Subject disposition will be summarized by treatment. The number of subjects in each cohort will be presented, in addition to the number of subjects who completed, the number of subjects who discontinued the study early along with the reasons for all post-randomization discontinuations.

The number and percentage of subjects in the analysis populations will be presented in the subject disposition tables.

The denominators for the percent calculations will be the number of subjects randomized.

A listing of subjects who participated in the study will also be presented, including participation (yes/no) and treatment received.

Listings of subjects excluded from the analysis sets will also be produced.

Inclusion/exclusion criteria definitions and all deviations will be listed. If no inclusion/exclusion criteria are reported, this will be noted in place of the listing.

8.2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographics and baseline characteristics (age, sex, race, ethnicity, body weight, height, and BMI) will be summarized using descriptive statistics (n, mean, SD, minimum, median and maximum, for continuous variables, and the proportion of subjects for categorical variables). Summaries will be presented by treatment for the Dose Selection Randomized Population. No formal statistical comparison between the groups will be performed.

8.3. OTHER BASELINE CHARACTERISTICS

8.3.1. Recreational Drug and Alcohol Use History

A history of all drugs used for recreational/non-medicinal purposes (i.e., psychoactive effects) and alcohol use will be collected during the Screening visit(s) and listed by subject for Dose Selection Randomized Population.

The number and percent of subjects with history in each drug class (cannabinoids, depressants, dissociative anesthetics, hallucinogens, opioids and morphine derivatives, stimulants and other compounds) will be presented by treatment for the Dose Selection Randomized Population. For each drug class, the proportion of subjects with a history of the given drug class are summarized.

For all recreational drugs, the following questions will be tabulated using standard summary statistics:

- Number of times used in past 2 years
- Number of recreational drugs used in past 2 years (1, 2, 3 or ≥4)

For the opioids drug class, the following two additional questions will be tabulated using standard summary statistics:

- Number of times opioids used in the past 8 weeks prior to Screening visit
- Number of times opioids used in the past 12 months

For subjects reporting more than one drug per drug class, number of times used will be summed over all drugs in that class.

The number and percentage of subjects reporting drinking alcohol will be presented by treatment for the Dose Selection Randomized Population. The average number of drinks in the past 2 years will be tabulated using standard summary statistics.

8.3.2. Nicotine Use

Nicotine use will be collected at Screening and listed only by subject for the Dose Selection Randomized Population.

8.4. MEDICAL HISTORY

Medical history will be listed by subject for the Dose Selection Randomized Population. Medical history will be coded into the most recent version of Medical Dictionary for Regulatory Activities (MedDRA) available (version 20.0 or later). 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 but shall not be listed.

8.5. PRIOR AND CONCOMITANT MEDICATION

Prior medication is defined as medication taken up to 30 days before the first screening date. Non-study medication taken from the first Screening visit until the completion of the Follow-up visit will be considered as concomitant. Prior and concomitant medications will be assigned a 12-digit code using the most recent version of the World Health Organization drug codes available (WHO Drug). The original verbatim terms collected in the electronic Case Report Form (eCRF) for prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) into drug class (Anatomical Therapeutic Chemical [ATC] Classification level 2) and preferred term (PT).

Prior and concomitant medications will be listed chronologically by subject including all data collected in the eCRF, along with coded variables for Dose Selection Randomized

Population. The incidence of concomitant antiemetic medication use will be tabulated by cohort (i.e., dose level) and treatment (active drug or placebo).

9. PHARMACODYNAMICS ASSESSMENTS AND ANALYSIS

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 (i.e., measures most predictive of the drug's abuse potential and reinforcing properties), measures of negative response (i.e., measures that potentially mitigate against abuse potential), measures of stimulant effects, measures of other effects and measures of cognitive and psychomotor effects.

9.1. PHARMACODYNAMIC ASSESSMENTS

9.1.1. 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 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.

Pupillometry will be recorded at the following time points:

- Pre-dose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12 and 24 hours post-dose.

PD pupillometry data in the Dose Selection Phase will be analyzed for the Dose Selection Safety Population. The exploratory endpoints are MPC, TMPC, and TA_PAOC.

9.1.2. Derived and Imputed Data

For each subject and treatment period, the parameters will be derived using the following rules:

- Analyses will be based on actual assessment times, except for pre-dose (baseline) times, which will automatically be considered as time 0 as appropriate for analysis. If the actual time is missing, the nominal time will be used.

- TMPC will be calculated as the time from time 0 to MPC.

- TA_PAOC is calculated as the area over the curve (AOC) divided by the time from time 0 (or the 0.25 hour time point if the VAS is not collected pre-dose) to the 24 hour time point. AOC is calculated using the linear trapezoidal rule applied to non-missing data.

- Missing data for subjects who are administered all scheduled study treatments for all the treatment periods will be considered as random non-informative missing for analysis purposes. Missing values will be examined on a case-by-case basis to confirm this. Reasons for missing data will be displayed in the listings. No further imputation will be applied to any missing values.

Assessments done outside the assessment windows may be excluded from by-time point summary statistics; this will be determined prior to unblinding.

10. ANALYSIS OF PHARMACOKINETICS

10.1. MEASUREMENTS

The Dose Selection Safety Population will be used for all individual plasma concentration listings, whilst all listings and summaries and pharmacokinetic analyses of PK data will be performed using the Dose Selection PK Population.

PK endpoints include plasma concentrations of nalbuphine and its corresponding metabolites (M1, M3, M4, and M5) at each collection time point and the derived PK parameters listed in Section 4.2.3.

10.2. PK SAMPLING SCHEDULE

During the Dose Selection Phase, blood samples will be collected at the following time points:

- Pre-dose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12 and 24 hours post-dose.

10.3. DERIVED AND IMPUTED DATA

- PK parameters (C_{max}, t_{max}, AUC_{last}, AUC_{inf}, $t_{½}$, k_{el}, CL/F and Vd/F) will be determined for nalbuphine and its metabolites based on concentrations in plasma and actual sampling times via non-compartmental analysis using validated Phoenix WinNonlin Version 6.4 or higher. For each subject, the PK parameters will be derived as follows: The apparent C_{max} and the corresponding t_{max} will be read directly from the concentration-time plot (observed data, not predicted data by the program);
- AUC_{last} and AUC_{inf} will be calculated using the linear up log down trapezoidal method;
- The elimination rate constant (k_{el}) will be determined by log-linear regression obtained on at least the three last quantifiable concentrations;
- The Terminal elimination half-life ($t_{½}$) will be calculated as $0.693/k_{el}$.
- AUC_{inf} is calculated by the program as:

  $AUC_{inf} = AUC_{last} + AUC_{t\text{-}inf}$ where t is the sampling time point of the last measurable concentration (t_{last}). $AUC_{t\text{-}inf}$ is calculated by the program as: C_{last}/k_{el}, where C_{last} is the last measurable concentration at time t and k_{el} is the elimination rate constant during the terminal elimination phase;
- CL/F will be derived by Dose/AUC_{inf} and Vd/F will be derived as CL/F divided by k_{el}.

The following reliability criteria will be used for the PK parameters:

- The adjusted square of the correlation coefficient (Rsquare adj.) for the goodness of fit of the regression line through the data points must be at least 0.80 for the k_{el} value to be considered reliable;
- The AUC extrapolation to infinity ($AUC_{t\text{-}inf}$) must be ≤20% of the total area for AUC_{inf} to be considered reliable;

For subjects with unreliable k_{el} (e.g. Rsquare adjusted ≤0.80), k_{el}, $t_{1/2}$ and AUC_{inf} will be flagged in the individual data Listings. For subjects with unreliable AUC_{inf} (because of extrapolation >20%), AUC_{inf}, CL/F and Vd/F will be flagged in the individual data Listings. Flagged PK parameters will be excluded from summarization and statistical analyses.

10.4. HANDLING OF MISSING DATA

Missing concentration data for subjects who were administered scheduled study treatments will be considered as random non-informative missing for analysis purposes and will not be imputed. Missing values will be examined on a case-by-case basis to confirm this.

- The data will be handled as follows for the graphical presentation of individual plasma concentrations and for the derivation of the PK parameters (using actual sampling times): The time of collection of the pre-dose sample will be set to zero (time 0);
- Actual post-dose sampling times are expressed relative to the time of dosing (if the actual time of sampling is missing, the planned time will be used);
- Pre-dose plasma concentrations below the lower limit of quantification (LLOQ) will be treated as zero for the derivation of PK parameters;
- Concentration values below LLOQ prior to the first quantifiable concentration will be treated as zero for the derivation of PK parameters.
- Post-dose below limit of quantification (BLQ) values after the first quantifiable time point will be set to missing for the derivation of PK parameters.
- For the summary and graphical presentation of plasma concentrations, any plasma concentrations that are BLQ will be treated as zero.
- If all samples are BLQ for a given concentration-time profile, PK parameters will not be derived for that profile.
- No further imputation will be applied to any missing values.

10.5. DATA SUMMARIZATION AND PRESENTATION

PK sample collection data, plasma concentrations and the derived PK parameters for nalbuphine and its metabolites (M1, M3, M4, and M5) will be listed by subject. Plasma concentration data and the PK parameters for the nalbuphine treatments and its metabolites will be summarized by dose level using the following statistics (Table 5):

Table 5 Summary Statistics for PK Analyses

Variable	Summarized with:
Plasma concentration at each time point	n; number of missing (if not zero); number and percent BLQ values; arithmetic mean, SD and coefficient of variation (CV%, calculated as 100*SD/mean); minimum, median and maximum
C_{max}, AUC_{last}, AUC_{inf}, CL/F, Vd/F	n; number of missing (if not zero); arithmetic mean, SD and coefficient of variation (CV%, calculated as 100*SD/mean); minimum, median, and maximum; geometric mean and geometric CV% (calculated as $100\% \times \sqrt{e^{z^2} - 1}$, where z^2 is the variance of the log-transformed data)
t_{max}	n; number of missing (if not zero); median, minimum, maximum, first quartile (Q1) add third quartile (Q3).
$t_{1/2}$, k_{el}	n; number of missing (if not zero); arithmetic mean, SD and CV (%); minimum, median, and maximum

AUC = area under the curve; BLQ = below the limit of quantification; C_{max} = maximum observed plasma concentration; CV = coefficient of variation; SD = standard deviation; t_{max} = time to maximum plasma concentration; $t_{1/2}$ = terminal elimination half-life; k_{el} = first-order elimination rate constant.

If more than 50% of values are BLQ or are missing, then only n, n (%) BLQ, minimum, median and maximum will be calculated and reported. If the calculated mean/median value is less than LLOQ, then that time point will be ignored for plotting the mean PK profiles.

The following graphical presentations will be made for nalbuphine:

- Mean PK plasma concentrations plotted vs time curve by dose level within the same figure using both linear and log-linear scales.
- Box-whisker plots of PK parameters including C_{max} and AUC_{last} by dose level using linear scale.
- By-subject time-concentration curves by dose level within the same figure using both linear and log-linear scales.

The PK parameters summary will be presented separately for a subset (if applicable) of subjects who do not vomit within 12 hours of dosing.

11. SAFETY

All safety analyses will be done using the Dose Selection Safety Population.

11.1. EXTENT OF EXPOSURE

Drug administration data for the Dose Selection Phase will be listed for the Dose Selection Randomized Population.

11.2. TREATMENT COMPLIANCE

Not Applicable (NA).

11.3. ADVERSE EVENTS / ADVERSE DRUG REACTIONS

Analysis of safety assessments will be performed using the Dose Selection 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 TEAE. TEAEs will also be tabulated by maximum severity and by maximum relationship to study drug. These summaries will be presented by body system and PT (MedDRA, version 20.0 or higher). SAEs and AEs resulting in discontinuation will be summarized separately. All AEs will be listed by subject for the Dose Selection Randomized Population.

Any AE occurring after treatment start will be considered as a TEAE. Rules related to assigning TEAEs to treatment and imputation related to missing data are described in the Section 7.3.

Subjects may be counted under multiple system organ classes (SOCs) and PTs, but for each SOC and PT, subjects are only counted once.

The number and percentages of subjects with TEAEs as well as the number of events will be displayed. SOCs will be sorted by descending frequency of subjects. Within each SOC the PTs will be sorted by descending frequency of subjects.

Imputation related to missing AE data is described in the Section 7.3.

11.4. LABORATORY EVALUATIONS

Blood and urine samples for hematology, clinical chemistry, and urinalysis (referred to collectively as safety laboratory data) will be collected according to the Time and Events Schedule (Table 2).

The following tests are included:

- **Clinical Chemistry:** alkaline phosphatase (ALP), calcium, chloride, creatinine, random glucose, potassium, alanine aminotransferase (ALT), aspartate

aminotransferase (AST), gamma-glutamyl transpeptidase, sodium, total bilirubin, and urea.

- **Hematology:** A peripheral blood smear to assess blood cell morphology, hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count, WBC differential (absolute counts), and numerical platelet count.
- **Urinalysis:** 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:** presence of ß-Human Chorionic Gonadotropin (HCG) in the blood serum or urine of all female subjects. Results of blood serum and urine pregnancy tests will be reported and determined to be negative prior to study continuation and/or dosing.
- **Follicle-Stimulating Hormone (FSH):** Post-menopausal status for female subjects 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.
- **Breath Alcohol:** 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:** Urine samples will be tested for the following drugs of abuse: THC, oxycodone and other opiates (i.e., the opiate panel will test for the presence of codeine, hydrocodone, hydromorphone, morphine, and oxymorphone), amphetamines (i.e., amphetamines and methamphetamines), cocaine, and benzodiazepines.

Laboratory data collected during the Dose Selection Phase will be summarized by the type of laboratory test and visit. Descriptive statistics (n, 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.

Continuous laboratory test results will be assigned a low/high/normal (LNH) classification by the central lab according to whether the value was below (L: Low), within (N: Normal), or above (H: High) the laboratory parameter's normal range; categorical laboratory test results were classified as normal (N) or abnormal (A).

Abnormal findings in laboratory data will be listed. Abnormal values, classified as Low/Normal/High (LNH), and clinically significant abnormalities (as determined by the investigator) will be flagged. Laboratory listings will be provided for the Dose Selection Randomized Population.

All laboratory test results will be reported in Standard International System of Units (SI) units.

11.5. VITAL SIGNS

Vital signs consist of systolic and diastolic blood pressure (mmHg), heart rate (beats per minute [bpm]), and respiratory rate (breaths/minute). Oral temperature (°C) will also be taken at some time points according to the Time and Events Schedules (Table [Dose Selection]).

In addition, pulse oximetry measurements (SpO_2) will be taken at designated time points after the continuous monitoring period.

Dose Selection Phase vital signs (blood pressure, respiratory rate, heart rate, SpO_2) will be analyzed as minimum, maximum, and final post-dose (i.e. 24 hours) values and summarized using descriptive statistics (n, mean, SD, minimum, median and maximum), since the analyses of these extremes are more meaningful than the analyses of individual time points. The individual time points and all off-treatment vital signs (i.e., Screening, and Follow-up) will be listed for the Dose Selection Randomized Population but not otherwise analyzed. Abnormal findings in vital signs data will be listed. In the Dose Selection Phase, baseline will be determined as the last observed measurement prior to the administration of study drug. In addition, minimum, maximum, and final post-dose individual values will be derived and individual data will be presented in data listings.

11.6. ECG

12-lead ECGs will be performed by the site according to the Time and Events Schedules (Table [Dose Selection]). The ECG will electronically measure and calculate ventricular heart rate and the PR, QRS, QT, QTcB, and QTcF intervals. ECG data will be classified as "Normal", "Abnormal, Not Clinically Significant" or "Abnormal, Clinically Significant".

12-lead ECG data (absolute values in heart rate and PR, QRS, QT, QTcB, and QTcF intervals) will be summarized by parameter and visit using descriptive statistics (n, mean, SD, minimum, median and maximum). Abnormal findings in ECG data will be listed. A summary table of overall ECG interpretation will show the number and percentage of subjects with normal, abnormal non-clinically significant (NCS) or abnormal clinically significant (CS) findings at each visit. ECG data will be listed for the Dose Selection Randomized Population.

11.7. PHYSICAL EXAMINATION

A complete physical examination including general appearance, eye, ear, nose and throat, head and neck, respiratory, cardiovascular, gastrointestinal, musculoskeletal, dermatological, peripheral vascular, lymphatic, neurological, mental status and other body system status, will be performed at Screening. Subsequent symptom-directed physical examinations will be performed according to the Time and Events Schedule (Table 2), 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. Height, weight, and BMI will be recorded at Screening only.

Physical examination abnormal results will be listed by subject and visit for the Dose Selection Randomized Population.

11.8. OTHER SAFETY

Two versions of the Columbia-Suicide Severity Rating Scale (C-SSRS) will be used in this study: the Baseline version to assess lifetime suicidal ideation and behavior at Screening, and the Since Last Visit version to assess suicidal thoughts or behaviors the subject may have had since the last time the C-SSRS was administered.

The Baseline and Since Last Visit C-SSRS results will be listed for the Dose Selection Randomized Population.

11.9. INTERIM ANALYSES

No interim analysis is planned for this trial.

12. REFERENCE LIST

1. U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research. Guidance for Industry: Assessment of Abuse Potential of Drugs. January 2017.

2. Bowdle TA, Radant AD, Cowley DS, Kharasch ED, Strassman RJ, Roy-Byrne PP. Psychedelic effects of ketamine in healthy volunteers: relationship to steady-state plasma concentrations. Anesthesiology. 1998;88(1):82–8.

3. Kaplan HL. Representation of on-line questionnaires in an editable, auditable database. Behaviour Research Models, Instruments & Computers. 1992;24:373–84.

4. Sternberg, S. High-speed scanning in human memory. Science. 1966;153(3736):652–4.

5. Chen L. An Overview of Regulatory Recommendations for Statistical Approaches to Evaluate Human Abuse Potential Study Data. Presented: Meeting on the Advancement in Abuse Potential Assessments – Building on the FDA Draft Guidance for Industry. Organized by the Cross Company Abuse Liability Council (CCALC), North Bethesda, MD, April 16-17, 2015.

6. Chen L, Tsong Y. Design and Analysis for Drug Abuse Potential Studies: Issues and Strategies for Implementing a Crossover Design. DIA Journal 2007; 41: 481-9.

7. Schoedel K, Shram M, Levy-Cooperman N et al. Defining clinically important differences in subjective abuse potential measures. Presented: 74th Annual Meeting of the College on Problems of Drug Dependence, Palm Springs, CA, 2012.

8. Eaton TA, Comer SD, Revicki DA, Trudeau JJ, van Inwegen RG, Stauffer JW et al. Determining the clinically important difference in visual analog scale scores in abuse liability studies evaluating novel opioid formulations. Qual Life Res. 2012 Aug; 21(6):975–981.

9. Chen L, Bonson K. An equivalence test for the comparison between a test drug and placebo in human abuse potential studies. J Biopharm Stat. 2013; 23:294-306.

10. Sun P. Using Proc Power To Perform Model-Based Power Analysis For Clinical Pharmacology Studies. PharmaSUG2010 – Paper SP05.

13. PROGRAMMING CONSIDERATIONS

All TLFs and statistical analyses will be generated using SAS® for Windows, Release 9.4 (SAS® Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output will adhere to the following specifications.

The PK analyses will be performed by Syneos Health using Phoenix WinNonlin® version 6.4 or higher (Certara USA, Inc., Princeton, NJ, USA).

13.1. GENERAL CONSIDERATIONS

- A separate SAS program will be created for each output.
- Each output will be stored in a separate file.
- Output files will be delivered in Word format. TLFs will be bundled separately with a table of contents for each.
- Numbering of TLFs will follow International Council for Harmonisation (ICH E3 guidance

13.2. TABLE, LISTING, AND FIGURE FORMAT

13.2.1. General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8.
- The data displays for all TLFs will have a minimum 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

13.2.2. Headers

- All output will have the following header at the top left of each page:

Trevi Therapeutics Inc. Protocol TR08 (Syneos Health Study Number 1008910)
Draft/Final Run DDMMMYYYY

- All output will have Page n of N at the top or bottom right corner of each page. TLFs will be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated will appear along with the program name as a footer on each page.

13.2.3. Display Titles

- Each TLF should be identified by the designation and a numeral. (i.e., Table 14.1.1). A decimal system (x.y and x.y.z) will be used to identify TLFs with related contents. The title is centered. The analysis population will be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the Column headers. There will be 1 blank line between the last title and the solid line.

```
Table x.y.z
First Line of Title
Second Line of Title if Needed
Analysis Population
```

13.2.4. Column Headers

- Column headings will be displayed immediately below the solid line described above in initial upper-case characters.
- In the case of PD tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values will be presented under the total column or in separate P-value column (if applicable). Within-treatment comparisons may have P-values presented in a row beneath the summary statistics for that treatment.
- For numeric variables, include "unit" in column or row heading when appropriate.
- Analysis population sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of subjects in the analysis population.

The order of treatments in the tables and listings will be Placebo first in the case of placebo controlled studies and Active comparators first in the case of active comparator trials, followed by a total column (if applicable).

13.2.5. Body of the Data Display

13.2.5.1. General Conventions

Data in columns of a table or listing should be formatted as follows:

- alphanumeric values are left-justified;
- whole numbers (e.g., counts) are right-justified; and
- numbers containing fractional portions are decimal aligned.

13.2.5.2. Table Conventions

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
mild	3
moderate	8
severe	0

  Where percentages are presented in these tables, zero percentages will not be presented and so any counts of 0 will be presented as 0 and not as 0 (0%).
- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups should be included.
- An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more subjects.
- Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more significant digit than the original values, and the SD should be printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

```
n                          xx
Mean (SD)                xxx.x (x.xx)
Median                   xxx.x
Minimum, Maximum         xxx, xxx
```

- P-values should be output in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places. Any P-value less than 0.001 will be presented as <0.001. If the P-value should be less than 0.0001 then present as <0.0001. If the P-value is returned as >0.999 then present as >0.999
- Percentage values will be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Unless otherwise noted, for all percentages, the number of subjects in the analysis population for the treatment group who have an observation will be the denominator. Percentages after zero counts will not be displayed and percentages equating to 100% will be presented as 100%, without any decimal places.

- Tabular display of data for medical history, prior / concomitant medications, and all tabular displays of AE data should be presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by PT), drugs (by ATC1 code), and AEs (by PT) should be displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or P-values which cannot be estimated should be reported as "-".
- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis population presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.
- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject will be included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.
- Where a category with a subheading (such as SOC) has to be split over more than one page, output the subheading followed by "(Cont.)" at the top of each subsequent page. The overall summary statistics for the subheading will only be output on the first relevant page.

13.2.5.3. Listing Conventions

- Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time.
- Missing data will be represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.
- Dates will be printed in SAS® DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates will be represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.
- All observed time values will be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available

13.2.5.4. Figure Conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

13.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes will always begin with “Note:” if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line where possible.
- Subject specific footnotes will be avoided, where possible.
- Footnotes will be used sparingly and must add value to the table, figure, or data listing. If more than six lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., ‘Program : myprogram.sas Listing source: 16.x.y.z’).

14. QUALITY CONTROL

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. Syneos Health Standard Operating Procedures (SOPs) 03.010 and 03.013 provide an overview of the development of such SAS programs. Syneos Health SOP 03.016.02 provides an overview of the pharmacokinetic data analyses and reporting.

Syneos Health SOP 03.009 describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

15. INDEX OF TABLES

The following tables will be produced (table numbers and titles may be different in the final versions):

Header	Table Number	Name	Analysis Population	Template
14.		Tables, Figures, and Graphs Referred to but not Included in the Text		
14.1		Subject Disposition and Demographic Data Summary Tables		
14.1.1		Subject Disposition		
	14.1.1.1	Disposition of Subjects – Dose Selection Phase, Part A	Dose Selection Randomized	T1.1
	14.1.1.2	Subject Populations – Dose Selection Phase, Part A	Dose Selection Randomized	T1.2
14.1.2		Demographic and Baseline Characteristics		
	14.1.2.1	Demographic and Baseline Characteristics – Dose Selection Phase, Part A	Dose Selection Randomized	T1.3
	14.1.2.2	Recreational Drug Use History – Dose Selection Phase, Part A	Dose Selection Randomized	T1.4
	14.1.2.3	Alcohol Use History – Dose Selection Phase, Part A	Dose Selection Randomized	T1.5
14.2		Pharmacokinetic and Pharmacodynamic Data Summary Tables and Figures		
14.2.1		Pharmacodynamic Data Summary Tables and Figures		
14.2.1.1		Pharmacodynamic Data in the Dose Selection Phase		
	14.2.1.1	Pupillometry – Pharmacodynamic Parameters – Dose Selection Phase, Part A	Dose Selection Safety	T2.1
14.2.2		Pharmacokinetic Data Summary Tables and Figures		
	14.2.2.1	Plasma Concentrations of Nalbuphine and its Metabolites M1, M3, M4, and M5 (ng/mL) Over Time by Treatment - Dose Selection Phase, Part A	Dose Selection PK	T3.1
	14.2.2.2	Pharmacokinetic Parameters of Nalbuphine and its Metabolites M1, M3, M4, and M5 (ng/mL) by Dose – Dose Selection Phase, Part A	Dose Selection PK	T3.2
14.3		Safety Data Summary Tables		
14.3.1		Display of Adverse Events		
	14.3.1.1	Treatment-Emergent Adverse Events (TEAEs) – Overall Summary - Dose Selection Phase, Part A	Dose Selection Safety	T4.1
	14.3.1.2	Treatment-Emergent Adverse Events (TEAEs) by System Organ Class and Preferred Term - Dose Selection Phase, Part A	Dose Selection Safety	T4.2
	14.3.1.3	Treatment-Emergent Adverse Events (TEAEs) by System Organ Class, Preferred Term, and Maximum Intensity - Dose Selection Phase, Part A	Dose Selection Safety	T4.
	14.3.1.4	Treatment-Emergent Adverse Events (TEAEs) by System Organ Class, Preferred Term, and Maximum Relationship - Dose Selection Phase, Part A	Dose Selection Safety	T4.4

Header	Table Number	Name	Analysis Population	Template
	14.3.2	Listings of Deaths, Other Serious and Significant Adverse Events - Dose Selection Phase, Part A	Dose Selection Safety	T4.5
14.3.4		Other Safety Data		
14.3.4.1		Clinical Laboratory Data		
14.3.4.1.1		Clinical Chemistry Data		
	14.3.4.1.1.1	Clinical Chemistry: Summary – Dose Selection Phase, Part A	Dose Selection Safety	T5.1
	14.3.4.1.1.2	Clinical Chemistry: Abnormal Results - Listing – Dose Selection Phase, Part A	Dose Selection Safety	T5.3
14.3.4.1.2		Hematology Data		
	14.3.4.1.2.1	Hematology: Summary – Dose Selection Phase, Part A	Dose Selection Safety	T5.1
	14.3.4.1.2.2	Hematology: Abnormal Results - Listing – Dose Selection Phase, Part A	Dose Selection Safety	T5.3
14.3.4.1.3		Urinalysis Data		
	14.3.4.1.3.1	Urinalysis: Summary of Continuous Tests – Dose Selection Phase, Part A	Dose Selection Safety	T5.1
	14.3.4.1.3.2	Urinalysis: Summary of Categorical Tests – Dose Selection Phase, Part A	Dose Selection Safety	T5.2
	14.3.4.1.3.3	Urinalysis: Abnormal Results - Listing – Dose Selection Phase, Part A	Dose Selection Safety	T5.3
14.3.4.2		Vital Signs		
	14.3.4.2.1	Summary of Vital Signs – Dose Selection Phase, Part A	Dose Selection Safety	T6.1
	14.3.4.2.2	Vital Signs: Abnormal Results – Listing – Dose Selection Phase, Part A	Dose Selection Safety	T6.2
14.3.4.3		Electrocardiogram (ECG) Data		
	14.3.4.3.1	Summary of Overall ECG Interpretation – Dose Selection Phase, Part A	Dose Selection Safety	T6.3
	14.3.4.3.2	Summary of ECG Continuous Data – Dose Selection Phase, Part A	Dose Selection Safety	T6.4
	14.3.4.3.3	ECG: Abnormal Results – Listing – Dose Selection Phase, Part A	Dose Selection Safety	T6.5

Templates are provided in Section 19.1.

16. INDEX OF LISTINGS

The following listings will be produced (listing numbers and titles may be different in the final versions):

Header	Listing Number	Name	Analysis Population	Template
16.1.7				
	16.1.7	Randomization Scheme and Code – Dose Selection Phase, Part A	Dose Selection Randomized	L1.1
	16.1.8	Subjects Randomized in Part A	Dose Selection Randomized	L1.2
16.2		Subject Data Listings		
	16.2.1	Subject Disposition and Completion / Discontinuation – Dose Selection Phase, Part A	Dose Selection Randomized	L2
	16.2.2	Protocol Deviations – Dose Selection Phase, Part A	Dose Selection Randomized	L3.1
16.2.3		Subjects Excluded from Analysis		
	16.2.3.1	Inclusion/Exclusion Criteria		L3.2
	16.2.3.2	Inclusion/Exclusion Criteria Violations – Dose Selection Phase, Part A	Dose Selection Randomized	L3.3
	16.2.3.3	Subject Exclusions from Analysis Populations – Dose Selection Phase, Part A	Dose Selection Randomized	L4
16.2.4		Demographics and Other Baseline Characteristics		
16.2.4.1		Demographic Data		
	16.2.4.1	Demographics and Informed Consent – Dose Selection Phase, Part A	Dose Selection Randomized	L5.1
16.2.4.2		Medical History		
	16.2.4.2	Medical History – Dose Selection Phase, Part A	Dose Selection Randomized	L5.2
16.2.4.3		Baseline Characteristics		
	16.2.4.3.1	Recreational Drug Use History – Dose Selection Phase, Part A	Dose Selection Randomized	L5.3
	16.2.4.3.2	Alcohol Use History – Dose Selection Phase, Part A	Dose Selection Randomized	L5.4
	16.2.4.3.3	Nicotine Use – Dose Selection Phase, Part A	Dose Selection Randomized	L5.5
16.2.4.4		Prior and Concomitant Medications		
	16.2.4.4	Prior and Concomitant Medications – Dose Selection Phase, Part A	Dose Selection Randomized	L5.6
16.2.5		Study Drug Administration		
	16.2.5	Study Drug Administration – Dose Selection Phase, Part A	Dose Selection Randomized	L6.1
16.2.6		Pharmacodynamic and Pharmacokinetic Data		
16.2.6.1		Pharmacodynamic Data – Dose Selection Phase		
	16.2.6.1	Pupillometry Data – Dose Selection Phase, Part A	Dose Selection Randomized	L7.1
16.2.6.2		Pharmacokinetic Data		
	16.2.6.2.1	Pharmacokinetic Sample Collection Data and Plasma Concentration Data for Nalbuphine and its Metabolites M1, M3, M4, and M5 (ng/mL) – Dose Selection Phase, Part A	Dose Selection Safety	L7.2

Header	Listing Number	Name	Analysis Population	Template
	16.2.6.2.2	Pharmacokinetic Parameters for Nalbuphine and its Metabolites M1, M3, M4, and M5 – Dose Selection Phase, Part A	Dose Selection PK	L7.3
16.2.7		Adverse Event Listings		
	16.2.7	Adverse Events – Dose Selection Phase, Part A	Dose Selection Randomized	L8a
16.2.8		Listing of Individual Laboratory Measurements by Patient		
16.2.8.1		Clinical Laboratory Data		
	16.2.8.1.1	Clinical Chemistry – Dose Selection Phase, Part A	Dose Selection Randomized	L9.1
	16.2.8.1.2	Hematology – Dose Selection Phase, Part A	Dose Selection Randomized	L9.1
	16.2.8.1.3	Urinalysis – Dose Selection Phase, Part A	Dose Selection Randomized	L9.1
	16.2.8.1.4	Pregnancy and FSH Tests – Dose Selection Phase, Part A	Dose Selection Randomized	L9.2
	16.2.8.1.5	Viral Screen – Dose Selection Phase, Part A	Dose Selection Randomized	L9.3
	16.2.8.1.6	Urine Drugs of Abuse Screen – Dose Selection Phase, Part A	Dose Selection Randomized	L9.4
	16.2.8.1.7	Breath Alcohol Test – Dose Selection Phase, Part A	Dose Selection Randomized	L9.5
16.2.8.2		Other Safety Data		
	16.2.8.2.1	Vital Signs – Dose Selection Phase, Part A	Dose Selection Randomized	L10.1
	16.2.8.2.2	ECG Data – Dose Selection Phase, Part A	Dose Selection Randomized	L10.2
	16.2.8.2.3	Physical Examination Abnormalities – Dose Selection Phase, Part A	Dose Selection Randomized	L10.3
	16.2.8.2.4	Baseline Columbia-Suicide Severity Rating Scale (C-SSRS) – Dose Selection Phase, Part A	Dose Selection Randomized	L10.4

Templates are provided in Section 19.2. These templates show what information will be contained in the listing, but the actual layout (e.g., order of columns, additional columns) may change to reflect what is actually received. Listings may be split into multiple listings if there are too many data points to fit on one page. Numbering of listings may be adjusted to accommodate split listings, listings that are added, listings that are omitted due to no records.

17. INDEX OF FIGURES

The following figures will be produced (figure numbers and titles may be different in the final versions):

Header	Figure Number*	Figure Title	Analysis Population	Tem-plate
14.2.2		Pharmacokinetic Data Summary Tables and Figures		
	14.2.2.1.1.1	Mean (± SD) Plasma Concentration Curves for Nalbuphine and its Metabolites M1, M3, M4, and M5 (ng/mL) by Dose – Linear Scale – Dose Selection Phase, Part A	Dose Selection PK	F2.1
	14.2.2.1.1.2	Mean (± SD) Plasma Concentration Curves for Nalbuphine and its Metabolites M1, M3, M4, and M5 (ng/mL) by Dose – Log-linear Scale – Dose Selection Phase, Part A	Dose Selection PK	F2.1
	14.2.2.1.2.1	Individual Plasma Concentration Curves for Nalbuphine and its Metabolites M1, M3, M4, and M5 (ng/mL) by Dose – Linear Scale – Dose Selection Phase, Part A	Dose Selection PK	F2.2
	14.2.2.1.2.2	Individual Plasma Concentration Curves for Nalbuphine and its Metabolites M1, M3, M4, and M5 (ng/mL) by Dose – Log-linear Scale – Dose Selection Phase, Part A	Dose Selection PK	F2.2
	14.2.2.2.1	Box Plot of C_{max} for Nalbuphine and its Metabolites M1, M3, M4, and M5 – Dose Selection Phase, Part A	Dose Selection PK	F2.3
	14.2.2.2.2	Box Plot of AUC_{last} for Nalbuphine and its Metabolites M1, M3, M4, and M5 – Dose Selection Phase, Part A	Dose Selection PK	F2.3

Templates are provided in Section 19.3.

18. APPENDICES

APPENDIX A: CALCULATIONS

Derived Variable	Variables used	Calculation	Notes
General:			
Age (years)	Date of Informed Consent (ICdate) Date of birth (DOB)	If Informed Consent Form (IC) signed on birthday, then Age = year(ICdate)-year(DOB); Otherwise, Age = INT(ICdate-DOB)/365.25)	The latter formula is only ~60% accurate on birthdays
Body Mass Index (BMI) (kg/m^2)	Weight (WT) (kg) Height (HT) (m)	$BMI = WT / HT^2$	
AE Duration (DD:HH:MM)	Onset date & time (start_dtm) Resolution date & time (stop_dtm)	Duration = stop_dtm - start_dtm	Calculated only for AEs which are resolved and start and stop times are known. If duration is in seconds, then it will be reported as "<1 min".
AE Duration (Days)	Onset date (start_date) Resolution date (stop_date)	Duration = stop_date - start_date+1	Calculated only for AEs that are resolved and start and/or stop times are unknown
Geometric Coefficient of Variation, CV (%)	Data x_i	$CV = 100\% \times \sqrt{e^{z^2} - 1}$, where z^2 is the variance of $\ln(x_i)$	
Derived PK parameters:			
C_{max}	Concentration at time i (C_i) over one inter-dosing interval	Max $_i$ $\{C_i\}$	Missing data are ignored
t_{max}	Concentrations C_i at times t_i over one inter-dosing interval	Smallest t_i at which C_{max} was observed	The first time of peak concentration is used if the peak is obtained more than once

Derived Variable	Variables used	Calculation	Notes
AUC_{last}	Concentrations C_i at times t_i	The area under the plasma concentration vs time curve from time 0 to last measurable concentration (AUC_{last}) is calculated using the formula: $AUC_{\text{last}} = \sum_{i=1}^{n-1} AUC_{(t_i - t_{i+1})}$, where $t_1 = 0$ and $t_n = t$. Concentrations C_i are measured at times t_i, i=1,…,n. Method: • Sections with increasing or equal concentrations ($C_{i+1} \geq C_i$) calculated by linear trapezoidal rule: $AUC_{(t_i - t_{i+1})} = \frac{1}{2} * (C_i + C_{i+1}) * (t_{i+1} - t_i)$ • Sections with decreasing concentrations ($C_{i+1} < C_i$) calculated by log-linear trapezoidal rule: $AUC_{(t_i - t_{i+1})} = \frac{(C_i - C_{i+1}) * (t_{i+1} - t_i)}{(\ln C_i - \ln C_{i+1})}$	The area under the serum concentration-time curve will be calculated using the linear up/ log down trapezoidal rule.
AUC_{inf}	Concentrations C_i at times t_i; C_{last} and k_{el}	$AUC_{\text{inf}} = AUC_{\text{last}} + AUC_{\text{t-inf}}$, where t is the sampling time point of the last measurable concentration. $AUC_{t\text{-}inf}$ is calculated as: C_{last}/k_{el}, where C_{last} is the last measurable concentration taken directly from the raw data.	The $AUC_{t\text{-}inf}$ must be ≤ 20% of the total area for AUC_{inf} to be considered reliable. For subjects with unreliable AUC_{inf} (because of extrapolation >20%), AUC_{inf} will be flagged in the individual data.
k_{el}	Concentrations C_i at times t_i	First order elimination rate constant (k_{el}) associated with the terminal (log-linear) portion of the curve (the negative gradient	At least three samples are needed during the terminal log-linear phase in order to reliably estimate the terminal rate constant. The adjusted

Derived Variable	Variables used	Calculation	Notes
		of the regression of log-concentration versus time in the elimination phase).	square of the correlation coefficient (R-square adjusted) for the goodness of fit of the regression line through the data points must be at least 0.85 for the k_{el} value to be considered reliable. k_{el}, $t_{1/2}$ and AUC_{inf} will be flagged in the individual data Listings if k_{el} value is not reliable.
$t_{½}$	Concentrations C_i at times t_i	Half-life ($t_{½}$), the time for half the drug to be eliminated is calculated as $\ln(2)/k_{el}$	Terminal elimination half-life, calculated as $\ln(2)/k_{el}$. If the time interval between the lower and upper time points used for the regression spans is less than the derived half-life itself then k_{el} and the associated $t_{½}$ will be considered unreliable. k_{el}, $t_{1/2}$ and AUC_{inf} will be flagged in the individual data listings if k_{el} and the associated $t_{½}$ value are not reliable. Flagged PK parameters will be excluded from summarization and statistical analyses.
Derived PD parameters:			
E_{max}	Response at time i (E_i) over one inter-dosing interval	$\text{Max}_{I}\{E_i\}$	Missing data are ignored
E_{min}	Response at time i (E_i) over one inter-dosing interval	$\text{Min}_{I}\{E_i\}$	Missing data are ignored

Derived Variable	Variables used	Calculation	Notes
TE_{max}	Response at time i (E_i) at times t_i over one inter-dosing interval Time at time i ($time_i$)	$TE_{max} = \max_j \{t_j \mid E_j > E_i \forall i\}$	The first time of peak response is used if the peak is obtained more than once
TE_{min}	Response at time i (E_i) at times t_i over one inter-dosing Interval Time at time i ($time_i$)	$TE_{min} = \min_j \{t_j \mid E_j < E_i \forall i\}$	The first time of trough response is used if the trough is obtained more than once
TA_AUE (AUE)	PD effect score E_i at actual elapsed times t_i over one inter-dosing interval.	$AUE_i = (t_i - t_{i-1}) \frac{(E_i + E_{i-1})}{2}$ Then: $AUE = \sum_{i=1}^{n} AUE_i$, summation over all time intervals until the last non-missing PD score.	Trapezoidal rule used to the 2 consecutive non-missing data points Missing data are ignored. The actual elapsed time t_0 for the pre-dose value is set to 0.

19. MOCK-UPS

Attachment: Trevi TR08_1008910_SAP_Mock TLFs_Final_v1.1_08Aug19