Worldwide Clinical Trials Controlled Quality Management Document		
WORLDWIDE CLINICAL TRIALS	Sponsor:	Opiant Pharmaceuticals
	Protocol Number:	OPNT003-PK-002

Statistical Analysis Plan

Title: An Open-Label, Three-Period, Three-Treatment, Six-Sequence, Randomized Crossover Study of the Pharmacokinetics of Intranasal Nalmefene in Healthy Volunteers using Three Dosing Regimens

Protocol Number: OPNT003-PK-002

Protocol Version: 1.0 / 06-AUG-2021

SAP Version 1.0

SAP Issue Date: 16-NOV-2021

SAP Authors: Sangli Therasanathan, MSc,

Kathryn Roupe, PhD

Previous SAP Versions

NA

Worldwide Clinical Trials Controlled Quality Management Document		
WORLDWIDE CLINICAL TRIALS	Sponsor:	Opiant Pharmaceuticals
	Protocol Number:	OPNT003-PK-002

SAP Amendments before database lock

Version	Issue Date	Section	Revision / Addition	Rationale
-				

Table of Contents

1 INTRODUCTION

This document details the planned statistical analyses for Opiant Pharmaceuticals, protocol "OPNT003-PK-002" study titled "An Open-Label, Three-Period, Three-Treatment, Six-Sequence, Randomized Crossover Study of the Pharmacokinetics of Intranasal Nalmefene in Healthy Volunteers using Three Dosing Regimens".

The proposed analyses are based on the contents of the final version of the protocol (dated 06-AUG-2021).

2 STUDY OBJECTIVES

The primary objective is to compare the pharmacokinetics (PK) of 3mg nalmefene hydrochloride IN spray:

- administered as a single dose in one nostril
- administered as a single dose in both the nostril
- administered as two doses in one nostril

The secondary objective is to

- Evaluate the safety and tolerability of IN nalmefene

3 ENDPOINTS

3.1 Pharmacokinetic Endpoints

The following plasma pharmacokinetic parameters for nalmefene will be calculated using non-compartmental analysis:

- Maximum plasma concentration (C_{max})
- Time to maximum plasma concentration (T_{max})
- Area under to curve to the final time with the concentration equal to or greater than the lower limit of quantification [AUC_{0-t}], to infinity [AUC_{inf}], and during the first 30 minutes [$AUC_{0-2.5\ mins}$, $AUC_{0-5\ mins}$, $AUC_{0-7.5\ mins}$, $AUC_{0-10\ mins}$, $AUC_{0-15\ mins}$, $AUC_{0-20\ mins}$ and $AUC_{0-30\ mins}$].
- Terminal elimination rate constant (λ_z)
- Half-life ($t_{½}$)
- Clearance (CL/F)
- Volume of distribution (V_z/F) uncorrected for bioavailability (F)
- Dose-normalized C_{max} and AUCs

3.2 Safety Endpoints

Safety endpoints will include:

- Adverse events (AEs)
- Vital signs (heart rate, sitting blood pressure, and respiration rate)
- Electrocardiogram (ECG)
- Clinical laboratory changes
- Numerical rating scale (NRS) measuring acute nasal pain and nasal irritation (erythema, edema, and erosion) determined from the nasal passage examination following each nasal administration of study drug

4 SAMPLE SIZE

This study is intended to obtain information regarding the PK of intranasal naloxone under the conditions of this study. Twenty-four (24) subjects are planned for this study. The sample size was estimated using a power of 80% and an alpha error of 5% for pair-wise comparisons. The power was defined as the probability of having a 90% confidence interval to a Test/Reference ratio within the acceptance criteria of 80.00 – 125.00%. A difference of zero on a log-scale was assumed for pharmacokinetic parameters across treatments. Assuming an inter-subject CV of approximately 10% (based on the ANOVA CV% for AUCinf determined in Protocol OPNT003-PK-001), at least 18 subjects should complete the study; to account for the possibility of dropouts and unexpected variability, 24 subjects will be enrolled. The number of subjects is deemed appropriate for this type of study.

5 RANDOMIZATION

Twenty-four (24) healthy subjects will be randomly assigned to 6 sequences (4 subjects per sequence). Each subject will receive one of the 3 treatments in each of the 3 treatment periods.

The 6 sequences will be assigned as follows:

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

Where,

- Treatment A: 3 mg, one 0.1 mL spray in one nostril.
- Treatment B: 6 mg, one 0.1 mL spray in each nostril.
- Treatment C: 6 mg, two 0.1 mL sprays in one nostril.

6 PLANNED ANALYSES

No statistical analysis plan (SAP) prepared in advance of the data can be absolutely definitive and the final Clinical Study Report (CSR) may contain additional tables or statistical tests if warranted by the data obtained. The justification for any such additional analyses will be fully documented in the final CSR.

6.1 Analysis Populations

Subjects excluded from the Populations and the reason for their exclusion will be listed in Appendix 16.2 of the CSR.

6.1.1 Safety Population

The safety population will include all subjects who receive at least one administration of the study drugs.

6.1.2 Pharmacokinetic Evaluation Population

Pharmacokinetic Analysis Population for Test 2 versus Test 1 Comparison (B vs. A)

The pharmacokinetic analysis population for Test 2 versus Test 1 comparison will include all subjects who have evaluable pharmacokinetic data on the Test 2 period and on the Test 1 period and did not deviate from the protocol in a way that might affect the evaluation of the pharmacokinetic endpoints.

Pharmacokinetic Analysis Population for Test 3 versus Test 1 Comparison (C vs. A)

The pharmacokinetic analysis population for Test 3 versus Test 1 comparison will include all subjects who have evaluable pharmacokinetic data on the Test 3 period and on the Test 1 period and did not deviate from the protocol in a way that might affect the evaluation of the pharmacokinetic endpoints.

Pharmacokinetic Analysis Population for Test 2 versus Test 3 Comparison (B vs. C)

The pharmacokinetic analysis population for Test 2 versus Test 3 comparison will include all subjects who have evaluable pharmacokinetic data on the Test 2 period and on the Test 3 period and did not deviate from the protocol in a way that might affect the evaluation of the pharmacokinetic endpoints.

6.2 Derived Data

This section describes the derivations required for statistical analysis. Unless otherwise stated, variables derived in the source data will not be re-calculated.

6.2.1 Study Period / Visits

Each visit as per study schedule will be mapped to treatment period and analysis visit for summary tables as given below. Listings will reflect actual period and visit as defined in protocol.

Collected Visit	Analysis Visit	Analysis Period
Screening	Screening	-
Day -1	Day -1	-
Day 1	Day 1	Period 1
Day 2	Day 2	Period 1
Day 3	Day 3	Period 1
Day 4	Day 4	Period 1
Day 5	Day 5	Period 1
Day 6	Day 6	Period 1
Day 7	Day 7	Period 2
Day 8	Day 8	Period 2
Day 9	Day 9	Period 2
Day 10	Day 10	Period 2
Day 11	Day 11	Period 2
Day 12	Day 12	Period 2
Day 13	Day 13	Period 3
Day 14	Day 14	Period 3
Day 15 (Discharge)	EOS / ET	-
Early Termination	EOS / ET	-
Follow-Up Phone Call	FUP	-

Any Discharge assessments taken more than once will be mapped as “DIS – Unscheduled” in listings.

6.2.2 Race

Where more than one race category has been selected for a subject, these race categories will be combined into a single category labeled “Multiple Race” in the summary tables. The listings will reflect the original selected categories.

6.2.3 Age

Age at informed consent will be calculated in SAS as

Age (years) = floor ((intck('month',BRTHDTC,RFICDTC) - (day(RFICDTC) < day(BRTHDTC))) / 12)

where BRTHDTC is reported birthdate and RFICDTC is informed consent date.

6.2.4 Baseline

Baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the subject receives the first dose of study drug.

For variables that will be summarized by treatment, the Baseline for each period is defined as the last non-missing value (either scheduled, unscheduled or repeat) that is collected before dosing, in the respective period.

Change from Baseline = Result at visit / timepoint – Result at Baseline

6.2.5 Duration / Study Day / Time

Study day will be calculated as the number of days from first dose of study drug.

- date of event – date of first dose of study drug + 1, for events on or after first dose
- date of event – date of first dose of study drug, for events before first dose

6.2.6 Conventions for Missing and Partial Dates

It is not expected that there will be any missing dates, however in the rare case that an Adverse Event (AE) start date or time is missing and it is unclear whether the AE is treatment emergent or not then a conservative approach will be taken and it will be assumed that the AE occurred after first dosing.

Similarly, if Concomitant medications have missing end date and it is unclear whether it is prior or concomitant, then a conservative approach will be taken, and it will be assumed that the medication was concomitant.

All dates presented in the individual subject listings will be as recorded on the Electronic Case Report Form (eCRF).

6.2.7 Inexact Values

In the case where a safety laboratory variable is recorded as "> x", "≥ x", "< x" or "≤ x", a value of x will be taken for analysis purposes.

6.2.8 Not Done / Missing

For safety assessments where shift summaries are required (such as, physical examination), records will be imputed for all subjects who received study drug in the respective part in all scheduled visits and marked as 'Not Done/Missing' if either the subjects did not attend the visit, or discontinued or had missing assessment at the respective visit.

6.2.9 Unscheduled Visits

Only scheduled post-baseline laboratory and vital signs values will be tabulated. Post-baseline repeat / unscheduled assessments will be disregarded, although these post-baseline assessments will be listed in the relevant appendices to the CSR.

6.2.10 PK Parameters

6.2.10.1 Concentration-Time Data

Blood samples for the characterization of nalmefene in plasma will be collected prior to dosing (within 15 minutes) and at approximately 2.5, 5, 7.5, 10, 15, 20, 30, 45 minutes and 1, 2, 3, 4, 6, 8, 12, 18, 24 and 48 hours after drug administration for each study period.

Treatments to be administered are:

- Treatment A: T1: 3 mg, one 0.1 mL spray in one nostril.
- Treatment B: T2: 6 mg, one 0.1 mL spray in each nostril.
- Treatment C: T3: 6 mg, two 0.1 mL sprays in one nostril.

Individual plasma concentrations of nalmefene will be listed by treatment and summarized by descriptive statistics: number of non-missing observations (n), arithmetic mean (mean), standard deviation (SD), median, minimum (min), maximum (max), and coefficient of variation (CV%). Individual and mean plasma concentrations versus time profiles will be presented graphically in linear and semi-logarithmic scale. For individual subject concentration-time data, spaghetti plots (all subjects in one plot per treatment) and individual subject plots (all three treatments in one plot

for each subject) will be created. Mean data will be plotted using nominal sample times and individual data will be plotted using actual times.

For the presentation of concentration-time data, concentrations that are below the limit of quantitation (BLQ) will be set to zero.

6.2.10.2 PK Parameters

Concentration-time data for nalmefene will be analyzed using noncompartmental methods in Phoenix™ WinNonlin® (Version 8.1 or higher, Certara, L.P.) in conjunction with the internet-accessible implementation of Pharsight® Knowledgebase Server™ (PKSO; Version 4.0.4, Certara, L.P.).

During the PK analysis, concentrations below the limit of quantitation (BLQ) up to the time of the first quantifiable concentration will be treated as zero. Embedded (values between 2 quantifiable concentrations) and terminal BLQ concentrations will be treated as "missing".

Calculation of the PK characteristics will be based on actual elapsed times [h] (relative to time of dose). If actual times are missing, nominal times may be used following discussion with Sponsor and will be documented in the CSR.

The following PK parameters will be calculated for nalmefene:

Parameter	Definition
C_{max}	Maximum concentration, determined directly from individual concentration-time data
C_{max}/Dose	C_{max} adjusted for the nominal administered dose
T_{max}	Time of maximum observed concentration, obtained directly from the observed concentration versus time data
AUC_{0-x}	The area under the concentration-time curve from time 0 (predose) to time x, where x = 2.5, 5, 7.5, 10, 15, 20, and 30 min; calculated by the linear-up/log-down trapezoidal method
AUC_{0-x}/Dose	AUC_{0-x} adjusted for the nominal administered dose
AUC_{0-t}	Area under the concentration–time curve from time-zero to the time of the last quantifiable concentration; calculated using the linear-up/log-down trapezoidal method

Parameter	Definition
AUC_{0-t}/Dose	AUC_{0-t} adjusted for the nominal administered dose
AUC_{inf}	Area under the concentration–time curve extrapolated to infinity, calculated as: $AUC_{inf} = AUC_{0-t} + C_{last}/\lambda_z$, where C_{last} is the last quantifiable concentration and λ_z is the terminal elimination rate constant. The percentage of AUC_{inf} based on extrapolation should be <30.0%
AUC_{inf}/Dose	AUC_{inf} adjusted for the nominal administered dose
$AUC_{\%Extrap}$ (%)	The percentage of AUC_{inf} based on extrapolation, calculated as: $(AUC_{inf}-AUC_{0-t})/AUC_{inf}] \times 100$
K_{el} (λ_z; Lambda-z)	Lambda-z (K_{el}, λ_z) is the terminal-phase elimination rate constant, estimated by linear regression of logarithmically-transformed concentration versus time data (linear-up/log-down trapezoidal method; additional criteria are summarized below)
$t_{½}$	The terminal phase half-life for drug concentrations in plasma is calculated as: $t_{½} = \ln(2)/\lambda_z$
CL/F	The apparent total plasma clearance, calculated as: CL/F=Dose/AUC_{inf}, where F is the bioavailability
Vz/F	The apparent volume of distribution, calculated as: V_z/F=Dose/($AUC_{inf} \times \lambda_z$), where F is the bioavailability
C_{last}	Last quantifiable concentration
T_{last}	Time of the last quantifiable concentration

Lambda-z (K_{el}) Criteria

The following criteria will be used to report K_{el}:

- At least three quantifiable concentrations will be used in the regression

- C_{max} or data prior to C_{max} will not be included in the regression.
- The adjusted regression coefficient (R^2 adj) should be ≥ 0.80.

If these acceptance criteria are not met, K_{el} and descriptive parameters (K_{el} time range, Adj R^2, etc.) will be retained in a parameter listing for informational purposes; K_{el} will be excluded from summary statistics. Parameters calculated using K_{el} ($t_{½}$, CL/F, V_z/F) will be reported as ND (not determinable).

If K_{el} acceptance criteria are met and AUC_{inf} is estimable, the following criteria are used to report AUC_{inf}:

- The percentage of AUC_{inf} based on extrapolation should be <30.0%.

If the percentage of AUC_{inf} based on extrapolation is 30.0% or greater, AUC_{inf} and $AUC_{\%extrap}$ will be excluded from summary statistics, subsequent PK calculations (e.g. CL/F, V_z/F), and statistical analysis (e.g. ANOVA).

Individual PK parameters will be listed by treatment and summarized by descriptive statistics: n, mean, SD, median, min, max, CV%, geometric mean, and geometric CV%.

6.3 Conventions

All clinical data listings, summaries, figures and statistical analyses will be generated using SAS (Version 9.4 or higher)[1].

Summaries of the clinical data will be presented by treatment and/or treatment sequence unless otherwise stated.

PK data listings, summaries, figures, and statistical analyses will be generated using Phoenix™ WinNonlin® (Version 8.1 or higher)[2] or SAS (Version 9.4 or higher)[1]. PK concentration data will be summarized by treatment at each nominal sample time. PK parameter data will be summarized by treatment.

Treatment labels will be displayed as follows:

Treatment A Treatment B Treatment C

Footnotes describing each treatment will be provided in each output.

Treatment sequence labels will be displayed as follows:

Sequence 1 Sequence 2 Sequence 3 Sequence 4 Sequence 5 Sequence 6

For safety assessment that are summarized by visit/timepoint, treatment and/or treatment sequence will be displayed in footnote as follows:

Treatment A: 3 mg (one 0.1 mL spray of 30 mg/mL nalmefene hydrochloride in one nostril)

Treatment B: 6 mg (one 0.1 mL sprays of 30 mg/mL nalmefene hydrochloride in each nostril)

Treatment C: 6 mg (two 0.1 mL sprays of 30 mg/mL nalmefene hydrochloride in one nostril)

"Sequence 1" represents subjects taking Treatment A in period 1, Treatment B in period 2 and Treatment C in period 3; "Sequence 2" represents subjects taking Treatment B in period 1, Treatment C in period 2 and Treatment A in period 3; "Sequence 3" represents subjects taking Treatment C in period 1, Treatment A in period 2 and Treatment B in period 3; "Sequence 4" represents subjects taking Treatment A in period 1, Treatment C in period 2 and Treatment B in period 3; "Sequence 5" represents subjects taking Treatment B in period 1, Treatment A in period 2 and Treatment C in period 3; "Sequence 6" represents subjects taking Treatment C in period 1, Treatment A in period 2 and Treatment B in period 3.

Listings will be sorted in the following order treatment sequence, subject, visit and parameter unless otherwise stated. All data will be listed.

For clinical data, continuous variables will be summarized by the number of non-missing observations, arithmetic mean, median, standard deviation, and minimum and maximum.

Categorical variables will be summarized by presenting the frequency and percent. Percentages will be based on the number of non-missing observations or the subject population unless otherwise specified. For each variable, all categories will be shown. Zero frequencies (but not the percent) within a category will be presented.

6.3.1 Decimal Places

Derived data where it is known in advance the result will be an integer for example, such as age, will be presented with zero decimal places.

Mean and median will be displayed to one more decimal place than the data, standard deviation will have two more decimal places, and the minimum and maximum will be displayed to the same number of decimal places as reported in the raw data. Percentages will be displayed with one decimal place.

For PK data, individual concentrations and PK parameters will be reported to 3 significant figures. For summary statistics, n will be reported as a whole number; mean, SD, median, min, max, geometric mean, CV%, and geometric CV% will be reported to the same precision as for individual

data. p-values will be reported to 4 decimal places. Percent ratios of the geometric least squares means and associated 90% confidence intervals will be reported to 2 decimal places. Time will be presented to 3 significant figures.

6.4 Subject Disposition

Subject disposition will be summarized for all randomized subjects as follows:

- The number of subjects who were randomized; number and percentage of subjects in each analysis population will be summarized by treatment sequence and overall.
- The number and percentage of subjects who completed the study and who terminated early, along reason for early termination, will be summarized based on the Safety Population.

The Safety and PK Evaluation Population will be based on actual treatment received. Percentage for safety population will be based on randomized subjects. Percentages for all other categories will be based on Safety Population. Percentage for "Reason for withdrawal" is based on number of non-completers.

A listing of population flags, disposition details and reason for exclusion from population will be provided.

In Mock Shells: Table 14.1.1.1, Listing 16.2.1.1, Listing 16.2.3.1.

6.5 Protocol Deviations

A listing of protocol deviations will be provided within Appendix 16.2 of the CSR.

In Mock Shells: Listing 16.2.2.1.

6.6 Demographics and Baseline Comparability

Subject demographics will be summarized by treatment sequence and overall. Categorical and continuous variables will be provided in the same table. The following variables will be presented: age at Informed Consent (years), sex, ethnicity, race, baseline height (cm), baseline weight (kg), baseline BMI (kg/m^2). Percentages will be based on the respective population.

The summaries will be repeated for Safety and PK Evaluation Populations (as per ICH E3 Guidelines). If the populations are the same, then demographic summary for PK Evaluable Population will be removed.

A listing of subject demographics, baseline characteristics and contraception details will be provided.

In Mock Shells: Table 14.1.2.1 to 14.1.2.2, Listing 16.2.4.1.

6.7 Medical History

Previous and ongoing conditions at screening will be listed for the Safety Population. Conditions will be coded using the Medical Dictionary of Regulated Activities (MedDRA, version 24.1 or higher) and primary SOC and PT will be presented in listings.

In Mock Shells: Listing 16.2.4.2.

Prior conditions are defined as all conditions starting and stopping before the date of first dose of study drug. Ongoing conditions are defined as conditions present on or after the date of first dose of study drug.

6.8 Prior and Concomitant Medications

Prior and concomitant medications will be listed for the Safety Population. Medications will be coded using the WHO Drug Dictionary (version Sep 2021 or later). Prior medications are defined as all medications that ended before the date of first dose of study drug. Concomitant medications are defined as medications ongoing on or after the date of first dose of study drug.

In Mock Shells: Listing 16.2.4.3.

6.9 Exposure to Study Drug

All dosing information will be listed.

In Mock Shells: Listing 16.2.5.1.

6.10 Pharmacokinetic Analyses

The dose-normalized pharmacokinetic parameters C_{max}, AUC_{inf}, $AUC_{0\text{-}2.5\ mins}$, $AUC_{0\text{-}5\ mins}$, $AUC_{0\text{-}7.5\ mins}$, $AUC_{0\text{-}10\ mins}$, $AUC_{0\text{-}15\ mins}$, $AUC_{0\text{-}20\ mins}$ and $AUC_{0\text{-}30\ mins}$ for nalmefene will be compared between the treatments using an analysis of variance (ANOVA) model with treatment, period, sequence, and subject within sequence as the factors using the natural logarithms (ln) of the dose-normalized parameters. The following comparisons will be made:

- 6 mg IN (2 x 3 mg in one nostril; T3, Treatment C) vs. 3 mg IN (in one nostril; T1, Treatment A)
- 6 mg IN (3 mg in each nostril; T2, Treatment B) vs. 3 mg IN (in one nostril; T1, Treatment A)
- 6 mg IN (3 mg in each nostril; T2, Treatment B) vs. 6 mg IN (2 x 3 mg in one nostril; T3, Treatment C)

Confidence intervals (CI) (90%) will be constructed for the geometric mean ratios, using the log-transformed data and the two one-sided t-tests procedure. The point estimates and confidence

limits will be exponentiated back to the original scale. Comparability between the nalmefene intranasal 2 sprays and nalmefene intranasal 1 spray will be assessed from the geometric mean ratios and 90% CIs. All three will be included in the same ANOVA model will separate contrasts defined for each comparison.

6.11 Safety Analyses

The safety analyses will be presented by the treatment received for the Safety Population.

6.11.1 Adverse Events

All AEs will be coded by system organ class (SOC) and preferred term (PT) using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA, version 24.1 or higher) and summarized by treatment and overall.

A treatment emergent adverse event (TEAE) is defined as:

- Any AE that has an onset on or after the first dose of study drug.
- Any pre-existing AE that has worsened in severity on or after the first dose of study drug.

The following rules will be used to assign a TEAE to a treatment group:

- A TEAE will be assigned to the treatment received immediately before onset.
- Any TEAE reported within the washout period between doses will be attributed to the previous treatment.
- Any TEAE continued to multiple periods will be attributed to the period where it is started.

A treatment-related AE is defined as an AE as being possibly, probably or definitely related to the study drug. If an AE has missing relationship it is assumed to be related to the study drug for analysis purposes.

Maximum severity will be assumed for an AE with missing severity.

The following tables will be presented for AEs:

- Overall incidence and the number of TEAEs, Related TEAEs, Serious TEAEs, Serious Related TEAEs, Severity and Relationship to IMP.
- TEAE by system organ class and preferred term, incidence, and number of events.
- Treatment related TEAE by system organ class and preferred term, incidence, and number of events.
- Serious TEAE by system organ class and preferred term, incidence, and number of events.

- Treatment related serious TEAE by system organ class and preferred term, incidence, and number of events.
- TEAE leading to early withdrawal by system organ class and preferred term, incidence
- TEAE by system organ class, preferred term and maximum severity, incidence. If a subject had multiple occurrences of the same PT within a treatment period, it is counted once with maximum severity under the PT; if a subject had multiple PTs within the SOC with different grades of maximum severity, it is counted once within each applicable severity grade within the SOC and Any TEAE categories.
- TEAE by system organ class, preferred term and closest relationship, incidence. If a subject had multiple occurrences of the same PT within a treatment period, it is counted once with closest relationship under the PT; if a subject had multiple PTs within the SOC with different grades of closest relationship, it is counted once within each applicable relationship category within the SOC and Any TEAE categories. Listing of Serious TEAEs (presented in the Table section of the appendices).
- Listing of Deaths (presented in the Table section of the appendices).
- Listing of Adverse events leading to Early Withdrawal (presented in the Table section of the appendices).

All AEs will be separately listed.

In Mock Shells: Tables 14.3.1.1 to 14.3.1.8, Tables 14.3.2.1 to 14.3.2.3, Listing 16.2.7.1

6.11.2 Laboratory Data

The following laboratory tests will be performed at Screening and during discharge (or early termination).

Hematology	Urinalysis	Serum Chemistry	Coagulation
Hemoglobin Hematocrit Red blood cells Total white blood cells Automated differential blood count Platelet count	Specific gravity Glucose Bilirubin Ketones Blood pH Protein Nitrite Leukocyte esterase	Total protein Albumin Blood urea nitrogen Creatinine Alkaline Phosphatase Alanine aminotransferase Aspartate aminotransferase Total bilirubin Sodium Potassium Chloride CO_2 Calcium Glucose Total cholesterol	Prothrombin time Activated partial thromboplastin time

Descriptive statistics of the observed values for Baseline and EOS/ET visit and change from Baseline (continuous data) to EOS/ET will be presented for each hematology, urinalysis, serum chemistry parameter and coagulation markers by treatment sequence and overall. Shift summaries of normal range indicators (Low, Normal and High) from Baseline to Discharge visit will be presented by treatment sequence.

All hematology, urinalysis, serum chemistry and coagulation markers data will be listed.

A separate listing of any out of range laboratory measurements recorded throughout the study will be presented.

All other laboratory data, including Viral Serology, Serum FSH, Pregnancy Test, and Urine Drug, Alcohol, Cotinine, Substance use and COVID-19 PCR Test will be listed only.

In Mock Shells: Tables 14.3.4.1 to 14.3.4.9, Listing 16.2.8.1 to 16.2.8.9

6.11.3 Vital Signs

All Vital signs except temperature will be tabulated for Baseline, 0.25 h, 0.5 h, 1 h, 2 h, 4 h, 8 h, 24 h and 48 h post-dose and the respective changes from Baseline, per treatment. Temperature will be tabulated for Baseline and EOS/ET and the change from Baseline, per treatment. In addition, vital signs values will be tabulated for Baseline, EOS/ET, and change from Baseline to EOS/ET by treatment sequence and overall.

Descriptive statistics for the following vital signs will be presented:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate (beats/min)
- Respiration rate (breath/min)
- Body temperature (°Celsius)

Also, Shift tables in relation to investigator assessment i.e. Normal, Abnormal NCS (Not Clinically Significant), and Abnormal CS (Clinically Significant), from Baseline to each post-baseline visits will be presented. EOS/ET visit will be presented by Treatment sequence and all other post-baseline visits will be presented by treatment.

All vital sign data, including details of any clinically significant values will be listed.

In Mock Shells: Tables 14.3.5.1 and 14.3.5.2, Listing 16.2.8.10

6.11.4 Electrocardiogram Data

ECG values will be tabulated for Baseline, day 6, day 12 and EOS/ET, and change from Baseline to day 6 and 12, and change from Baseline to EOS by treatment sequence and overall. Parameters will be listed in the order given below and in units collected.

- Ventricular rate (bpm)
- PR Duration (ms)
- RR interval (ms)
- QRS Duration (ms)
- QT interval (ms)
- QTc interval (ms) [Fridericia's formula - QTcF]

Shift tables in relation to the overall interpretation i.e. Normal, Abnormal NCS, and Abnormal CS, from Baseline to each follow-up visit will be presented.

All ECG data, including details of any abnormalities, will be listed.

In Mock Shells: Table 14.3.6.1 and 14.3.6.2, Listing 16.2.8.11

6.11.5 Physical Examination

Shift in physical examination data (Normal, Abnormal NCS, Abnormal CS) from baseline to EOS/ET will be summarized by treatment sequence and overall.

All data, including details of clinically significant findings will be listed.

In Mock Shells: Table 14.3.6.3, Listing 16.2.8.12

6.11.6 Nasal Passage Examination

Nasal passage examination results will be presented for Baseline, 5 minutes, 1, 8, 24 and 48 hour post-dose by treatment. Shift in results from Baseline to all post-dose measurements will be presented by treatment.

Nasal irritation will be determined on the following scale:

Nasal Irritation Scale

0 - Normal appearing mucosa, no bleeding

1 - Inflamed mucosa (erythema/edema), no bleeding

2 - Minor bleeding which stops within 1 minute

3 - Minor bleeding, taking 1-5 minutes to stop

4 - Substantial bleeding for 4-60 minutes, does not require medical intervention

5 - Ulcerated lesions, bleeding which requires medical intervention

A shift table for nasal irritation scale from Baseline to post-baseline time points will be presented.

All nasal passage examination data will be listed for the Safety Population.

In Mock Shells: Table 14.3.6.4.1 and 14.3.6.4.2, Listing 16.2.8.13

6.11.7 Numerical Rating Scale

Descriptive statistics of NRS data at Baseline, 15 minutes and 60 minutes post-dose will be presented by treatment and overall. A listing of all NRS data will be provided for the Safety Population.

In Mock Shells: Table 14.3.6.5, Listing 16.2.8.14

6.11.8 Smell Test

Descriptive statistics of smell test score for Baseline and post-baseline time points will be presented by treatment and overall. Additionally, all smell test data will be listed for the Safety Population.

In Mock Shells: Table 14.3.6.6, Listing 16.2.8.15

7 CHANGES TO PLANNED PROTOCOL ANALYSIS

During the analysis and reporting process, any deviations from the statistical analysis plan will be described and justified in writing in the CSR.

8 REFERENCES

1. SAS Institute Inc., Cary, NC, 27513, USA
2. Phoenix™ WinNonlin® (Version 8.1, Certara, L.P.)

9 LIST OF TABLES, FIGURES AND LISTINGS

The following table includes details of the tables, figures and listings to be included within each section of the electronic common technical document (eCTD). The eCTD section is shown in bold. The following validation methods maybe used:

- Independent programming of numbers and manual review of format (IP)
- Independent programming by statistician of numbers and manual review of format (Stat IP)
- Manual review (MR)
- Code review (CR)

Table Number	Table Title	Validation Method	Shell Number (if repeat)
Items in bold are not table titles but references to the section headings within eCTD.			
14.1	**Demographics Data**		
14.1.1	**Disposition**		
14.1.1	Subject Disposition, Analysis Populations – All Randomized Subjects	IP	-
14.1.2	**Demographics**		
14.1.2.1	Summary of Demographics - Safety Population	IP	-
14.1.2.2	Summary of Demographics - PK Population	IP	14.1.2.2
14.1.3	**Baseline Characteristics**		
	Not Applicable		
14.2	**Efficacy Data**		
	Not Applicable		
14.3	**Safety Data**		
14.3.1	**Displays of Adverse Events**		
14.3.1.1	Overall Summary of Treatment Emergent Adverse Events (TEAEs) – Safety Population	IP	-
14.3.1.2	TEAEs By Primary System Organ Class and Preferred Term – Safety Population	IP	-
14.3.1.3	Treatment Related TEAEs By Primary System Organ Class and Preferred Term – Safety Population	IP	14.3.1.2
14.3.1.4	Serious TEAEs By Primary System Organ Class and Preferred Term – Safety Population	IP	14.3.1.2
14.3.1.5	Related Serious TEAEs by Primary System Organ Class and Preferred Term – Safety Population	IP	14.3.1.2
14.3.1.6	Treatment Emergent Adverse Events leading to Early Withdrawal by SOC and PT – Safety Population	IP	14.3.1.2

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.3.1.7	Treatment Emergent Adverse Events by SOC, PT and Maximum Severity - Safety Population	IP	-
14.3.1.8	Treatment Emergent Adverse Events by SOC, PT and Closest Relationship - Safety Population	IP	-
14.3.2	**Listings of Deaths, Other Serious and Significant Adverse Events**		
14.3.2.1	Listing of SAEs – Safety Population	IP	16.2.7.1
14.3.2.2	Listing of Deaths – Safety Population	IP	16.2.7.1
14.3.2.3	Listing of TEAEs Leading to Early Withdrawal – Safety Population	IP	16.2.7.1
14.3.3	**Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events**		
14.3.4	**Abnormal Laboratory Values**		
14.3.4.1	Hematology Data, Descriptive Statistics - Safety Population	IP	-
14.3.4.2	Clinical Chemistry Data, Descriptive Statistics - Safety Population	IP	14.3.4.1
14.3.4.3	Coagulation Data, Descriptive Statistics - Safety Population	IP	14.3.4.1
14.3.4.4	Urinalysis Data, Descriptive Statistics - Safety Population	IP	14.3.4.1
14.3.4.5	Hematology Data, Shift Summary - Safety Population	IP	-
14.3.4.6	Clinical Chemistry Data, Shift Summary - Safety Population	IP	14.3.4.5
14.3.4.7	Clinical Chemistry Data, Shift Summary - Safety Population	IP	14.3.4.5
14.3.4.8	Urinalysis Data, Shift Summary - Safety Population	IP	16.2.8.1
14.3.4.9	Listing of Out of Range Laboratory Data – Safety Population	IP	-
14.3.5	**Vital Signs and Physical Examination**		
14.3.5.1	Vital Signs, Change from Baseline – Safety Population	IP	-
14.3.5.2	Vital Signs, Shift Summary – Safety Population	IP	-
14.3.6	**Other Safety**		
14.3.6.1	12 Lead ECG, Descriptive Statistics - Safety Population	IP	-
14.3.6.2	12 Lead ECG, Shift Summary - Safety Population	IP	-
14.3.6.3	Physical Examination Data, Shift from Baseline - Safety Population	IP	-

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.3.6.4.1	Nasal Cavity Examination Data, Descriptive Statistics - Safety Population	IP	-
14.3.6.4.2	Nasal Cavity Examination Data, Shift from Baseline - Safety Population	IP	-
14.3.6.5	Numerical Rating Scale Data, Descriptive Statistics - Safety Population	IP	-
14.3.6.6	Brief Smell Identification Score Data, Descriptive Statistics - Safety Population	IP	-
14.3.7	**Concomitant Medication**		
	Not Applicable		
14.4	**PK Tables**		
14.4.1	Descriptive Statistics for Concentration-Time Data of Nalmefene after IN Administration of 3 mg Nalmefene HCl in One Nostril (T1, Treatment A), 3 mg (6 mg Total Dose) Nalmefene HCl in Each Nostril (Treatment B, T2), and 6 mg Nalmefene HCl in One Nostril (Treatment C, T3) – PK Evaluation Population	IP	-
14.4.2	Plasma PK Parameters of Nalmefene after IN Administration of 3 mg Nalmefene HCl in One Nostril (T1, Treatment A), 3 mg (6 mg Total Dose) Nalmefene HCl in Each Nostril (Treatment B, T2), and 6 mg Nalmefene HCl in One Nostril (Treatment C, T3) – PK Evaluation Population	IP	-
14.4.3	Plasma PK Partial AUCs of Nalmefene after IN Administration of 3 mg Nalmefene HCl in One Nostril (T1, Treatment A), 3 mg (6 mg Total Dose) Nalmefene HCl in Each Nostril (Treatment B, T2), and 6 mg Nalmefene HCl in One Nostril (Treatment C, T3) – PK Population	IP	-
14.4.4	Plasma Dose-Normalized Parameters of Nalmefene after IN Administration of 3 mg Nalmefene HCl in One Nostril (T1, Treatment A), 3 mg (6 mg Total Dose) Nalmefene HCl in Each Nostril (Treatment B, T2), and 6 mg Nalmefene HCl in One Nostril (Treatment C, T3) – PK Population	IP	-
14.4.5	Dose-Normalized Plasma PK Partial AUCs of Nalmefene after IN Administration of 3 mg Nalmefene	IP	-

Table Number	Table Title	Validation Method	Shell Number (if repeat)
	HCl in One Nostril (T1, Treatment A), 3 mg (6 mg Total Dose) Nalmefene HCl in Each Nostril (Treatment B, T2), and 6 mg Nalmefene HCl in One Nostril (Treatment C, T3) – PK Population		
14.4.6	Statistical Analysis of the Natural Log-Transformed, Dose-Normalized Exposure Parameters of Nalmefene Comparing 6 mg Nalmefene Hydrochloride in One Nostril (Treatment C, T3, Test) and 3 mg Nalmefene Hydrochloride in One Nostril (Treatment A, T1, Reference) – PK Evaluation Population	IP	-
14.4.7	Statistical Analysis of the Natural Log-Transformed, Dose-Normalized Exposure Parameters of Nalmefene Comparing 3 mg Nalmefene Hydrochloride in Each Nostril (6 mg Total Dose, Treatment B, T2, Test) and 3 mg Nalmefene Hydrochloride in One Nostril (Treatment A, T1, Reference) – PK Evaluation Population	IP	-
14.4.8	Statistical Analysis of the Natural Log-Transformed, Dose-Normalized Exposure Parameters of Nalmefene Comparing 3 mg Nalmefene Hydrochloride in Each Nostril (6 mg Total Dose, Treatment B, T2, Test) and 6 mg Nalmefene Hydrochloride in One Nostril (Treatment C, T3, Reference) – PK Evaluation Population	IP	-
14.5	**PD Tables**		
14.6	**Other Data**		

Worldwide Clinical Trials Controlled Quality Management Document		
WORLDWIDE CLINICAL TRIALS	Sponsor:	Opiant Pharmaceuticals
	Protocol Number:	OPNT003-PK-002

Figure Number	Figure Title	Validation Method	Shell Number (if repeat)
14.4.1	Nalmefene Concentration-Time Data, Mean Profiles on Linear and Semi-Logarithmic Scales after Intranasal (IN) Administrations of 3 mg Nalmefene Hydrochloride in One Nostril (T1), 2 x 3 mg Nalmefene Hydrochloride in Each Nostril (6 mg Total Dose, T2), and 6 mg Nalmefene Hydrochloride in One Nostril (T3) – PK Evaluation Population	IP	-
14.4.2	Nalmefene Concentration-Time Data, All Subject Profiles on Linear and Semi-Logarithmic Scales after Intranasal (IN) Administrations of 3 mg Nalmefene Hydrochloride in One Nostril (T1), 2 x 3 mg Nalmefene Hydrochloride in Each Nostril (6 mg Total Dose, T2), and 6 mg Nalmefene Hydrochloride in One Nostril (T3) – PK Evaluation Population	IP	-
14.4.3	Nalmefene Concentration-Time Data, Individual Profiles on Linear and Semi-Logarithmic Scales after Intranasal (IN) Administrations of 3 mg Nalmefene Hydrochloride in One Nostril (T1), 2 x 3 mg Nalmefene Hydrochloride in Each Nostril (6 mg Total Dose, T2), and 6 mg Nalmefene Hydrochloride in One Nostril (T3) – PK Evaluation Population	IP	-
14.4.4	Concentration-Time Profiles for Nalmefene with Linear Regression for Estimating the Terminal Elimination Rate - PK Evaluation Population	IP	-

Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
16.2	**Subject Data Listings**		
16.2.1	**Discontinued Subjects**		
16.2.1.1	Subject Disposition – All Randomized Subjects	IP	-
16.2.2	**Protocol Deviations**		
16.2.2.1	Protocol Deviations – Safety Population	IP	-
16.2.3	**Subjects Excluded from the Efficacy Analyses**		
16.2.3.1	Analysis Populations – All Randomized Subjects	IP	-
16.2.4	**Demographic Data**		
16.2.4.1	Demographic Data – Safety Population	IP	-
16.2.4.2	Medical History – Safety Population	IP	-
16.2.4.3	Prior and Concomitant Medications - Safety Population	IP	-
16.2.5	**Compliance and / or Drug Concentration Data**		
16.2.5.1	Exposure Data – Safety Population	IP	-
16.2.6	**Individual Efficacy Response Data**		
16.2.6.1	Nalmefene Concentration-Time Data Listing – Safety Population	IP	-
16.2.6.2	Terminal Elimination Rate of Nalmefene in Plasma for Individual Subjects – PK Evaluation Population	IP	-
16.2.6.3	PK Output Text – PK Evaluation Population	IP	-
16.2.6.4	SAS Output Text (ANOVA) – PK Evaluation Population	IP	-
16.2.7	**Adverse Event Listings**		
16.2.7.1	Adverse Event Data – Safety Population	IP	-
16.2.8	**Individual Laboratory Measurements and Other Safety**		
16.2.8.1	Hematology Data – Safety Population	IP	-
16.2.8.2	Serum Chemistry Data – Safety Population	IP	16.2.8.1
16.2.8.3	Coagulation Data – Safety Population	IP	16.2.8.1
16.2.8.4	Urinalysis Data – Safety Population	IP	16.2.8.1
16.2.8.5	Drug and Alcohol Screen – Safety Population	IP	-
16.2.8.6	Serology Data – Safety Population	IP	16.2.8.5
16.2.8.7	Pregnancy Test Data – Safety Population	IP	-
16.2.8.8	Substance Use Data - Safety Population	IP	-

Worldwide Clinical Trials Controlled Quality Management Document		
WORLDWIDE CLINICAL TRIALS	Sponsor:	Opiant Pharmaceuticals
	Protocol Number:	OPNT003-PK-002

Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
16.2.8.9	COVID-19 PCT Test Data – Safety Population	IP	-
16.2.8.10	Vital Signs Data – Safety Population	IP	-
16.2.8.11	ECG Data – Safety Population	IP	-
16.2.8.12	Physical Examination Data – Safety Population	IP	-
16.2.8.13	Nasal Cavity Examination Data - Safety Population	IP	-
16.2.8.14	Nasal Numerical Rating Scale (NRS) Data - Safety Population	IP	-
16.2.8.15	Brief Smell Identification Score Data - Safety Population	IP	-

Worldwide Clinical Trials Controlled Quality Management Document		
WORLDWIDE CLINICAL TRIALS	Sponsor:	Opiant Pharmaceuticals
	Protocol Number:	OPNT003-PK-002
POST DATABASE LOCK STATISTICAL ANALYSIS PLAN ADDENDUM		

Statistical Analysis Plan

Post Database Lock Addendum

An Open-Label, Three-Period, Three-Treatment, Six-Sequence, Randomized Crossover Study of the Pharmacokinetics of Intranasal Nalmefene in Healthy Volunteers using Three Dosing Regimens

Protocol Number: OPNT003-PK-002

Protocol Version: 1.0 / 06-AUG-2021

SAP Version 1.0 / 16-NOV-2021

Addendum Version: 1.0

Addendum issue Date: 29-MAR-2022

Previous Addenda

Not Applicable

Worldwide Clinical Trials Controlled Quality Management Document		
WORLDWIDE CLINICAL TRIALS	Sponsor:	Opiant Pharmaceuticals
	Protocol Number:	OPNT003-PK-002

POST DATABASE LOCK STATISTICAL ANALYSIS PLAN ADDENDUM

1. BACKGROUND

This document details changes and / or additions to the planned statistical analyses for Opiant Pharmaceuticals, protocol "OPNT003-PK-002" study previously described in V1.0 of the Statistical Analysis Plan (SAP) dated 16-NOV-2021.

These amendments were made post database lock.

Rationale for Addendum:

1) In electrocardiogram assessments, results were summarized only by sequence. Since the data is collected during treatment periods, tables is updated to presented results by both treatment and sequence.
2) Truncated mean, all subject, and individual subject plots through 4 hours postdose were added to illustrate early nalmefene exposure.

2. CHANGES TO EXISTING SAP

2.1 Change 1

2.1.1 Original text

6.11.4 Electrocardiogram Data

ECG values will be tabulated for Baseline, day 6, day 12 and EOS/ET, and change from Baseline to day 6 and 12, and change from Baseline to EOS by treatment sequence and overall. Parameters will be listed in the order given below and in units collected.

2.1.2 New text

6.11.4 Electrocardiogram Data

ECG values will be tabulated for Baseline, 20 mins, 1h and 6h, and change from baseline to 20 mins, 1h and 6h by treatment periods. In addition, ECG results will be tabulated for Baseline, EOS/ET, and change from Baseline to EOS/ET by treatment sequence and overall.

2.2 Change 2

2.2.1 Original text

6.3 Conventions

"Sequence 1" represents subjects taking Treatment A in period 1, Treatment B in period 2 and Treatment C in period 3; "Sequence 2" represents subjects taking Treatment B in period 1, Treatment C in period 2 and Treatment A in period 3; "Sequence 3" represents subjects taking Treatment C in period 1, Treatment A in period 2 and Treatment B in period

3; "Sequence 4" represents subjects taking Treatment A in period 1, Treatment C in period 2 and Treatment B in period 3; "Sequence 5" represents subjects taking Treatment B in period 1, Treatment A in period 2 and Treatment C in period 3; **"Sequence 6" represents subjects taking Treatment C in period 1, Treatment A in period 2 and Treatment B in period 3.**

2.2.2 New text

6.3 Conventions

"Sequence 1" represents subjects taking Treatment A in period 1, Treatment B in period 2 and Treatment C in period 3; "Sequence 2" represents subjects taking Treatment B in period 1, Treatment C in period 2 and Treatment A in period 3; "Sequence 3" represents subjects taking Treatment C in period 1, Treatment A in period 2 and Treatment B in period 3; "Sequence 4" represents subjects taking Treatment A in period 1, Treatment C in period 2 and Treatment B in period 3; "Sequence 5" represents subjects taking Treatment B in period 1, Treatment A in period 2 and Treatment C in period 3; **"Sequence 6" represents subjects taking Treatment C in period 1, Treatment B in period 2 and Treatment A in period 3.**

2.3 Change 3

Titles of few outputs were not matching with SAP section 9 List of Tables, Figures and Listings. SAP is updated to have the same names of TFLs as in TFL Mock Shells.

3. ADDITIONS TO EXISTING SAP

3.1 Addition 1

Truncated mean, all subject, and individual subject concentration-time profiles through 4 hours postdose were added to illustrate early nalmefene exposure.

4. CHANGES TO TABLES, FIGURES AND LISTINGS (TFL) SHELL TABLE OF CONTENT (TOC) WITHIN SAP

New TOC attached: ☒ yes ☐ no

5. CHANGES TO TFL SHELL

Previous version of TFL Shells: 1.0 / 16-Nov-2021

New version of TFL shells: 1.1 / 29-Mar-2022

- Safety population definition was incorrect in few tables. It is corrected to "Safety Population includes subjects who took at least one dose of study drug".
- All TFLs – In footnote, treatment sequence 6 definition was incorrect. It has been updated as "Sequence 6" represents subjects taking Treatment C in period 1, Treatment B in period 2 and Treatment A in period 3.
- Tables 14.3.1.1 and Table 14.3.1.8 – "Unknown" row is removed from relationship category.
- Table 14.3.1.2, Table 14.3.1.7, Table 14.3.1.8 and Listing 16.2.7.1 – MedDRA version is updated to 24.1.
- Table 14.3.4.7 – Title was incorrect. It has been updated to "Coagulation Data".
- Table 14.3.5.1 and Table 14.3.5.2 - Reference listing number was incorrect. It has been corrected as 'Listing 16.2.8.10'.
- Table 14.3.6.1 and Table 14.3.6.2 – Table is revamped to present ECG results by both treatment and treatment sequence.
- Table 14.3.6.1 and Table 14.3.6.2 - Reference listing number was incorrect. It has been corrected as 'Listing 16.2.8.11'.
- Table 14.3.6.3 - Reference listing number was incorrect. It has been corrected as 'Listing 16.2.8.12'.
- Table 14.3.6.4.1 – "Not Done / Missing" column has been added.
- Table 14.3.6.4.2 – "Not Done / Missing" row and column has been added.
- Table 14.3.6.4.1 and Table 14.3.6.4.2 - Reference listing number was incorrect. It has been corrected as 'Listing 16.2.8.13'.
- Table 14.3.6.4.2 – "Not Done / Missing" row and column has been added.
- Table 14.3.6.5 - Reference listing number was incorrect. It has been corrected as 'Listing 16.2.8.14'.
- Table 14.3.6.6 - Reference listing number was incorrect. It has been corrected as 'Listing 16.2.8.15'.
- Figures 14.4.1.1, 14.4.2.1, and 14.4.3.1 for truncated mean, all subject, and individual subject concentration-time profiles were added.
- Listing 16.2.4.1 – there was a spelling mistake in title. It has been updated to "Demographic Data".
- Listing 16.2.4.3 – WHODD version updated as "Sep 2021".
- Listing 16.2.8.8 – "Occurrence" column has been added. "Category" column moved prior to that.

- 14.3.6.3 – Title was incorrect. It has been updated to "Physical Examination Data, Shift Summary".
- 14.3.6.4.2 – Title was incorrect. It has been updated to "Nasal Cavity Examination Data, Shift Summary".

Table Number	Table Title	Validation Method	Shell Number (if repeat)
Items in bold are not table titles but references to the section headings within eCTD.			
14.1	**Demographics Data**		
14.1.1	**Disposition**		
14.1.1.1	Subject Disposition, Analysis Populations – All Subjects	IP	-
14.1.2	**Demographics**		
14.1.2.1	Subject Demographics - Safety Population	IP	-
14.1.2.2	Subject Demographics - PK Evaluation Population	IP	14.1.2.2
14.1.3	**Baseline Characteristics**		
	Not Applicable		
14.2	**Efficacy Data**		
	Not Applicable		
14.3	**Safety Data**		
14.3.1	**Displays of Adverse Events**		
14.3.1.1	Adverse Events, Overall Summary – Safety Population	IP	-

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.3.1.2	Adverse Events, Treatment Emergent Adverse Events by SOC and PT – Safety Population	IP	-
14.3.1.3	Adverse Events, Related Treatment Emergent Adverse Events by SOC and PT – Safety Population	IP	14.3.1.2
14.3.1.4	Adverse Events, Serious Treatment Emergent Adverse Events by SOC and PT – Safety Population	IP	14.3.1.2
14.3.1.5	Adverse Events, Related Serious Treatment Emergent Adverse Events by SOC and PT – Safety Population	IP	14.3.1.2
14.3.1.6	Adverse Events, Treatment Emergent Adverse Events leading to Early Withdrawal by SOC and PT – Safety Population	IP	14.3.1.2
14.3.1.7	Adverse Events, Treatment Emergent Adverse Events by SOC, PT and Maximum Severity - Safety Population	IP	-
14.3.1.8	Adverse Events, Treatment Emergent Adverse Events by SOC, PT and Closest Relationship - Safety Population	IP	-
14.3.2	**Listings of Deaths, Other Serious and Significant Adverse Events**		
14.3.2.1	Serious Adverse Event Data – Safety Population	IP	16.2.7.1
14.3.2.2	Adverse Event Leading to Death – Safety Population	IP	16.2.7.1
14.3.2.3	Adverse Event Leading to Early Withdrawal – Safety Population	IP	16.2.7.1
14.3.3	**Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events**		

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.3.4	**Abnormal Laboratory Values**		
14.3.4.1	Hematology Data, Descriptive Statistics - Safety Population	IP	-
14.3.4.2	Clinical Chemistry Data, Descriptive Statistics - Safety Population	IP	14.3.4.1
14.3.4.3	Coagulation Data, Descriptive Statistics - Safety Population	IP	14.3.4.1
14.3.4.4	Urinalysis Data, Descriptive Statistics - Safety Population	IP	14.3.4.1
14.3.4.5	Hematology Data, Shift Summary - Safety Population	IP	-
14.3.4.6	Clinical Chemistry Data, Shift Summary - Safety Population	IP	14.3.4.5
14.3.4.7	Coagulation Data, Shift Summary - Safety Population	IP	14.3.4.5
14.3.4.8	Urinalysis Data, Shift Summary - Safety Population	IP	16.2.8.1
14.3.4.9	Out of Range Laboratory Data – Safety Population	IP	-
14.3.5	**Vital Signs and Physical Examination**		
14.3.5.1	Vital Signs, Descriptive Statistics – Safety Population	IP	-
14.3.5.2	Vital Signs, Shift Summary – Safety Population	IP	-
14.3.6	**Other Safety**		
14.3.6.1	12 Lead ECG, Descriptive Statistics - Safety Population	IP	-

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.3.6.2	12 Lead ECG, Shift Summary - Safety Population	IP	-
14.3.6.3	Physical Examination Data, Shift Summary - Safety Population	IP	-
14.3.6.4.1	Nasal Cavity Examination Data, Descriptive Statistics - Safety Population	IP	-
14.3.6.4.2	Nasal Cavity Examination Data, Shift Summary - Safety Population	IP	-
14.3.6.5	Numerical Rating Scale Data, Descriptive Statistics - Safety Population	IP	-
14.3.6.6	Brief Smell Identification Score Data, Descriptive Statistics - Safety Population	IP	-
14.3.7	**Concomitant Medication**		
	Not Applicable		
14.4	**PK Tables**		
14.4.1	Descriptive Statistics for Concentration-Time Data of Nalmefene after IN Administration of 3 mg Nalmefene HCl in One Nostril (T1, Treatment A), 3 mg (6 mg Total Dose) Nalmefene HCl in Each Nostril (Treatment B, T2), and 6 mg Nalmefene HCl in One Nostril (Treatment C, T3) – PK Evaluation Population	IP	-
14.4.2	Plasma PK Parameters of Nalmefene after IN Administration of 3 mg Nalmefene HCl in One Nostril (T1, Treatment A), 3 mg (6 mg Total Dose) Nalmefene HCl in Each Nostril (Treatment B, T2), and 6 mg	IP	-

Table Number	Table Title	Validation Method	Shell Number (if repeat)
	Nalmefene HCl in One Nostril (Treatment C, T3) – PK Evaluation Population		
14.4.3	Plasma PK Partial AUCs of Nalmefene after IN Administration of 3 mg Nalmefene HCl in One Nostril (T1, Treatment A), 3 mg (6 mg Total Dose) Nalmefene HCl in Each Nostril (Treatment B, T2), and 6 mg Nalmefene HCl in One Nostril (Treatment C, T3) – PK Population	IP	-
14.4.4	Plasma Dose-Normalized Parameters of Nalmefene after IN Administration of 3 mg Nalmefene HCl in One Nostril (T1, Treatment A), 3 mg (6 mg Total Dose) Nalmefene HCl in Each Nostril (Treatment B, T2), and 6 mg Nalmefene HCl in One Nostril (Treatment C, T3) – PK Population	IP	-
14.4.5	Dose-Normalized Plasma PK Partial AUCs of Nalmefene after IN Administration of 3 mg Nalmefene HCl in One Nostril (T1, Treatment A), 3 mg (6 mg Total Dose) Nalmefene HCl in Each Nostril (Treatment B, T2), and 6 mg Nalmefene HCl in One Nostril (Treatment C, T3) – PK Population	IP	-
14.4.6	Statistical Analysis of the Natural Log-Transformed, Dose-Normalized Exposure Parameters of Nalmefene Comparing 6 mg Nalmefene Hydrochloride in One Nostril (Treatment C, T3, Test) and 3 mg Nalmefene Hydrochloride in One Nostril (Treatment A, T1, Reference) – PK Evaluation Population	IP	-
14.4.7	Statistical Analysis of the Natural Log-Transformed, Dose-Normalized Exposure Parameters of Nalmefene Comparing 3 mg Nalmefene Hydrochloride in Each Nostril (6 mg Total Dose, Treatment B, T2, Test) and	IP	-

Table Number	Table Title	Validation Method	Shell Number (if repeat)
	3 mg Nalmefene Hydrochloride in One Nostril (Treatment A, T1, Reference) – PK Evaluation Population		
14.4.8	Statistical Analysis of the Natural Log-Transformed, Dose-Normalized Exposure Parameters of Nalmefene Comparing 3 mg Nalmefene Hydrochloride in Each Nostril (6 mg Total Dose, Treatment B, T2, Test) and 6 mg Nalmefene Hydrochloride in One Nostril (Treatment C, T3, Reference) – PK Evaluation Population	IP	-
14.5	**PD Tables**		
14.6	**Other Data**		

Figure Number	Figure Title	Validation Method	Shell Number (if repeat)
14.4.1	Nalmefene Concentration-Time Data, Mean Profiles on Linear and Semi-Logarithmic Scales after Intranasal (IN) Administrations of 3 mg Nalmefene Hydrochloride in One Nostril (T1), 2 x 3 mg Nalmefene Hydrochloride in Each Nostril (6 mg Total Dose, T2), and 6 mg Nalmefene Hydrochloride in One Nostril (T3) – PK Evaluation Population	IP	-
14.4.1.1	Nalmefene Concentration-Time Data, Mean Profiles on Linear and Semi-Logarithmic Scales after Intranasal (IN) Administrations of 3 mg Nalmefene Hydrochloride in One Nostril (T1), 3 mg Nalmefene Hydrochloride in Each Nostril (6 mg Total Dose, T2), and 6 mg Nalmefene Hydrochloride in One Nostril (T3) (X-Axis Truncated to 4 h Post Dose) – PK Evaluation Population	IP	
14.4.2	Nalmefene Concentration-Time Data, All Subject Profiles on Linear and Semi-Logarithmic Scales after Intranasal (IN) Administrations of 3 mg Nalmefene Hydrochloride in One Nostril (T1), 2 x 3 mg Nalmefene Hydrochloride in Each Nostril (6 mg Total Dose, T2), and 6 mg Nalmefene Hydrochloride in One Nostril (T3) – PK Evaluation Population	IP	-
14.4.2.1	Nalmefene Concentration-Time Data, All Subject Profiles on Linear and Semi-Logarithmic Scales after Intranasal (IN) Administrations of 3 mg Nalmefene Hydrochloride in One Nostril (T1), 3 mg Nalmefene Hydrochloride in Each Nostril (6 mg Total Dose, T2), and 6 mg Nalmefene Hydrochloride in One Nostril (T3) (X-Axis Truncated to 4 h Post Dose) – PK Evaluation Population	IP	
14.4.3	Nalmefene Concentration-Time Data, Individual Profiles on Linear and Semi-Logarithmic Scales after	IP	-

Figure Number	Figure Title	Validation Method	Shell Number (if repeat)
	Intranasal (IN) Administrations of 3 mg Nalmefene Hydrochloride in One Nostril (T1), 2 x 3 mg Nalmefene Hydrochloride in Each Nostril (6 mg Total Dose, T2), and 6 mg Nalmefene Hydrochloride in One Nostril (T3) – PK Evaluation Population		
14.4.3.1	Nalmefene Concentration-Time Data, Individual Profiles on Linear and Semi-Logarithmic Scales after Intranasal (IN) Administrations of 3 mg Nalmefene Hydrochloride in One Nostril (T1), 3 mg Nalmefene Hydrochloride in Each Nostril (6 mg Total Dose, T2), and 6 mg Nalmefene Hydrochloride in One Nostril (T3) (X-Axis Truncated to 4 h Post Dose) – PK Evaluation Population	IP	
14.4.4	Concentration-Time Profiles for Nalmefene with Linear Regression for Estimating the Terminal Elimination Rate - PK Evaluation Population	IP	-

Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
16.2	**Subject Data Listings**		
16.2.1	**Discontinued Subjects**		
16.2.1.1	Subject Disposition – All Subjects	IP	-
16.2.2	**Protocol Deviations**		
16.2.2.1	Protocol Deviations – Safety Population	IP	-
16.2.3	**Subjects Excluded from the Efficacy Analyses**		
16.2.3.1	Analysis Populations – All Subjects	IP	-
16.2.4	**Demographic Data**		
16.2.4.1	Demographic Data – Safety Population	IP	-
16.2.4.2	Medical History – Safety Population	IP	-
16.2.4.3	Prior and Concomitant Medications - Safety Population	IP	-
16.2.5	**Compliance and / or Drug Concentration Data**		
16.2.5.1	Exposure Data – Safety Population	IP	-
16.2.6	**Individual Efficacy Response Data**		
16.2.6.1	Nalmefene Concentration-Time Data Listing – Safety Population	IP	-

Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
16.2.6.2	Terminal Elimination Rate of Nalmefene in Plasma for Individual Subjects – PK Evaluation Population	IP	-
16.2.6.3	PK Output Text – PK Evaluation Population	IP	-
16.2.6.4	SAS Output Text (ANOVA) – PK Evaluation Population	IP	-
16.2.7	**Adverse Event Listings**		
16.2.7.1	Adverse Event Data – Safety Population	IP	-
16.2.8	**Individual Laboratory Measurements and Other Safety**		
16.2.8.1	Hematology Data – Safety Population	IP	-
16.2.8.2	Serum Chemistry Data – Safety Population	IP	16.2.8.1
16.2.8.3	Coagulation Data – Safety Population	IP	16.2.8.1
16.2.8.4	Urinalysis Data – Safety Population	IP	16.2.8.1
16.2.8.5	Drug, Alcohol and Cotinine Screen – Safety Population	IP	-
16.2.8.6	Serology Data – Safety Population	IP	16.2.8.5
16.2.8.7	Pregnancy Test Data – Safety Population	IP	-
16.2.8.8	Substance Use Data - Safety Population	IP	-
16.2.8.9	COVID-19 PCR Test Data – Safety Population	IP	-
16.2.8.10	Vital Signs Data – Safety Population	IP	-

Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
16.2.8.11	ECG Data – Safety Population	IP	-
16.2.8.12	Physical Examination Data – Safety Population	IP	-
16.2.8.13	Nasal Cavity Examination Data - Safety Population	IP	-
16.2.8.14	Nasal Numerical Rating Scale (NRS) Data - Safety Population	IP	-
16.2.8.15	Brief Smell Identification Score Data - Safety Population	IP	-