Statistical Analysis Plan

Title: A Two-Period, Two-Treatment, Randomized Crossover Study of the Pharmacokinetics of Nalmefene by Intranasal and Intramuscular Administration in Healthy Volunteers

Protocol Number: OPNT003-PK-001

Protocol Version: 5.0 / 11-Nov-2020

SAP Version 1.0

SAP Issue Date: 09-Feb-2021

Previous SAP Versions

NA

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-001" study titled "A Two-Period, Two-Treatment, Randomized Crossover Study of the Pharmacokinetics of Nalmefene by Intranasal and Intramuscular Administration in Healthy Volunteers".

The proposed analyses are based on the contents of the final version of the protocol (dated 11-NOV-2020) and the protocol clarification letter (dated 04-JAN-2021).

This will be an inpatient, open-label, randomized, 2-period, 2-treatment, 2 sequence, crossover study in healthy volunteers. Each subject will receive 2 treatments during the 2 dosing periods (1 treatment per dosing period):

Treatment A (Test)	3 mg nalmefene hydrochloride IN dose (one 0.1 mL spray of a 30 mg/mL solution in one nostril)
Treatment B (Reference)	1.0 mg nalmefene IM dose (1.0 mL of 1.108 mg/mL nalmefene hydrochloride solution as a single dose in the gluteal muscle)

2 STUDY OBJECTIVES

The primary objective is to

- Determine the pharmacokinetics (PK) of 3mg nalmefene hydrochloride IN compared to a 1.0 mg dose of nalmefene administered IM, to demonstrate systemic exposure comparable to an approved IM dose

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 the curve to the final time with a concentration equal to or greater than the lower limit of quantitation [$AUC_{(0-t)}$], to infinity [$AUC_{(inf)}$], and during the first 30 minutes [$AUC_{0\text{-}2.5\ mins}$, $AUC_{0\text{-}5\ mins}$, $AUC_{0\text{-}10\ mins}$, $AUC_{0\text{-}15\ mins}$, $AUC_{0\text{-}20\ mins}$ and $AUC_{0\text{-}30\ mins}$]
- Terminal elimination rate constant (λz)
- Half-life ($t_{½}$)
- Clearance (CL/F)
- Volume of distribution (Vz/F) uncorrected for bioavailability (F)

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 designed to obtain information regarding the PK of IN nalmefene under the conditions of this study. The number of subjects has been determined based on the data from the pilot study.

The sample size was based on Geometric Means Ratio (GMR) and Intrasubject Variability (ISCV) results obtained for partial AUC in the pilot study, covering the initial 30 minutes. Sample size calculations are based on the non-inferiority t-test for log-normal distributed data and were performed for study designs: 2x2x2 (2 treatments x 2 sequences x 2 periods), using a target power of 80% and alpha level of 5%.

Parameter	Total ISCV %	GMR %	Sample size estimation	Expected power
$AUC_{0\text{-}5\ mins}$/Dose	178.15	149.40	48	81.0
$AUC_{0\text{-}10\ mins}$/Dose	129.21	127.06	60	81.1
$AUC_{0\text{-}15\ mins}$/Dose	159.69	108.76	168	80.1
$AUC_{0\text{-}20\ mins}$/Dose	127.97	125.68	60	81.0
$AUC_{0\text{-}30\ mins}$/Dose	74.40	123.57	32	81.5

Based on these findings a sample size of 60 subjects has been selected. For this study 68 subjects will be enrolled.

5 RANDOMIZATION

Subjects will be randomized to a sequence order of receipt of IN or IM doses after establishing eligibility and completing admission procedures. Subjects will be assigned to each of the 2 possible sequences.

The 2 sequences will be assigned as follows:

Sequence	Period 1	Period 2
I	Treatment A	Treatment B
II	Treatment B	Treatment A

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

The evaluable population will include all subjects who complete at least one treatment with all sampling time points taken to derive meaningful PK parameters. The PK population will be used for PK analysis. PK data for subjects who experience AEs (e.g. emesis) that may impact the PK results will be reviewed to assess the potential effect.

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 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.

6.2.2 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, but after check-in for the relevant period.

6.2.3 Early Terminations Assessments

Data collected during Early Termination assessments will be summarized alongside EOS procedures. All Early Termination data will be displayed as "Early Termination" in the listings, along with relevant Study Day.

6.2.4 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

6.2.5 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.

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

6.2.6 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.

6.2.7 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.

6.2.8 PK Parameters

Concentration-time data will be analyzed using noncompartmental methods in Phoenix™ WinNonlin® (Version 8.1 or higher, Certara, L.P.)[2] in conjunction with the internet-accessible implementation of Pharsight® Knowledgebase Server™ (PKSO; Version 4.0.4 or comparable product, Certara, L.P.). PKSO provides protected and structured storage, audit trails, and version control for study data, analyses, and related files, supporting 21 CFR Part 11 compliance.

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. PK analysis will be based on actual elapsed sample times, relative to time of dose.

The following PK parameters will be calculated:

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 to reach maximum concentration
$AUC_{0\text{-}2.5min}$	Area under the concentration–time curve from time-zero to 2.5 min; calculated using the linear trapezoidal rule allowing for extrapolation/interpolation to 2.5 min
$AUC_{0\text{-}5min}$	Area under the concentration–time curve from time-zero to 5 min; calculated using the linear trapezoidal rule allowing for extrapolation/interpolation to 5min
$AUC_{0\text{-}10min}$	Area under the concentration–time curve from time-zero to 10 min; calculated using the linear trapezoidal rule allowing for extrapolation/interpolation to 10min
$AUC_{0\text{-}20\ min}$	Area under the concentration–time curve from time-zero to 20 min; calculated using the linear trapezoidal rule allowing for extrapolation/interpolation to 20min

$AUC_{0\text{-}30min}$	Area under the concentration–time curve from time-zero to 30 min; calculated using the linear trapezoidal rule allowing for extrapolation/interpolation to 30min
AUC_{last} ($AUC_{0\text{-}t}$)	Area under the concentration–time curve from time-zero to the time of the last quantifiable concentration; calculated using the linear trapezoidal rule
AUC_{last}/Dose	AUC_{last} adjusted for the nominal administered dose
AUC_{inf}	Area under the concentration–time curve extrapolated to infinity, calculated as: $AUC_{inf} = AUC_{last} + C_{last}/\lambda_z$, 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: $\%AUC_{Extrap} = (AUC_{inf} - AUC_{last})/AUC_{inf}*100$
λ_z	The observed elimination rate constant (λz); estimated by linear regression in the terminal phase of the log concentration-time profile; see additional criteria below
$T_{1/2}$	The observed terminal elimination half-life calculated as: $T½ = \ln(2)/\lambda_z$
C_{last}	The last quantifiable concentration, determined directly from individual concentration-time data
T_{last}	Time of the last quantifiable concentration
CL/F	Apparent total body clearance after extravascular administration, calculated as: $CL/F = Dose/AUC_{inf}$
Vz/F	Apparent volume of distribution following extravascular administration based on the terminal phase, calculated as: $Vz/F = Dose/(AUC_{inf}*\lambda_z)$
Frel	Ratio of dose-adjusted AUC_{inf} following IN administration of the test product relative to dose-adjusted AUC_{inf} following IM administration of the reference product

λ_z and AUC_{inf} Criteria

The following criteria will be used to report λ_z:

- 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, $\underline{\lambda_z}$ and descriptive parameters ($\underline{\lambda_z}$ time range, Adj R^2, etc.) will be retained in a parameter listing for informational purposes; $\underline{\lambda_z}$ will be excluded from summary statistics. Parameters calculated using $\underline{\lambda_z}$ (AUC_{inf}, $T_{1/2}$, CL/F, etc.) will be reported as ND (not determinable).

If $\underline{\lambda_z}$ 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 pharmacokinetic parameter calculations (e.g. CL/F, V_z/F), and statistical analysis (e.g. ANOVA).

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 overall 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 analyte and treatment at each nominal sample time. PK parameter data will be summarized by analyte and treatment.

Treatment labels will be displayed as follows:

Treatment A Treatment B

Footnotes describing each treatment will be provided in each output.

Treatment sequence labels will be displayed as follows:

Sequence AB Sequence BA Overall

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, mean (Gmean and Amean), median, standard deviation, and minimum and maximum.

PK data (concentration-time data and PK parameters) will be summarized by the number of non-missing observations (n), mean, standard deviation (SD), median, minimum (min), maximum (max), and coefficient of variation (CV%), calculated as (SD/Mean)*100. In addition, the geometric mean and geometric CV%, calculated as SQRT[exp(SD^2 of log transformed data)-1]*100, will be reported for C_{max} and AUCs.

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, day will be presented with zero decimal places.

Means, medians and percentiles will be displayed to one more decimal place than the data**,** dispersion statistics (e.g. 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 will be reported to 3 significant figures and individual PK parameters will be reported to 3 significant figures. For summary statistics, n will be reported as a whole number; mean, standard deviation, median, minimum, maximum, and geometric mean will be reported to the same precision as for individual data. CV% and geometric CV% will be reported to 3 significant figures; p-values will be reported to 3 significant figures. Percent ratios of the geometric least squares means and associated 90% confidence intervals will be reported to 2 decimal places.

6.4 Subject Disposition

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

- The number of subjects who were randomized and who are in each analysis population will be summarized by treatment sequence and overall.
- The number of early withdrawals and the reasons for withdrawals will be tabulated by treatment sequence and overall.

6.5 Protocol Deviations

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

6.6 Baseline Comparability

The comparability of treatment sequences with respect to subject demographics and Baseline characteristics will be assessed in a descriptive manner, but no formal statistical testing will be performed.

Standard continuous or categorical variable summaries will be presented by treatment sequences and overall for the following variables based on the Safety Population.

6.6.1 Demographic Data

Standard continuous or categorical variable summaries will be presented by treatment sequence and overall for the following variables based on the Safety Population.

- Age at Informed Consent (years)
- Gender
- Ethnicity
- Race, where more than one race is selected the subject will be presented under the 'Multiple Races' category in the summary but each selected race will be identified in the listing.
- Weight at Screening (kg)
- Height at Screening (cm)
- BMI at Screening (kg/m^2)

6.7 Medical History

Listings of previous and ongoing conditions at screening will be presented for the Safety Population. Conditions will be coded using the Medical Dictionary of Regulated Activities (MedDRA) version 23.1 or higher.

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 Substance Use

All substance use data will be listed for the Safety Population.

6.9 Prior and Concomitant Medications

Prior and concomitant medications will be listed for the Safety Population.

Prior medications are defined as all medications starting and stopping before the date of first dose of study drug. Concomitant medications are defined as medications taken on or after the date of first dose of study drug.

Medications will be coded using World Health Organization Drug Dictionary (WHODD) Version September 2020.

6.10 Exposure to Study Drug

All dosing information will be listed.

6.11 PK Analyses

Blood samples for determination of plasma concentrations of nalmefene will be collected at:

Predose (0 h), and at 2.5, 5, 7.5, 10, 15, 20, 30, and 45 minutes and 1, 2, 3, 4, 6, 8, 12, 18, 24, 36, and 48 hours post dose.

Concentration-time data will be tabulated by nominal time, analyte, and treatment using descriptive statistics. For presentation of the individual data and summary statistics, concentrations below the limit of quantitation (BLQ) will be set to zero.

Individual subject and mean plasma concentration-time data will be presented graphically on linear and semi-logarithmic scales. Mean data will be plotted using nominal sample times, and individual data will be plotted using actual times.

PK parameters for nalmefene will be calculated as described in section 5.2.13.

PK parameters will be summarized by analyte and treatment using descriptive statistics.

Comparison of the log-transformed PK parameters C_{max}, $AUC_{0\text{-}2.5min}$, $AUC_{0\text{-}5min}$, $AUC_{0\text{-}10min}$, $AUC_{0\text{-}15min}$, $AUC_{0\text{-}20min}$, and $AUC_{0\text{-}30min}$, AUC_{last}, and AUC_{inf} across treatments will be performed using an analysis of variance (ANOVA) model and the two one-sided t-tests procedure at the $\alpha = 0.05$ level of significance. The model will include sequence, treatment, and period as fixed effects and subject nested within sequence as the random effect. The following comparison(s) will be made:

- Test Product (Treatment A) vs. Reference Product (Treatment B)

The ratios of the geometric means (Test / Reference) and 90% confidence intervals will be reported. The analysis will be performed in SAS using PROC GLM.

Conclusions regarding the results of the statistical analysis (ANOVA) of PK parameters across treatments will be based on the ratio of the geometric means (Test / Reference) and the 90% confidence interval about the ratio. No significant difference will be demonstrated if the 90% confidence intervals are fully contained within the limits of 80.00% to 125.00%.

6.12 Safety Analyses

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

6.12.1 Adverse Events

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.
- If the severity of a TEAE increases in a later period the TEAE at the increased severity will be assigned to the treatment received immediately before the increase in severity.

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, SAEs, Related SAEs, TEAEs leading to withdrawal.
- 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.
- TEAE by system organ class, preferred term and maximum severity, incidence.
- Treatment related TEAE by system organ class, preferred term and maximum severity, incidence.
- TEAE by system organ class, preferred term and relationship, incidence
- TEAEs leading to early withdrawal by system organ class and preferred term, incidence.
- Listing of Serious TEAEs (presented in the Table section of the appendices).
- Listing of Deaths (presented in the Table section of the appendices).

In counting the number of AEs reported, a continuous event (i.e. reported more than once and which did not cease), will be counted only once; non-continuous AE reported several times by the same subject will be counted as multiple events.

All AEs will be listed.

6.12.2 Laboratory Data

The following laboratory tests will be performed at Screening and prior to 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 end of study (EOS) visit and change from Baseline (continuous data) to EOS will be for each hematology, urinalysis, serum chemistry parameter and coagulation markers will be presented by treatment sequence and overall. Each measurement (continuous data) will be classed as below, within, or above normal range, based on ranges supplied by the laboratory used. Shift tables in relation to the normal range from Baseline to EOS visit will be presented.

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

A separate listing of any clinically significant laboratory measurements recorded throughout the study will be presented.

All other laboratory data, for example Viral Serology, Serum FSH, Pregnancy Test, and Urine Drug, Alcohol and Cotinine, will be listed only.

6.12.3 Vital Signs

Vital signs 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. In addition, vital signs values will be tabulated for Baseline, EOS, and change from Baseline to EOS 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 (bpm)
- Respiration rate (breath/min)
- Body temperature (degrees 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 follow-up visit will be presented.

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

6.12.4 Electrocardiogram Data

12-lead ECGs will be tabulated for Baseline, 0.33 h, 1 h, and 10 h post-dose and the respective changes from Baseline, per treatment. In addition, ECG values will be tabulated for Period 1 Baseline, day 4 and EOS, and change from Baseline to day 4 and change from Baseline to EOS by treatment sequence and overall.

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.

6.12.5 Physical Examination

The body systems within the physical examination data at the EOS will be summarized by treatment sequence and overall (Normal, Abnormal NCS, Abnormal CS) as a shift from Baseline table.

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

6.12.6 Nasal Passage Examination

Nasal passage examination will be conducted at Screening, Admission/Baseline, pre-dose, and at approximately 5 minutes and ± 15 minutes of the nominal blood collections at 1 h and 8 h post-dose, and at approximately 24 h and 48 h post-dose, after the IN dose. The nasal passage will be examined by a physician (or qualified medical professional) for evidence of irritation (erythema, edema, and erosion).

The number and percentage of subjects reporting each nasal irritation scale at Baseline, 5 mins, 1 h, 8 h, 24 h and 48 h post-dose will be provided for the Safety Population.

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.

6.12.7 Numerical Rating Scale

Numerical rating scale (NRS) assessments will be conducted pre-dose and at 15 (± 2 min) and 60 (± 10 min) minutes post-dose (IN period).

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

6.12.8 Smell Test

Smell test will be conducted at Screening, pre-dose and ± 15 minutes of the nominal blood collections at 1 h and 4 h, and at approximately 24 h post-dose after the IN dose, and final discharge.

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

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	Summary of Demographics - Safety Population	IP	
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	
14.3.1.4	Serious TEAEs By Primary System Organ Class and Preferred Term – Safety Population	IP	
14.3.1.5	TEAEs By Primary System Organ Class Preferred Term and Maximum Severity – Safety Population	IP	
14.3.1.6	Treatment Related TEAEs By Primary System Organ Class Preferred Term and Maximum Severity – Safety Population	IP	

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.3.1.7	TEAEs By Primary System Organ Class Preferred Term and Relationship – Safety Population	IP	
14.3.1.8	TEAEs Leading to Early Withdrawal by Primary System Organ Class and Preferred Term – Safety Population	IP	
14.3.2	**Listings of Deaths, Other Serious and Significant Adverse Events**		
14.3.2.1	Listing of SAEs – Safety Population	MR	
14.3.2.2	Listing of Deaths – Safety Population	MR	
14.3.3	**Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events**		
14.3.4	**Abnormal Laboratory Values**		
14.3.4	Listing of Clinically Significant Abnormal Laboratory Values – Safety Population	MR	
14.3.5	**Extent of Exposure, Dosage Information, And Compliance**		
14.3.6	**Vital Signs and Physical Examination**		
14.3.6.1	Vital Signs, Change from Baseline – Safety Population	IP	
14.3.6.2	Vital Signs, Normal Range Shift – Safety Population	IP	
14.3.6.3	Physical Examination, Shift from Baseline – Safety Population	IP	
14.3.6.4.1	Summary of Nasal Irritation Scale – Safety Population	IP	
14.3.6.4.2	Nasal Irritation Scale, Shift from Baseline – Safety Population	IP	
14.3.6.5	NRS Assessment, Descriptive Statistics – Safety Population	IP	
14.3.6.6	Smell Test Score, Descriptive Statistics – Safety Population	IP	
14.3.7	**Other Safety**		
14.3.7.1	Hematology Data, Change from Baseline – Safety Population	IP	
14.3.7.2	Hematology Data, Normal Range Shift – Safety Population	IP	
14.3.7.3	Serum Chemistry Data, Change from Baseline – Safety Population	IP	
14.3.7.4	Serum Chemistry Data, Normal Range Shift – Safety Population	IP	

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.3.7.5	Coagulation Data, Change from Baseline – Safety Population	IP	
14.3.7.6	Coagulation Data, Normal Range Shift – Safety Population	IP	
14.3.7.7	Urinalysis Data, Change from Baseline – Safety Population	IP	
14.3.7.8	Urinalysis Data, Normal Range Shift – Safety Population	IP	
14.3.7.9	ECG Data, Change from Baseline – Safety Population	IP	
14.3.7.10	ECG Data, Shift from Baseline in Overall Interpretation	IP	
14.3.8	**Concomitant Medication**		
	Not Applicable		
14.4	**PK Tables**		
14.4.1	Descriptive Statistics for Concentration-Time Data of Nalmefene after Intranasal (IN) Administration of 3.0 mg Nalmefene Hydrochloride (Treatment A) and Intramuscular (IM) Administration of 1.0 mg of Nalmefene Hydrochloride (Treatment B) – PK Polulation	IP	
14.4.2	PK Parameters of Nalmefene after Intranasal (IN) Administration of 3.0 mg Nalmefene Hydrochloride (Treatment A) and Intramuscular (IM) Administration of 1.0 mg of Nalmefene Hydrochloride (Treatment B) – PK Polulation	IP	
14.4.3	Statistical Analysis of the Natural Log-Transformed Systemic Exposure of Nalmefene Comparing 3.0 mg Nalmefene hydrochloride (IN) (Treatment A, Test) to 1.0 mg of Nalmefene Hydrochloride (IM) (Treatment B, Reference) – PK Polulation	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) Administration of 3.0 mg Nalmefene Hydrochloride (Treatment A) and Intramuscular (IM) Administration of 1.0 mg of Nalmefene Hydrochloride (Treatment B) – PK Population	MR	
14.4.2	Nalmefene Concentration-Time Data, All Subject Profiles on Linear and Semi-Logarithmic Scales after Intranasal (IN) Administration of 3.0 mg Nalmefene Hydrochloride (Treatment A) and Intramuscular (IM) Administration of 1.0 mg of Nalmefene Hydrochloride (Treatment B) – PK Population	MR	
14.4.3	Nalmefene Concentration-Time Data, Individual Profiles on Linear and Semi-Logarithmic Scales after Intranasal (IN) Administration of 3.0 mg Nalmefene Hydrochloride (Treatment A) and Intramuscular (IM) Administration of 1.0 mg of Nalmefene Hydrochloride (Treatment B) – PK Population	MR	
14.4.4	Concentration-Time Profiles for Nalmefene with Linear Regression for Estimating the Terminal Elimination – Rate PK Population	MR	

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	MR	
16.2.2	**Protocol Deviations**		
16.2.2.1	Protocol Deviations – Safety Population	MR	
16.2.3	**Subjects Excluded from the Efficacy Analyses**		
16.2.3.1	Analysis Populations – All Randomized Subjects	MR	
16.2.4	**Demographic Data**		
16.2.4.1	Demographic Data – Safety Population	MR	
16.2.4.2	Previous Medical History – Safety Population	MR	
16.2.4.3	Ongoing Medical History – Safety Population	MR	
16.2.4.4	Substance Use – Safety Population	MR	
16.2.4.5	Prior and Concomitant Medications – Safety Population	MR	
16.2.5	**Compliance and / or Drug Concentration Data**		
16.2.5.1	Dosing Information – Safety Population	MR	
16.2.5.2	PK Sampling Information – Safety Population	MR	
16.2.6	**Individual Efficacy Response Data**		
16.2.6.1	Nalmefene Concentration-Time Data Listing – Safety Population	MR	
16.2.6.2	Terminal Elimination Rate of Nalmefene in Plasma for Individual Subjects – PK Population	MR	
16.2.6.3	PK Output Text	MR	
16.2.6.4	SAS Output Text (ANOVA)	MR	
16.2.7	**Adverse Event Listings**		
16.2.7.1	Adverse Event Data – Safety Population	MR	
16.2.8	**Individual Laboratory Measurements and Other Safety**		
16.2.8.1	Hematology Data – Safety Population	MR	
16.2.8.2	Serum Chemistry Data – Safety Population	MR	
16.2.8.3	Urinalysis Data – Safety Population	MR	
16.2.8.4	Drug and Alcohol Screen – Safety Population	MR	
16.2.8.5	Serology Data – Safety Population	MR	
16.2.8.6	Pregnancy Test Data – Safety Population	MR	
16.2.8.7	Physical Examination Data – Safety Population	MR	
16.2.8.8	Vital Signs Data – Safety Population	MR	
16.2.8.9	ECG Data – Safety Population	MR	

Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
16.2.8.10	Nasal Passage Examination Data – Safety Population	MR	
16.2.8.11	NRS Assessment Data – Safety Population	MR	
16.2.8.12	Smell Test Data – Safety Population	MR	