U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA217470
Supplement #:	Original Submission
Drug Name:	(b) (4)® (nalmefene) nasal spray
Indication(s):	For the complete or partial reversal of opioid drug effects, including respiratory depression, induced by either natural or synthetic opioids; In the emergency treatment of known or suspected opioid overdose
Applicant:	Opiant Pharmaceuticals, Inc.
Date(s):	Submission Date: November 22, 2022 PDUFA goal date: May 22, 2023
Review Priority:	Priority
Biometrics Division:	DBI
Statistical Reviewer:	Yunfan Deng, Ph.D.
Concurring Reviewer(s):	Sue-Jane Wang, Ph.D., Deputy Director
Medical Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine
Clinical Team:	Tanya Brescia-Oddo, MD Robert Shibuya, MD, Team Leader
Project Manager:	Sandy Truong

Keywords: pharmacodynamic (PD), single-center, open-label, crossover, non-inferiority (NI)

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

This NDA seeks approval of [redacted] (b) (4) ® (nalmefene) nasal spray, 2.7mg for the complete or partial reversal of opioid drug effects, including respiratory depression, induced by either natural or synthetic opioids.

Nalmefene hydrochloride, as a sterile solution for intravenous (IV), intramuscular (IM), and subcutaneous (SC) administration, was approved by the FDA in 1995 as REVEX® (nalmefene hydrochloride injection) for complete or partial reversal of opioid drug effects, including respiratory depression, induced by either natural or synthetic opioids and in the management of known or suspected opioid overdose. REVEX® was withdrawn from the US market in 2008 for reasons other than safety or effectiveness (Federal Register-2017). There has been considerable renewed interest in developing nalmefene as an alternative to naloxone for opioid reversal for use by non-medically trained laypersons. An ANDA (212955) for nalmefene hydrochloride for IV, IM, and SC administration, has been approved by the FDA in 2022.

The Applicant (Opiant Pharmaceuticals) developed Nalmefene Nasal Spray, a single-use nasal spray device intended for intranasal delivery of 100 µL of nalmefene hydrochloride solution as a 2.7 mg dose of active ingredient (nalmefene), to treat opioid overdose as a nasal spray. The Applicant conducted one study (OPNT0003-OOD-001) to evaluate the effectiveness of [redacted] (b) (4) nasal spray in reversing opioid induced respiratory depression. Study OPNT0003-OOD-001 was a single-center, randomized, open-label, 2-period, 2-treatment, active-controlled, crossover study in healthy volunteers evaluated the pharmacodynamic (PD) effects of 2.7 mg [redacted] (b) (4) Nasal Spray compared to 4 mg IN naloxone hydrochloride (an active-control) to reverse remifentanil-induced suppression of CO2 induced increases in minute ventilation (MV).

Study OPNT003-OOD-001 demonstrated similarity in post-dosing minute ventilation between nalmefene and naloxone (Table 1). However, the study was a single-center, open-label trial without any justification for the chosen non-inferiority (NI) margin, from statistical perspective, the study was not an adequate, well-controlled study; [redacted] (b) (4) [redacted] (b) (4) PD results of Study OPNT003-OOD-001 [redacted] could be included the PD Section (Section 12.2) of the label.

Table 1: Minute Ventilation and Change in Minute Ventilation from Nadir Baseline

	Naloxone				Nalmefene			
Minutes in Relation to Study Drug Administration	**n**	**Mean MV (L/min) (SD)**	**n**	**Change from Baseline (L/min) (SD)**	**n**	**Mean MV (L/min) (SD)**	**n**	**Change from Baseline (L/min) (SD)**
-15 (Remifentanil baseline)	59	17.36 (6.46)	-	-	62	17.19 (5.10)		-
0 (Nadir Baseline)	59	10.55 (4.65)	58	-0.68 (3.02)	61	10.63 (4.02)	61	-0.70 (2.46)
2.5	59	12.25 (4.37)	59	1.70 (4.05)	60	13.24 (4.06)	60	2.55 (2.97)
5	59	13.98 (4.53)	59	3.43 (4.70)	60	16.44 (5.27)	60	5.74 (4.83)
7.5	59	14.56 (4.39)	59	4.01 (4.82)	61	17.01 (6.26)	61	6.38 (5.51)
10	59	15.51 (4.91)	59	4.96 (5.30)	61	17.21 (5.22)	61	6.58 (5.17)

15	59	16.05 (5.23)	59	5.55 (4.94)	61	17.75 (5.90)	61	7.12 (6.00)
20	59	16.44 (5.55)	59	5.93 (5.24)	60	17.46 (5.55)	60	6.79 (5.53)
30	59	8.55 (1.81)	58	-1.95 (4.61)	60	8.50 (2.66)	60	-2.18 (3.93)
45	59	8.02 (1.89)	58	-2.53 (4.59)	59	8.06 (2.15)	59	-2.56 (3.92)
60	59	12.99 (4.22)	58	2.52 (4.39)	60	13.60 (4.55)	60	2.92 (4.36)
90	57	12.67 (3.93)	56	2.14 (4.66)	59	13.42 (4.38)	59	2.71 (4.56)
95	57	8.23 (3.55)	56	-2.32 (6.16)	59	8.10 (2.92)	59	-2.61 (4.26)
100	56	7.00 (1.89)	55	-3.56 (4.93)	59	7.81 (2.48)	59	-2.91 (4.03)
110	55	7.93 (2.20)	54	-2.53 (4.20)	59	8.59 (2.27)	59	-2.13 (4.05)
120	57	12.49 (3.91)	56	2.02 (3.86)	59	13.59 (4.60)	59	2.88 (4.60)

MV = Minute Ventilation; SD = Standard Deviation
Source: Tables 14.2.1.3.1, 14.2.1.3.2, and 14.2.1.3.3 of Study OPNT0003-OOD-001 Clinical Study Report (CSR).

2 INTRODUCTION

2.1 Overview

2.1.1 Drug Class and Indication

Nalmefene is a μ-opioid receptor antagonist that is a derivative of naltrexone. Another μ-opioid receptor antagonist naloxone has been approved by the Food and Drug Administration (FDA) since 1971 to treat opioid overdose, originally as a needle-and-syringe injection and more recently as a nasal spray (NARCAN®, KLOXXADO®) and intramuscular (IM) auto-injector (EVZIO®).

Nalmefene hydrochloride, as a sterile solution for intravenous (IV), IM, and subcutaneous (SC) administration, was approved by the FDA in 1995 as REVEX® (nalmefene hydrochloride injection) for complete or partial reversal of opioid drug effects, including respiratory depression, induced by either natural or synthetic opioids and in the management of known or suspected opioid overdose. REVEX® was withdrawn from the US market in 2008 for reasons other than safety or effectiveness. An ANDA (212955) for nalmefene hydrochloride for intravenous (IV), IM, and subcutaneous (SC) administration, has been approved by the FDA in 2022.

2.1.2 History of Drug Development

The Applicant developed Nalmefene Nasal Spray to treat opioid overdose as an easy-to-administer nasal spray.

In December 2019, the Applicant had the initial submission for Nalmefene Nasal Spray under IND136851. The Applicant proposed to conduct a clinical study entitled "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" to support their NDA application. (b) (4)

(b) (4) The Agency determined that (b) (4) was not an acceptable comparator for the proposed relative bioavailability study to establish scientific bridge. (b) (4) he IND was put on hold due to potential safety concerns of the medical device. Subsequently, the Applicant had a Type A meeting with the Division on April 2nd, 2020 to discuss the necessity of conducting additional biocompatibility studies with investigational device. The clinical hold was removed following the assessment of the Applicant's proposal.

On April 27th, 2020, the Applicant had a Type C meeting with the Agency to discuss the design of a clinical study (OPNT003-OOD-001) comparing naloxone hydrochloride nasal spray with nalmefene hydrochloride nasal spray that they believed was appropriate and sufficient to address FDA's concerns around the onset and effectiveness of intranasal nalmefene in reversing opioid overdose. The Applicant agreed to use minute ventilation as the primary endpoint to establish efficacy in comparison to naloxone.

On December 14th, 2020, the Applicant had another Type C meeting with the Agency to discuss the regulatory pathway for filing Nalmefene Nasal Spray as a 505(b)(2) application referring to the approved REVEX® NDA and to confirm the design of the proposed safety and efficacy study OPNT003-OOD-001 entitled "A Two-Period, Two-Treatment, Randomized Crossover Study of the Pharmacodynamic Effects of Intranasal Nalmefene Compared to Intranasal Naloxone in Healthy Volunteers under Steady-State Opioid Agonism". During the meeting discussion, the Agency strongly encourage the Applicant to discuss with the Division the results from Part 1 of the OPNT003-OOD-001 study before proceeding to Part 2. It should be noted that the study was submitted as a Phase 1 study throughout the IND review stage.

On March 30th, 2022, the Applicant had a Type B pre-NDA meeting to obtain agreement on the suitability of the available clinical data for filing as an NDA application, to confirm certain aspects of the data package and regulatory filing strategy. The statistical reviewer had the following review comments for the pre-NDA meeting backgrounder:

> *"a. A statistical analysis plan was submitted to the Agency, but there was no discussion around the selected non-inferiority margin or proposed approaches before initiating Part 2 of the study. As such, the appropriateness of the non-inferiority margin will be determined during review of the NDA.*
>
> *b. The non-inferiority analysis in the statistical analysis plan includes a bullet that "no individual subject has a change in minute ventilation on nalmefene that is less than 50% of the change in minute ventilation on naloxone." Please provide additional details on how this criterion is being assessed (e.g., comparing subject-level changes in minute ventilation between treatments at 5 minutes)."*

(b) (4) In addition, the Applicant clarified their primary scientific bridge was a pharmacokinetics (PK) study between nalmefene

nasal spray and Revex and that the pharmacodynamic (PD) study, OPNT003-OOD-001, was a supportive study to ensure nalmefene nasal spray would not be inferior to the current standard of care in the community setting. The Division agreed that the PD study was not the only study that would be relied upon in the NDA submission and that the Division would be reviewing the totality of the data from the development program including any references to Revex.

2.1.3 Studies Reviewed

This review focuses on one study (OPNT0003-OOD-001) to evaluate the effectiveness of (b) (4) nasal spray in reversing opioid induced respiratory depression. Study OPNT0003-OOD-001 was a single-center, randomized, open-label, 2-period, 2-treatment, crossover study in healthy volunteers evaluated the PD effects of 2.7 mg (b) (4) Nasal Spray compared to 4 mg intranasal (IN) naloxone hydrochloride to reverse remifentanil-induced suppression of CO2 induced increases in minute ventilation (MV). As subjects were not treated with the study investigational products in Part 1, this review will focus on the randomized, treatment part (Part 2) of the study. Table 2 below contains a summary of this study.

Table 2: Summary of Efficacy Study to be assessed in the Statistical Review

Study No	Design	Objective	Treatment / Sample Size	Study Population	Endpoints
OPNT0003-OOD-001	Single center, randomized, open-label, parallel group, active-controlled, crossover	Part 1: to determine the relationship between remifentanil dose on suppression of CO2-induced increases in minute ventilation Part 2: to evaluate the PD effects of IN nalmefene compared to IN naloxone to reverse remifentanil-induced suppression of CO2-induced increases in minute ventilation	Part 1: 7 subjects Part 2: Nalmefene / 61 Naloxone / 60	healthy adult male and female nondependent opioid experienced users	Primary: minute ventilation associated with treatment conditions

Source: Statistical Reviewer's Summary.

2.2 Data Sources

The data sources for this review include clinical study reports, protocols, statistical analysis plan (SAP), and datasets. The study report, protocol, and SAP for Study OPNT0003-OOD-001 were electronic submitted and located at:
\\CDSESUB1\evsprod\NDA217470\0004\m5\53-clin-stud-rep\534-rep-human-pd-stud\5341-healthy-subj-pd-stud-rep\opnt003-ood-001

The datasets were electronic submitted and located at
\\CDSESUB1\evsprod\NDA217470\0004\m5\datasets\opnt003-ood-001

The SAS programs for the study were submitted after the statistical reviewer's request and located at
\\CDSESUB1\evsprod\NDA217470\0014\m5\datasets\opnt003-ood-001\analysis\adam\programs

The change from baseline of the minute ventilation (MV) were included in the "adxp.xpt" dataset with the identifying value of "VE Change" of the variable "PARAM" and the variable name "AVAL" for the outcomes. The treatment variable, given both as numeric (TRTPN) and character (TRTP), was also included in the dataset.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Overall, the submitted data were of good quality with definitions provided for each variable. Results of the PD endpoints can be verified with minor data manipulation. The statistical analyses were primarily based on the analysis datasets.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

This was a single-center, open-label, 2-part study; this review will focus on the randomized, treatment part (Part 2) of the study.

Part 1 and Part 1 extension was a pilot study to determine the relationship between remifentanil dose and suppression of CO_2-induced increases in minute ventilation in healthy volunteers with prior opioid exposure. Part 2 was a randomized, 2-period, 2-treatment crossover study to evaluate the pharmacodynamic (PD) effects of IN nalmefene hydrochloride compared to IN naloxone hydrochloride to reverse remifentanil-induced suppression of CO_2-induced increases in minute ventilation, in healthy volunteers with prior opioid exposure.

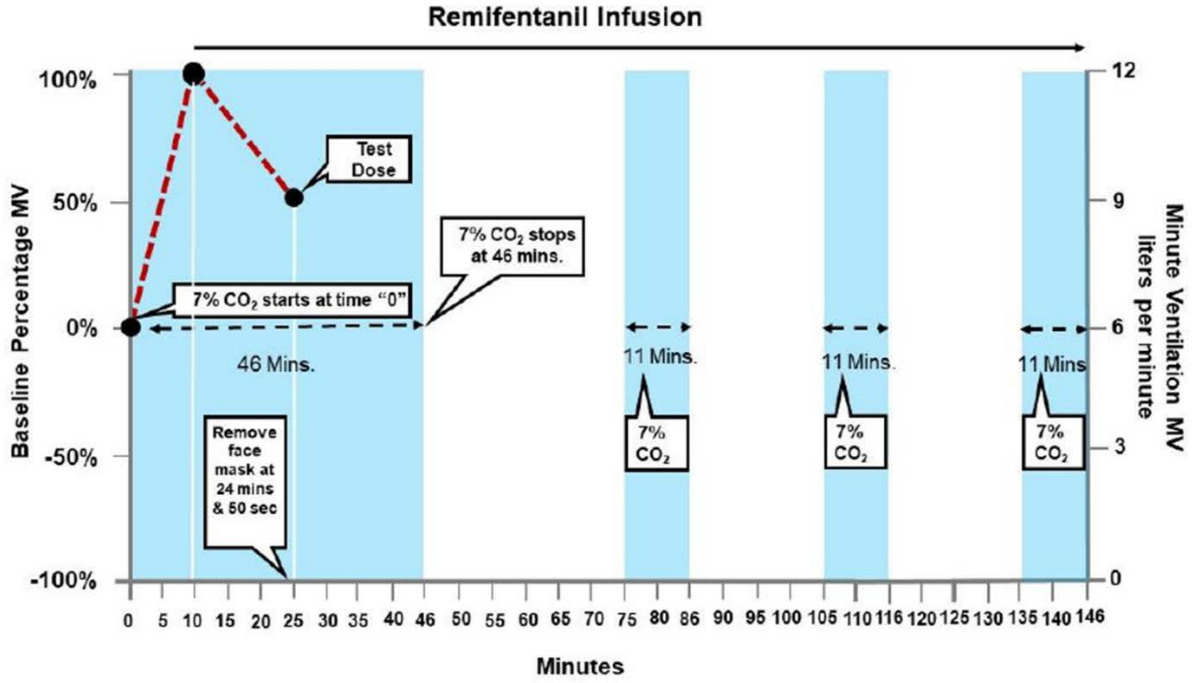
In Part 2, eligible subjects were admitted to the clinical research unit (CRU) following naloxone challenge test and eligibility review on Day -1 and remained in the CRU for 8 days to complete the Treatment Phase of Part 2. After a naloxone challenge test, eligibility review and completion of admission procedures, each subject was randomized to receive either IN nalmefene hydrochloride or IN naloxone hydrochloride in a 2-period crossover manner. On the day of clinic admission (Day -1), a naloxone challenge test was performed to ensure the subject was not physically dependent on opioids, and eligibility was reviewed confirming all the relevant inclusion criteria and none of the exclusion criteria had been met. Subjects who enter Part 2 of the study were randomized to 1 of 2 treatment sequences (XY and YX, where X = test medication [Nalmefene] and Y = reference medication [Naloxone]) in a 1:1 ratio.

On days of study drug administration (Days 1 and 5), subjects fasted for a period of at least 8 hours received pretreatment (30 minutes to 1 hour prior to remifentanil infusion) with famotidine (20 mg IV), ondansetron (8 mg, oral), and sodium citrate (30 mL, oral). Subjects started receiving a hypercapnic gas mixture (50% O_2, 43% N_2, 7% CO_2) using a ventilatory response to hypercapnia (VRH) face mask at Time 0 minutes, followed by a remifentanil hydrochloride infusion at Time 10 minutes, at a rate of 0.175 μg/kg/min, using an initial bolus (0.5 μg/kg) to achieve an expected steady-state. Minute ventilation was continuously measured. The washout period between doses were approximately 4 days.

To administer the IN nalmefene hydrochloride and IN naloxone hydrochloride, the VRH face mask was removed at Time 24 minutes and 50 seconds for approximately 10 seconds. During that time, subjects were asked to hold their breath and IN nalmefene hydrochloride or naloxone hydrochloride was administered at Time 25 minutes. After IN administration of nalmefene hydrochloride or naloxone hydrochloride, the VRH face mask was reapplied to continue to assess the effect on respiration, and remifentanil infusion continued for a further 121 minutes period up to Time 146 minutes. The VRH face mask was removed at Time 46 minutes (i.e., 21 minutes after IN administration of nalmefene hydrochloride or naloxone hydrochloride). The VRH face mask was then reapplied for 11 minutes at Time 75 minutes, at Time 105 minutes and at Time 135 minutes, respectively (i.e., between 50 to 61 minutes, 80 to 91 minutes and 110 to 121 minutes after IN administration of nalmefene hydrochloride or naloxone hydrochloride).

The flow chart of Part 2 displays in the following figure.

Figure 1: Study OPNT0003-OOD-001 Part 2 Schematic



Source: Figure 1 of Study OPNT0003-OOD-001 Clinical Study Report (CSR).

The key inclusion criteria were:

1) Informed consent, and if applicable assent, given according to local regulations
2) Male or female subject aged 18 to 55 years, with Body mass index (BMI) of 18.0 to 32.0 kg/m^2, and ≥ 50 kg, inclusive, at screening
3) Healthy subjects who were nondependent opioid experienced users. Opioid experience defined as exposure to an opioid on at least 1 occasion prior to screening. Healthy status was defined by the absence of evidence of any clinically significant (CS), in the opinion of the Investigator, active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, serology, and urinalysis.
4) Subjects with adequate tolerability of VRH mask and who passed a CO_2 challenge at screening.
5) Following vital signs criteria needed to be met on Day -1 or pre-dose (Day 1) (with subject semi-recumbent before obtaining measures) (Vital signs could be repeated once):
    - Systolic blood pressure: ≤140 mm Hg and ≥90 mm Hg
    - Diastolic blood pressure: ≤90 mm Hg and ≥55 mm Hg
    - Heart rate: ≤100 beats per minute (bpm) and ≥55 bpm
    - Respiratory rate: ≤20 respirations per minute (rpm) and ≥10 rpm
6) Subjects passed a naloxone challenge test at Day -1 to ensure that they were not opioid-dependent (Part 1 extension and Part 2 only).

The Applicant-defined primary endpoint for Part 2 was the change in minute ventilation from remifentanil-induced nadir to 5 minutes after study drug administration.

3.2.2 Statistical Methodologies

The intent to treat (ITT) set consisted of all subjects who are assigned a randomization number and who received at least one dose of any study drug in the Treatment Phase of Part 2. This set was used for the PD parameter summaries and analyses for Part 2. This set were analyzed as randomized.

The Applicant-defined primary endpoint of interest was the change in minute ventilation from remifentanil-induced nadir to 5 minutes ($V_{E\ Change}$ at 5 minutes) after study drug administration in Part 2. The statistical analyses of noninferiority were performed using the ITT set for Part 2 with ExSpiron® Device. The primary endpoint of $V_{E\ Change}$ at 5 minutes after study drug administration were analyzed using the linear model for a two-treatment, two-period crossover trial. The model were treatment, period and sequence as fixed effects, and subject nested within sequence as a random effect.

The least squares (LS) means and the mean difference (naloxone – nalmefene) of change in minute ventilation and corresponding 2-sided 95% confidence interval (CI) were estimated. The Applicant considered that noninferiority (NI) could be demonstrated if:

- the upper limit of the 95% confidence interval is less than 20% of the mean change in minute ventilation for naloxone
  AND
- no individual subject has a change in minute ventilation on nalmefene that is less than 50% of the change in minute ventilation on naloxone

As noted in the pre-NDA meeting, there was no discussion around the selected NI margin or proposed approaches before initiating Part 2 of the study. In this NDA submission, the Applicant didn't provide any data to justify the chosen NI margin. Justification of the NI margin should be provided in terms of M_1 (benefit of active drug over placebo) and M_2 (acceptable loss of effect relative to control while preserving 50% of the control drug effect). The Applicant didn't submit any data of previously conducted placebo-controlled studies for the active control drug (naloxone) to justify the proposed 0.6 L/min margin, nor did they give any specification regarding why any treatment difference within 0.6 L/min would be considered clinically irrelevant.

Additionally, we have reservations about the use of the single-center, open-label design for a pivotal trial because potential bias could be introduced, especially for a non-inferiority study that intended to demonstrate the similarity between the two treatments.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

In Part 2 of the study, 68 subjects were planned to be enrolled. In total, 75 subjects were randomized to 1 of 2 treatment sequences. Seven subjects were replacement subjects. Sixty-nine subjects were included in the analysis sets. Of these, 51 (73.9%) subjects completed the study, 50 subjects were included in the analysis for the primary endpoint (49 subjects who completed the study and 1 early termination subject who had data for the primary endpoint), and 18 (26.1%) subjects were discontinued. Six (8.7%) subjects met protocol-specified withdrawal criteria, 5 (7.2%) subjects discontinued the study by withdrawing their consent, 4 (5.8%) subjects were discontinued due to AEs, 2 (2.9%) subjects were discontinued by the study physician, and 1 (1.4%) subject was discontinued due to other reasons.

Table 3: Summary of Subject Disposition

	Part 2 (N=69) n (%)
Completed Study	51 (73.9)
Discontinued Study	18 (26.1)
Reason for study discontinuation	
Adverse Event	4 (5.8)
Protocol Deviation	0
Lost to Follow-Up	0
Withdrawal by Subject	5 (7.2)
Study Terminated by Sponsor	0
Pregnancy	0
Death	0
Physician Decision	2 (2.9)
Sponsor Request	0
Protocol-Specified Withdrawal Criterion Met	6 (8.7)
Other	1 (1.4)

Source: Table 8 of Study OPNT0003-OOD-001 CSR.

Sixty-nine subjects in Part 2 of the study were included in the Safety Set, ITT Set. Naloxone hydrochloride (4 mg) was administered to 60 subjects and nalmefene hydrochloride (3 mg) was administered to 61 subjects.

Table 4 presents a summary of subject demographics. Majority of the randomized subjects were male (69.6%), not of Hispanic or Latino ethnicity (84.1%), and white (82.6%). Subjects had a mean (SD) age of 29.1 (7.79) years and BMI of 25.27 (3.32) kg/m^2.

Table 4: Summary of Demographics

	Part 2 (N=69) n (%)
Gender	
Male	21 (30.4)
Female	48 (69.6)

Ethnicity	
Hispanic or Latino	11 (15.9)
Not Hispanic or Latino	58 (84.1)
Age	
n	69
Mean (SD)	29.1 (7.79)
Median	27.0
Min, Max	18, 52
Race	
American Indian or Alaska Native	3 (4.3)
Asian	2 (2.9)
Black or African American	6 (8.7)
White	57 (82.6)
Native Hawaiian or Other Pacific Islander	1 (1.4)
Height (m)	
Mean (SD)	175.6 (10.21)
Median	176.0
Min – Max	143 – 198
Weight (kg)	
Mean (SD)	78.3 (14.21)
Median	79.1
Min – Max	50.0 – 108.5
BMI (kg/m^2)	
Mean (SD)	25.27 (3.32)
Median	24.9
Min – Max	18.1 - 31.7

BMI=body mass index; max=maximum; min=minimum; n=number of subjects; SD=standard deviation.
Source: Tables 10 of Study OPNT0003-OOD-001 CSR.

3.2.4 Results and Conclusions

3.2.4.1 Summary of Minute Ventilation (MV) in Part 2

In Part 2, naloxone hydrochloride (4 mg) was administered to 60 subjects and nalmefene hydrochloride (3 mg) was administered to 61 subjects.

For naloxone-treated subjects:

- At gas baseline the mean minute volume was 10.15 L/min. Following hypercapnic gas mixture administration, the mean minute volume increased and reached 17.36 L/min in 10 minutes.

- Prior to infusion of remifentanil (remifentanil baseline), the mean minute volume was 17.30 L/min. Following administration of remifentanil at 0.175 μg/kg/min infusion rate, the mean minute ventilation decreased to 10.55 L/min in 15 minutes (nadir baseline).
- Following administration of naloxone hydrochloride, the maximum minute ventilation value from nadir baseline was 16.44 L/min (mean change: 5.93) after 20 minutes of naloxone hydrochloride administration. The mean minute ventilation and mean change in minute ventilation from nadir baseline after naloxone hydrochloride administration at different timepoints until 120 minutes post-administration are described in the table below.

Table 5: Minute Ventilation and Change in Minute Ventilation from Nadir Baseline for Naloxone

Minutes in Relation to Study Drug Administration	n	Mean MV (L/min) (SD)	n	Change from Baseline (L/min) (SD)
-15 (Remifentanil baseline)	59	17.36 (6.46)	-	-
0 (Nadir Baseline)	59	10.55 (4.65)	58	-0.68 (3.02)
2.5	59	12.25 (4.37)	59	1.70 (4.05)
5	59	13.98 (4.53)	59	3.43 (4.70)
7.5	59	14.56 (4.39)	59	4.01 (4.82)
10	59	15.51 (4.91)	59	4.96 (5.30)
15	59	16.05 (5.23)	59	5.55 (4.94)
20	59	16.44 (5.55)	59	5.93 (5.24)
30	59	8.55 (1.81)	58	-1.95 (4.61)
45	59	8.02 (1.89)	58	-2.53 (4.59)
60	59	12.99 (4.22)	58	2.52 (4.39)
90	57	12.67 (3.93)	56	2.14 (4.66)
95	57	8.23 (3.55)	56	-2.32 (6.16)
100	56	7.00 (1.89)	55	-3.56 (4.93)
110	55	7.93 (2.20)	54	-2.53 (4.20)
120	57	12.49 (3.91)	56	2.02 (3.86)

Source: Tables 14.2.1.3.1 and 14.2.1.3.3 of Study OPNT0003-OOD-001 CSR.

For nalmefene-treated subjects:

- At gas baseline the mean minute volume was 10.12 L/min. Following hypercapnic gas mixture administration, the mean minute volume increased and reached 17.19 L/min in 10 minutes.
- Prior to infusion of remifentanil (remifentanil baseline), the mean minute volume was 16.63 L/min. Following administration of remifentanil at 0.175 μg/kg/min, the mean minute ventilation decreased to 10.63 L/min in 15 minutes (nadir baseline).
- Following administration of nalmefene hydrochloride, the maximum minute ventilation value from nadir baseline to was 17.75 L/min. (mean change: 7.12) after 15 minutes of nalmefene hydrochloride administration. The mean minute ventilation and mean change in minute ventilation from nadir baseline after nalmefene hydrochloride administration at different timepoints until 120 minutes post-administration are described in the table below.

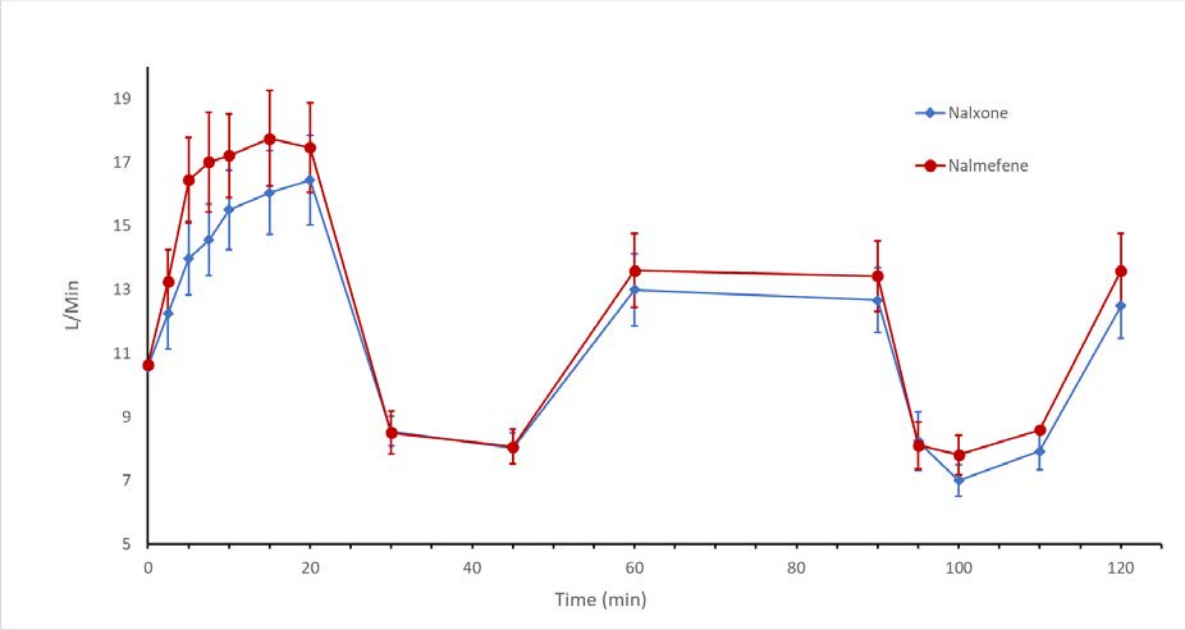
Table 6: Minute Ventilation and Change in Minute Ventilation from Nadir Baseline for Nalmefene

Minutes in Relation to Study Drug Administration	n	Mean MV (L/min) (SD)	n	Change from Baseline (L/min) (SD)
-15 (Remifentanil baseline)	62	17.19 (5.10)		-
0 (Nadir Baseline)	61	10.63 (4.02)	61	-0.70 (2.46)
2.5	60	13.24 (4.06)	60	2.55 (2.97)
5	60	16.44 (5.27)	60	5.74 (4.83)
7.5	61	17.01 (6.26)	61	6.38 (5.51)
10	61	17.21 (5.22)	61	6.58 (5.17)
15	61	17.75 (5.90)	61	7.12 (6.00)
20	60	17.46 (5.55)	60	6.79 (5.53)
30	60	8.50 (2.66)	60	-2.18 (3.93)
45	59	8.06 (2.15)	59	-2.56 (3.92)
60	60	13.60 (4.55)	60	2.92 (4.36)
90	59	13.42 (4.38)	59	2.71 (4.56)
95	59	8.10 (2.92)	59	-2.61 (4.26)
100	59	7.81 (2.48)	59	-2.91 (4.03)
110	59	8.59 (2.27)	59	-2.13 (4.05)
120	59	13.59 (4.60)	59	2.88 (4.60)

Source: Tables 14.2.1.3.1 and 14.2.1.3.3 of Study OPNT0003-OOD-001 CSR.

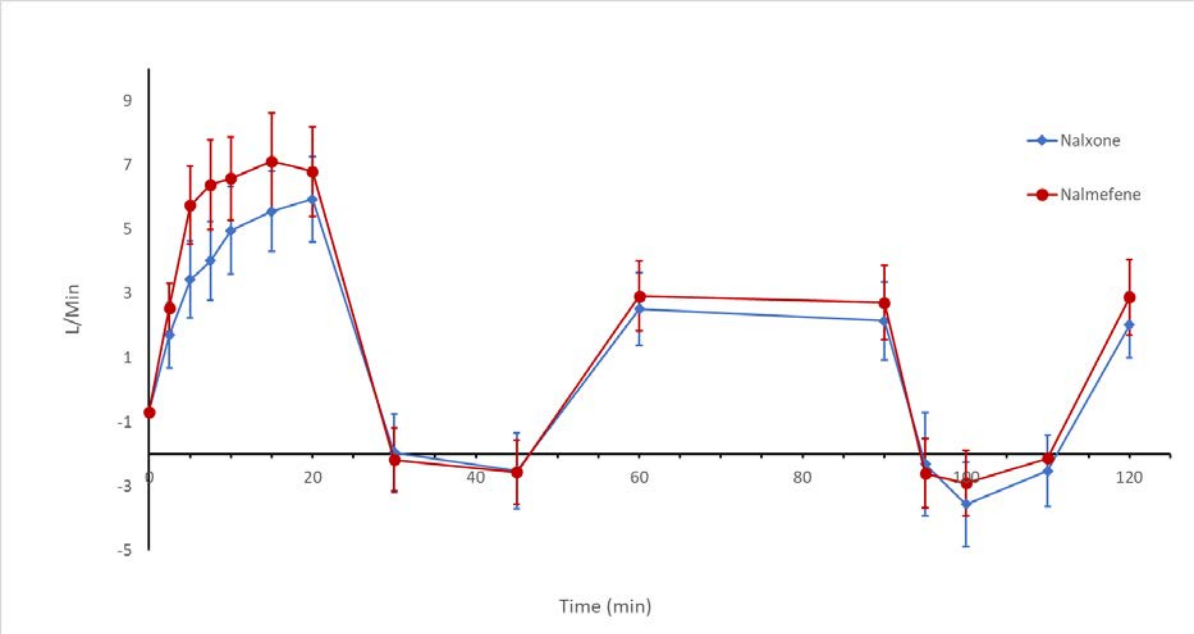
The following figures illustrate the mean MV and the change from baseline of MV from the start of the study treatment administration to 120 minutes post-treatment administration, where the 95% confidence interval (CI) at each time point for each treatment were included as the error bar.

Figure 2: Minute Ventilation (L/Min) from the Start of the Study Treatment Administration to 120 Minutes Post-Administration



Source: Statistical Reviewer's Analyses.

Figure 3: Change from Baseline of Minute Ventilation (L/Min) from the Start of the Study Treatment Administration to 120 Minutes Post-Administration



Source: Statistical Reviewer's Analyses.

These summary statistics indicate that the minute ventilation and the change in minute ventilation from remifentanil-induced nadir to 120 minutes after study drug administration was similar between nalmefene and naloxone.

3.2.4.2 Applicant-Defined Primary Endpoint

The Applicant-defined primary objective for Part 2 was to demonstrate noninferiority of IN nalmefene hydrochloride compared to IN naloxone hydrochloride on minute ventilation during steady-state remifentanil infusion. The statistical analysis of noninferiority was performed using the ITT set for Part 2 with ExSpiron® Device. Only subjects who took both treatments and completed the data collection for 5 minutes post dose, were included in the analysis. As demonstrated in the following table, the upper limit of the 95% CI (-1.175) of the treatment difference between naloxone and nalmefene at 5 minutes post-dose was less than 20% of the Least Squares (LS) mean change in minute ventilation for naloxone (0.6022). Although this result appears favoring nalmefene, it should be noted that the study design and the proposed statistical approach had not been discussed with the Agency before the initiation of Part 2.

Table 7: Applicant-Conducted Statistical Analysis of Nalmefene Versus Naloxone at 5-minute Post-dose - Part 2

	LS Mean						
	Hypercapnic Gas Mixture+Remifentanil+Naloxone (Ref)		Hypercapnic Gas Mixture+Remifentanil+Nalmefene (Test)		LS Mean Difference (Ref-Test)		
Parameter	n	Result	n	Result	Estimate	95%CI	20%*LS Mean Naloxone
VE Change(L/min)	50	3.011	50	5.745	-2.73	(-4.293, -1.175)	0.6022

CI=confidence interval; LS=least squares; VE Change=post dose change in minute ventilation from nadir baseline at selected timepoints.

Analysis was performed using a linear mixed effects model with treatment, period, and sequence as fixed effects and subject nested within sequence as a random effect.

Source: Table 17 of Study OPNT0003-OOD-001 CSR.

3.2.4.3 Conclusion

Although Study OPNT003-OOD-001 demonstrated similarity in minute ventilation between nalmefene (test product) and naloxone (active control), the study was a single-center, open-label trial without NI margin justification, from statistical perspective, the study was not an adequate, well-controlled study; (b) (4)

3.3 Evaluation of Safety

For a comprehensive review of safety, please refer to Dr. Tanya Brescia-Oddo's clinical review.

4 SUMMARY AND CONCLUSIONS

4.1 Statistical Issues

Following are the major statistical issues identified:

- There was no data to justify the chosen NI margin. Justification of the non-inferiority margin should be provided in terms of M_1 (benefit of active drug over placebo) and M_2 (acceptable loss of effect relative to control). The Applicant didn't provide any data from placebo-controlled studies of the active control drug (naloxone) to justify the proposed 0.6 L/min NI margin, nor did they give any specification regarding why any treatment difference within 0.6 L/min would be considered as clinically acceptable loss of effect.
- We have reservations about the use of the single-center, open-label design as a pivotal trial because potential bias could be introduced, especially for a non-inferiority study that intended to demonstrate the similarity between the two treatments.

- If the non-inferiority margin cannot be justified, a three-arm design incorporating a vehicle arm would be scientifically meaningful.

4.2 Conclusions and Recommendations

Study OPNT003-OOD-001 demonstrated similarity in minute ventilation between nalmefene (test product) and naloxone (active control). However, from statistical perspective, the study was not an adequate, well-controlled study; (b) (4)

4.3 Labeling Recommendations

Therefore, (b) (4) PD results of Study OPNT003-OOD-001 (b) (4) could be included the PD Section (Section 12.2) of the label (b) (4)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

YUNFAN DENG
05/05/2023 03:11:12 PM

SUE JANE WANG
05/08/2023 11:27:28 AM