Office of Clinical Pharmacology Review

NDA or BLA Number	217470
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Submission Date	11/22/2022 Clinical Data Submission in this Rolling NDA.
Submission Type	*[Priority review]*
Brand Name	Opvee
Generic Name	Nalmefene HCl Nasal Spray
Dosage Form and Strength	2.7 mg nalmefene nasal Spray
Route of Administration	Intranasal route
Proposed Indication	Reversal of known of suspected opioid overdose-induced respiratory and CNS depression.
Applicant	Opiant Pharmaceuticals, Inc. a wholly-owned subsidiary of Indivior Inc.
Associated IND	*[IND 136851]*
OCP Division:	*Division of Neuropsychiatric Pharmacology*
OND Division:	*Division of Anesthesiology, Addiction Medicine and Pain Medicine*
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1. EXECUTIVE SUMMARY

1.1 Recommendations

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Clinical Pharmacology studies provide the pivotal evidence of effectiveness.
General dosing instructions	Administer one spray, call emergency services, and administer second dose if no response is observed.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Same as general dosing instruction for all patients 12 years and older.
Labeling	Describe results of nalmefene pharmacodynamics pertaining to reversal of opioid-induced respiratory depression in section 12.2 Pharmacodynamics.
Bridge between the to-be-marketed and clinical trial formulations	To-be-marketed formulation and device were used in the clinical studies.
Other (specify)	

1.2 Post-Marketing Requirements and Commitments

The applicant proposed a pediatric study in the agreed initial pediatric study plan (iPSP) during the pre-NDA timeline as follows: Conduct a clinical pharmacokinetic-pharmacodynamic and safety study of Opvee in pediatric patients aged from birth to less than 12 years of age from an at-risk population. At the time of composing this review, the post-marketing requirements and commitments were still being finalized; hence, the final wording might be subject to change.

Note: Opvee is the brand name for the intranasal (IN) nalmefene hydrochloride (HCl) 3 mg. In addition, 3 mg nalmefene HCl salt is the same as 2.7 mg nalmefene base. As the brand name was finalized later in the review cycle, various parts of the review use various names referring to the same product. For example, Opvee, IN nalmefene, intranasal nalmefene, intranasal nalmefene 3 mg spray, IN spray nalmefene 2.7 mg and other variations refer to the same product.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

This is a 505(b)(2) NDA application, which relies on the previous Agency findings of safety and efficacy for the reference listed drug REVEX (nalmefene hydrochloride injection) NDA 020459. REVEX is indicated for the complete or partial reversal of opioid drug effects, including respiratory depression, induced by either natural or synthetic opioids. REVEX is also indicated in the management of known or suspected opioid overdose. The pharmacology and pharmacokinetics (PK) of Opvee, nalmefene nasal spray, have been characterized in two Phase 1 clinical studies in healthy subjects as well as a population PK report that included data from one pharmacokinetic-pharmacodynamic study (PK-PD).

Mechanism of Action: Nalmefene is a well-known opioid antagonist that binds to opioid receptors and prevents or reverses the effects of opioids, including respiratory depression, sedation, and hypotension.

Summary of Pharmacokinetics of Opvee: Following Opvee administration, quantifiable plasma nalmefene levels were observed at the first time point of blood collection that 2.5 minutes. Plasma levels of single nasal spray of Opvee were higher at all timepoints compared to 1 mg intramuscular (IM) injection of nalmefene (lowest effective dose); thus, efficacy of Opvee is implied. Peak plasma levels of nalmefene were noted approximately 15 minutes after single nasal spray administration of Opvee. The applicant states that "While plasma concentrations following IV administration were not reported at earlier time points for REVEX, immediately (e.g., 1 minute) following IV administration plasma concentrations are likely to exceed Cmax concentrations following 1-2 doses of nalmefene nasal spray." It is reasonable to assume that peak plasma nalmefene concentrations of 0.5 to 1 mg nalmefene injection will be higher immediately post bolus administration.

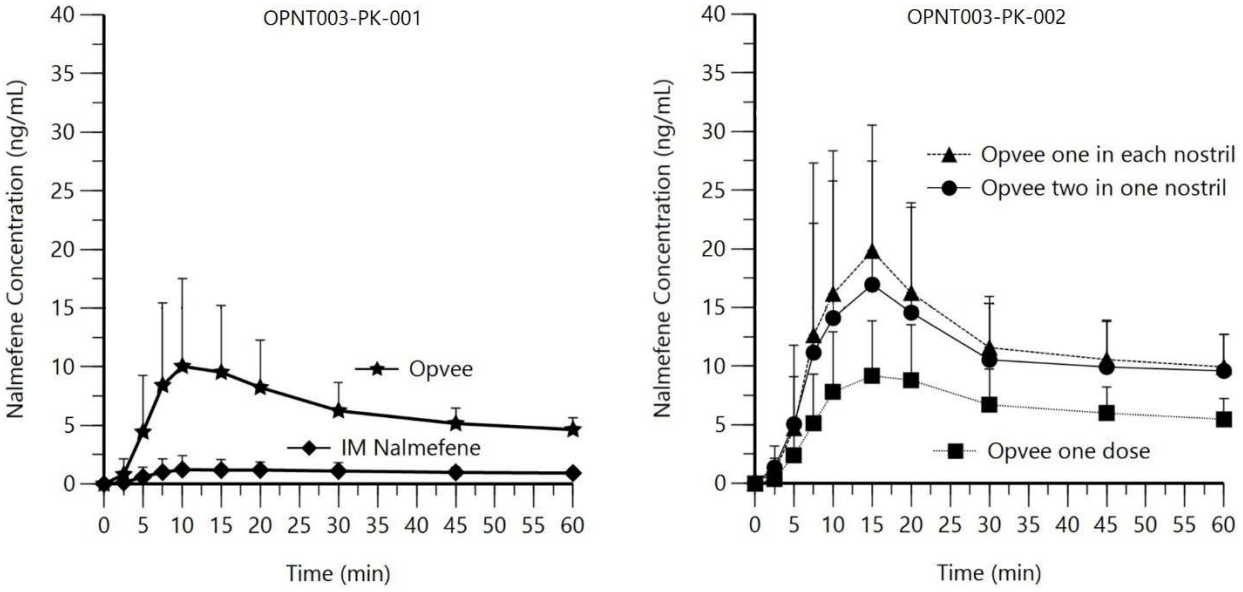


Figure 1: Pharmacokinetics of nalmefene (mean ± SD) following Opvee administration from relative bioavailability study (Left) and repeat dose PK study (Right) truncated to the first hour.

It is anticipated that if the patient does not respond, opioid overdose reversal products may be administered repeatedly until emergency services arrive. Pharmacokinetics of single spray, and two spray doses of Opvee administered as one spray in each nostril and two sprays in one nostril were evaluated in Study OPNT003-PK-002. A dose-proportional increase in Cmax and AUC is noted when comparing single dose and two doses of Opvee administered in each nostril. Approximately 21% higher Cmax was noted when two doses of Opvee were administered one in each nostril compared to two doses in one nostril; AUC was similar between these treatments. Based on Revex injection (NDA 20459) label, nalmefene exhibited dose proportional pharmacokinetics following intravenous administration of 0.5 mg to 2.0 mg. The calculated AUC of label approved dose and data from publication (Kaplan 1999) were used to compared with observed and simulated doses of Opvee nasal spray. The systemic levels (AUC) of up to three doses of Opvee nasal spray are expected to be lower than the highest safe dose of nalmefene (**Table 1**).

Table 1: Systemic exposure of nalmefene (observed and simulated) with Opvee nasal spray and nalmefene Injection.

Parameter	**Single Dose IV (mg)***			**Label indicated 0.5 mg followed by one dose of 1 mg (Simulation)**	**Kaplan et al., 1999, 2 mg x four doses (Simulation)**	**Nasal Spray 2.7 mg**		
						Observed		**Simulation (Three doses administered 5 minutes apart)**
	0.5	1	2			1 dose	2 doses	3 doses
AUC ng*h/mL	8.3	16.6	34.3	24.9	137.2	46.8	89.5	123.92

Source: Revex label Table 1. https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/020459s006lbl.pdf

Simulated doses of three or four doses were conducted with nalmefene nasal spray doses administered with a 5-minute gap between doses. Nonparametric superposition method was employed using Phoenix 32-bit version 8.3.4.295 to generate various PK parameters.

Since both Cmax and AUC of up to three doses of Opvee nasal spray are expected to be below the Cmax and AUC of highest safe and effective doses of IV nalmefene, the safety of two doses of Opvee nasal spray is implied.

Pharmacodynamics: In study OPNT003-OOD-001, following Opvee nasal spray administration the reversal of opioid-induced respiratory depression was noted within 2.5 to 5 minutes in an experimental clinical pharmacology study conducted in opioid-experienced but non-dependent healthy volunteers. In the same study, maximum reversal effect of nalmefene in reversing respiratory depression was noted in 15 minutes (see **Table *12***). Naloxone (Narcan nasal spray) was also included as a positive-control, or an assay sensitivity or validity measure. The observations from the PK-PD study were fit well with Office of Clinical Pharmacology's (OCP) opioid-effects model that was previously published. The OCP's opioid-effects model was developed to translate the systemic exposure of different opioid agonists and antagonists into clinically interpretable outcome such as minute ventilation, blood gas tensions, and cardiac output [3].

Starting from time 0, subjects breathed in a hyperoxic and hypercapnic gas mixture. This resulted in an increase of MV. Starting from 10 min, the remifentanil (0.175 ug/kg/min) infusion began, resulting in a decrease of MV. At the 25th minute, IN nalmefene (A) or naloxone (B) was administered, leading to a recovery (increase) of MV. For the nalmefene group (A), it took less than 10 min for MV to recover to the pre-opioid level (thick horizontal red dash line). For the naloxone group (B), it took at least 20 min. For the nalmefene group (C), 20 min after the IN administration, $ETCO_2$ has recovered (decreased) to the pre-opioid level (thick horizontal red dash line). For the naloxone group (D), 20 min after the IN administration, $ETCO_2$ has not fully recovered (still above the pre-opioid level).

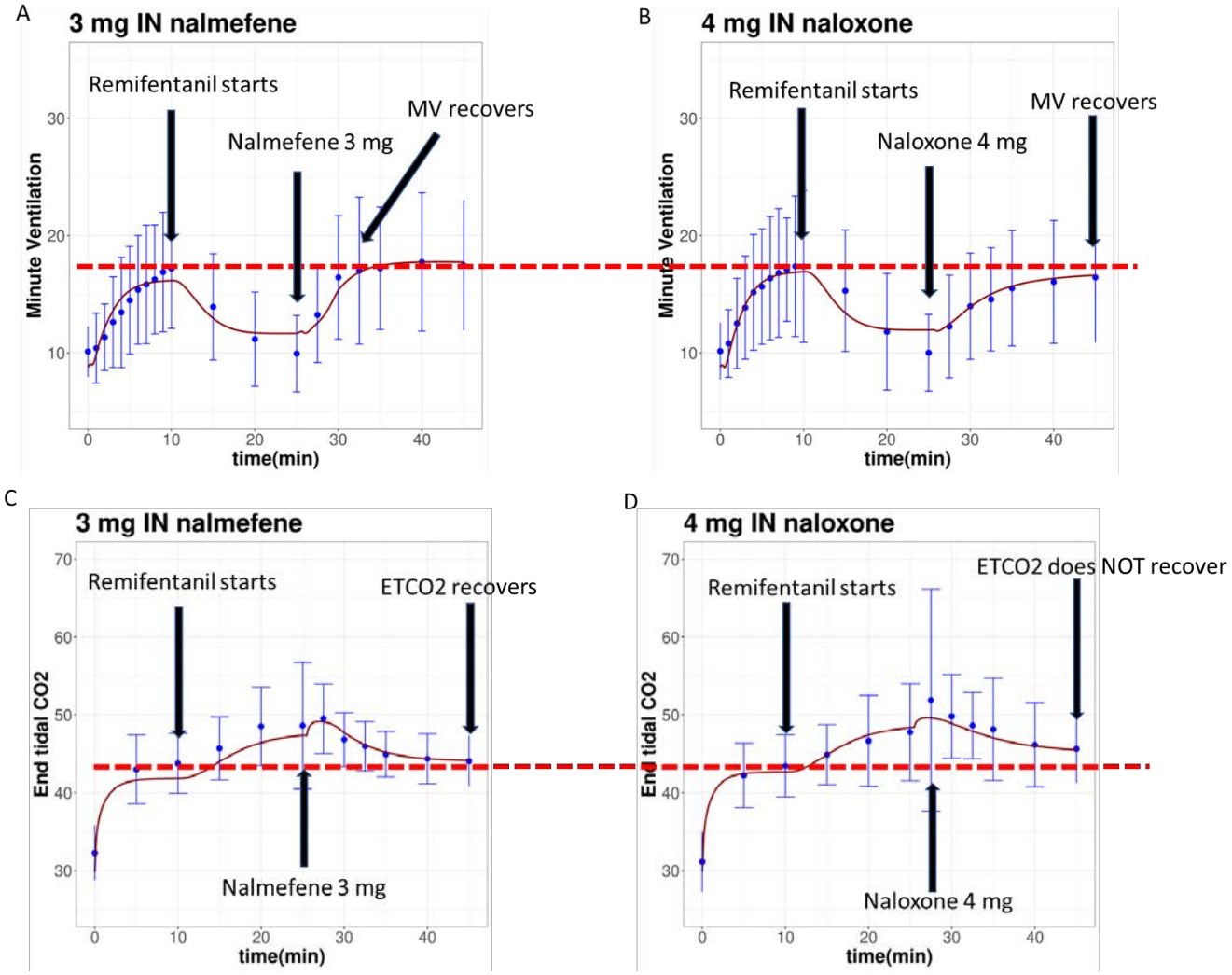


Figure 2: Pharmacologic effects of nalmefene IN 3 mg (A & C) and naloxone IN 4 mg (B & D) on minute ventilation (MV) and end-tidal CO2 ($ETCO_2$) in Study OPNT003-OOD-001.
Figure 2 A and B show effects on MV. Figure 2 C and D show effects on $ETCO_2$. Blue error bars: mean and standard deviation from the study OPNT003-OOD-001. Thin red lines: model simulation of a typical subject.

In addition, OCP's Independent Modeling and Simulation confirmed the time to onset of action, duration of pharmacodynamic effects in terms of hypoxia, cardiac arrest, and preventing renarcotization in virtual population representative of opioid use disorder patients (See DARS Review appended in Section 4.3).

Opvee nasal spray was not evaluated in any specific populations. As such no dosage adjustment is needed in elderly, renal impairment patients or hepatic impairment patients. The basis for the recommendation is reliance on label for nalmefene injection. Based on population PK simulations, compared to an adult population (mean weight 75.42 kg), 12-year-old virtual subjects with a median weight 50.6 kg (range 27.6 to 126.8 kg) are expected to have 7.6% higher mean C_{max} and 25.5% higher mean $AUC_{0-\infty}$. Since such anticipated differences in exposure may not adversely affect safety yet provide effective plasma nalmefene concentrations, dosage adjustment of Opvee nasal spray in adolescent patients is not needed.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

Recommended dose for the reversal of known or suspected opioid overdose in patients 12 years and older is a single spray of Opvee. Emergency medical services should be called after the first dose. If the patient does not respond within two to five minutes, a second dose of Opvee may be administered. If the patient responds to Opvee, repeat dosing may not be necessary, particularly while in care of emergency services personnel.

2.2.2 Therapeutic individualization

General dosing recommendations apply to patients 12 years and older. Adolescent patients (average bodyweight 50 kg) are expected to have similar exposure to nalmefene as adults. Titration or dosage adjustment with regard age, gender, bodyweight, hepatic impairment, and renal impairment is not necessary.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The applicant proposed two-pack presentation of Opvee nasal spray is acceptable. A single spray in patients over 12 years and older is recommended for reversal of known or suspected opioid overdose. If necessary, an additional dose of Opvee two to five minutes after the first dose is adequate.

Descriptive observations regarding time to onset, time to peak effect and duration of effect of nalmefene in reversing opioid-induced respiratory depression following Opvee administration from Study OPNT003-OOD-001 should be described in Section 12.2 Pharmacodynamics.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Opiant Pharmaceuticals submitted rolling 505(b)(2) NDA 217470 for nalmefene nasal spray (Brand name Opvee) which relies on the previous Agency findings of safety and efficacy for the reference listed drug REVEX (nalmefene hydrochloride injection) NDA 020459. Clinical datasets and study reports rolled in on 11/22/2022. REVEX is indicated for the complete or partial reversal of opioid drug effects, including respiratory depression, induced by either natural or synthetic opioids. REVEX is also indicated in the management of known or suspected opioid overdose. Opvee Nasal Spray comprises 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). The applicant intends to market the product as a two-pack presentation.

In addition to the study that accomplishes scientific bridge between Opvee nasal spray and Revex injection, the submission has significant claims regarding dosing & administration, onset of action, duration of action, section 12.2 Pharmacodynamics, (b) (4) that rely on the following studies:

- OPNT003-PK-001 is an "open-label, randomized, 2-period, 2-treatment, 2-sequence, crossover study in 68 healthy volunteers to evaluate bioavailability of nalmefene comparing Revex Intranasal Spray with a Opiant manufactured intramuscular nalmefene injection." This study supports the scientific bridge between the to-be-marketed Revex nasal spray to the previously approved NDA 020459 Revex injection.

At the time of nalmefene nasal spray development, the reference drug Revex Injection was discontinued for reasons other than safety and efficacy considerations. After thorough deliberations within the Agency, the applicant was advised that in this limited circumstance use of the applicant proposed comparator product in the PK study could be appropriate for the purpose of establishing a scientific bridge (post-meeting note in IND 136851 meeting minutes dated 1-13-2021).

- OPNT003-PK-002 is 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 reversal of opioid overdose in community setting involves administration of first dose followed by calling in emergency medical service personnel. In anticipation of repeated use of the product, while waiting for arrival of emergency medical services, the applicant conducted this study to assess PK of nalmefene with repeated dose (two). The applicant would like to market prescription nalmefene nasal spray as a two-pack presentation.

- OPNT003-OOD-001 is an "A Two-Part Open-Label Study of the Pharmacodynamic Effects of Intranasal Nalmefene Compared to Intranasal Naloxone in Healthy Volunteers Under Steady-State Opioid Agonism."

As previously mentioned, the reference drug Revex is effective in reversing known or suspected opioid overdose-induced respiratory depression and central nervous system depression. This study was initiated after Agency's advice letter dated 11/7/2019 issued to all nalmefene product developers to address the onset of action, duration of action, and need for titration. This experimental pharmacological model was previously described in Ultiva (remifentanil) label (Drugs@fda), and similar studies evaluated effect of naloxone and nalmefene on reversal of opioid-induced respiratory depression and central nervous system depression in healthy subjects (for example, Glass P.S.A. et al., Anesth. Analg. 1994; 78:536-541). Utilizing remifentanil-induced opioid agonism/opioid-induced respiratory depression, the applicant determined the time to onset of action, and possibly the duration of action of nalmefene. While there was no placebo employed in this model, and use of naloxone (Narcan nasal spray) served as a positive-control or an assay sensitivity or validity measure.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Characteristic	Drug Information
Established Pharmacological Class	Opioid receptor antagonist
Mechanism of Action	Nalmefene is an opioid antagonist that binds to opioid receptors and prevents or reverses the effects of opioids, including respiratory depression, sedation, and hypotension.
Active Moieties	Nalmefene
Bioanalysis	Nalmefene is detected in plasma using a validated by LC-MS-MS method.
Pharmacodynamics (Reversal of respiratory depression) **Note:** An experimental clinical pharmacology study evaluated recovery of respiratory drive with nalmefene nasal spray remifentanil infusion in CO_2 stimulated minute ventilation in adult volunteers.	
Time onset	After single nasal spray of Opvee reversal of respiratory depression was observed within 2.5 to 5 minutes.
Time to peak effect	Maximum recovery of respiratory drive was observed around 15 minutes after single nasal spray administration of Opvee.
Duration of effect	The time duration for which plasma concentrations are above the EC50 (concentration at which pharmacological effect is half maximum) was 5.94 hours following a single administration of Opvee nasal spray
Pharmacokinetics	
Dose-proportionality	Dose-proportional pharmacokinetics are observed with 1 – 2 Opvee doses. Dose-normalized Cmax, AUClast, and AUCinf were similar after one spray of Opvee, and two sprays administered in each nostril (two doses).
Absorption	Quantifiable levels of nalmefene are noted in 2.5 minutes following Opvee nasal spray administration. Plasma nalmefene concentration with single Opvee nasal spray are higher than 1 mg IM injection at all time points. Nalmefene IM and subcutaneous (SC) Injection: Therapeutic plasma concentrations are likely to be reached within 5-15 minutes after a 1 mg dose in an emergency.
Bioavailability	The mean relative bioavailability of intranasal nalmefene hydrochloride was 0.81 (CV 11%) relative to IM injection after dose normalization. Single dose Opvee resulted in AUCinf 40.3 ng.hr/mL.

Tmax	Peak plasma levels of nalmefene are noted at a median of 15 minutes (5 minutes to 2 hours) following Opvee nasal spray administration.
Distribution	Nalmefene distributes into brain. Based on population pharmacokinetics the central volume of distribution was 65.7 liters and peripheral volume of distribution was 102 liters.
Elimination	Terminal elimination half-life of nalmefene is 11.4 hours (%CV 20.8). Apparent clearance of nalmefene is 75.7 L/hr (%CV 23.8) based on noncompartmental analysis.
Metabolism	Nalmefene is metabolized by the liver, primarily by glucuronide conjugation and into trace amounts of N-dealkylated metabolites.
Excretion	Nalmefene is and its metabolites are excreted in the urine. Data also suggests nalmefene undergoes enterohepatic circulation.
Intrinsic Factors and Specific Population	
Bodyweight	No dosage adjustment is needed for adolescents and adults with regard to body weight. Effect of body weight was assessed in population PK analysis and PK-PD analysis generated from studies that used Opvee nasal spray. Compared to the mean PK values across the full population in the PK dataset (median weight 74.70 kg), the 1st quartile of body weight (50.4 to 64.8 kg) had + 5.2% higher Cmax and + 15.7% and AUC0-∞ and the 4th quartile of body weight (91 to 106.8 kg) had – 4.4% lower Cmax and – 11.6% and AUC0-∞. Body weight does not affect the maximum effect (Rmax), time to maximum effect (TRmax), or time to achieve a concentration associated with half-maximum effect (EC50).
Age	No dosage adjustment is needed for elderly patients. Pharmacokinetics of Opvee nasal spray were not evaluated in elderly patients. Nalmefene Injection: Pharmacokinetics of IV nalmefene were similar in young adults and elderly men, and dose-proportional in elderly men.
Renal Impairment	No dosage adjustment is needed for patients with renal impairment. Pharmacokinetics of Opvee nasal spray were not evaluated in patients with renal impairment. Nalmefene injection: There was a decrease in plasma clearance of nalmefene in the end-stage renal disease (ESRD) population during dialysis compared to control subjects. For single episodes of opioid antagonism, adjustment of nalmefene injection dosage is not required.
Hepatic Impairment	No dosage adjustment is needed for elderly patients. Pharmacokinetics of Opvee nasal spray were not evaluated in patients with hepatic impairment. Nalmefene injection: Subjects with hepatic disease, when compared to matched normal controls, had a 28.3% decrease in plasma clearance of nalmefene following IV injection. For single episodes of opioid antagonism, adjustment of nalmefene injection dosage is not required.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

Clinical pharmacology submission provides pivotal support of effectiveness. PK study OPNT003-PK-001 provides the scientific bridge between listed drug Revex (IM nalmefene injection) and nalmefene nasal

spray. PK study OPNT003-PK-002 supports repeated dosing with up to two doses of nalmefene nasal spray. PK-PD study OPNT003-OOD-001 addresses the clinical concerns raised during the drug development.

Study OPNT003-PK-001: As with any opioid overdose reversal drug, initial concentrations of nalmefene after drug administration are important. Plasma concentrations and partial AUCs for time points starting at 2.5 minutes up to 30 minutes were higher following nalmefene nasal spray (2.7 mg nalmefene base) compared to IM nalmefene injection (1 mg nalmefene base)(**Figure 3** and

Table *2*). Maximum nalmefene exposure (Cmax) was approximately 6.86-fold higher, partial AUCs were approximately 4.57-fold to 8.37-fold higher, and total exposure (AUClast and AUCinf) were approximately 2.41- to 2.43-fold higher after IN administration compared to after IM administration. Time to peak plasma concentrations were noted at median 0.25 hours and 0.333 hours following IN spray and IM injection, respectively. AUCinf of IM nalmefene injection corroborates with label described pharmacokinetic measures. The mean relative bioavailability of intranasal nalmefene hydrochloride was 0.81 (CV 11%) relative to intramuscular administration after dose normalization. Full details of the PK study results can be found in the appended synopsis 4.2.1.

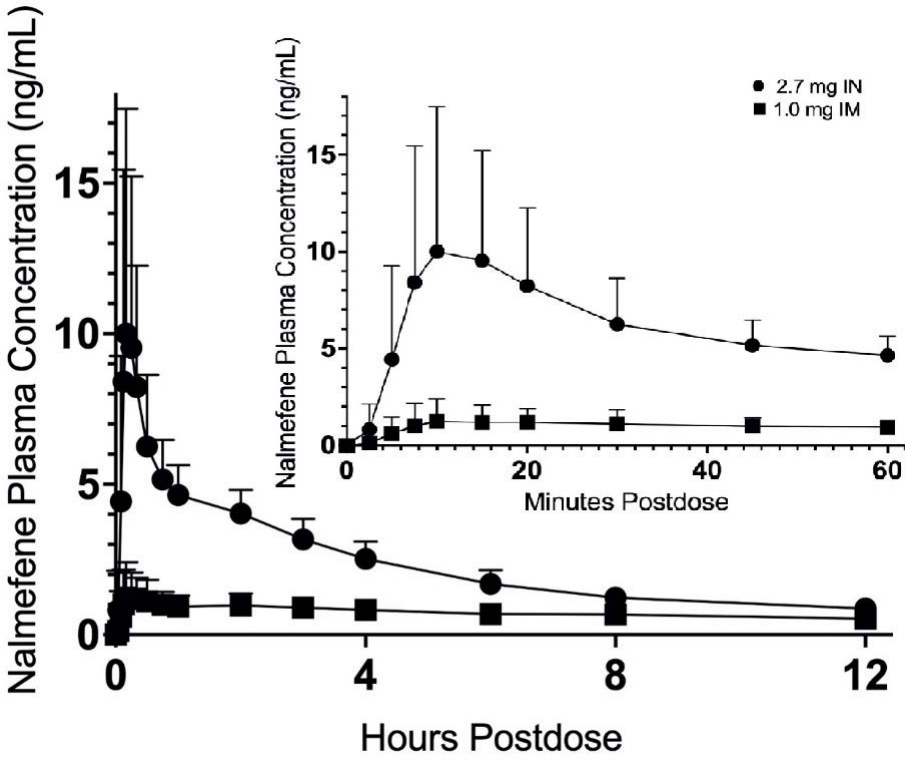


Figure 3: Plasma nalmefene profile (mean ± SD) over time truncated to 12 hours (inset up to 60 minutes) following IM nalmefene injection and nalmefene nasal spray (3 mg nalmefene HCl or 2.7 mg nalmefene base) in 64-68 healthy volunteers.

Table 2: Statistical analysis comparing Nalmefene nasal spray (3.0 mg Nalmefene Hydrochloride or 2.7 mg base (Treatment A, Test)) to 1.0 mg of IM Nalmefene Hydrochloride Injection (Treatment B, Reference).

Dependent	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]				ANOVA
Variable	Test	Ref	(Test/Ref)	Lower	Upper	Power	p-value[d]	CV%
C_{max} (ng/mL)	10.3	1.50	685.98	609.14	772.51	0.9262	<0.0001	42.64
$AUC_{0\text{-}2.5min}$ (ng.h/mL)	0.008	0.002	456.58	331.53	628.80	0.3106	<0.0001	153.66
$AUC_{0\text{-}5min}$ (ng.h/mL)	0.060	0.010	584.17	458.02	745.06	0.4464	<0.0001	100.73
$AUC_{0\text{-}10min}$ (ng.h/mL)	0.514	0.064	803.98	682.79	946.68	0.7282	<0.0001	60.96
$AUC_{0\text{-}15min}$ (ng.h/mL)	1.19	0.142	837.01	724.57	966.91	0.8176	<0.0001	52.85
$AUC_{0\text{-}20min}$ (ng.h/mL)	1.87	0.228	821.20	722.79	933.00	0.8919	<0.0001	46.12
$AUC_{0\text{-}30min}$ (ng.h/mL)	3.04	0.405	752.66	671.80	843.27	0.9436	<0.0001	40.65
AUC_{last} (ng.h/mL)	38.9	16.0	243.15	237.91	248.50	1.0000	<0.0001	7.50
AUC_{inf} (ng.h/mL)	40.3	16.8	240.61	235.14	246.21	1.0000	<0.0001	7.92

[a] Geometric Mean for Treatment A, Test Product (Test) and Treatment B, Control Product (Ref) based on Least Squares Mean of
log-transformed parameter values
[b] Ratio (%) = Geometric Mean (Test)/Geometric Mean (Ref)
[c] 90% Confidence Interval
[d] p-value for the difference between treatments; Significant difference defined *a priori* as $p < 0.05$
Source data: Study Report OPNT003-PK-001, Table 14.4.3 and Listing 16.2.6.5

Study OPNT003-PK-002: It is reasonable to assume that a repeat dose may be administered two to five minutes later if no response is observed after the first dose. The applicant proposes to market the product as a two-pack presentation. Initial concentrations of nalmefene after drug administration are important. Quantifiable nalmefene concentrations were observed at the first sample collection time (2.5 min) for each treatment, that is after single intranasal spray (Treatment A or T1), one intranasal spray in each nostril (Treatment B or T2), and two intranasal sprays in one nostril (Treatment C or T3). Peak plasma concentrations of nalmefene were observed at approximately 0.250 h to 0.267 h (15 to 16 min) post-dose for all treatments; median (range) Tmax values for Treatments A (T1), B (T2), and C (T3) were 0.267 h (0.167 – 2.03 h), 0.250 h (0.117 – 3.00 h), and 0.250 h (0.117 – 2.03), respectively. Mean Cmax, AUClast, and AUCinf values were approximately 2-fold higher after the 6.0 mg treatments (Treatment B, T2 and Treatment C, T3) compared to the 3.0 mg treatment (Treatment A, T1). Mean half-life (t1/2), clearance (CL/F), and volume of distribution (Vz/F) values were similar across treatments (See additional details in **Table 7**).

Based on dose-normalized results, peak nalmefene exposure (Cmax) was approximately 21% higher after 3 mg administered to each nostril (Treatment B, T2) compared to that after 6 mg administered to

one nostril (Treatment C, T3). Dose-normalized total nalmefene exposure (AUClast and AUCinf) were similar for both treatments (geometric mean ratios were 105.56% and 105.53%, respectively).

Repeated doses of nalmefene were administered without delay in this study, unlike the proposed two-to-five-minute wait time. It is important to note that detectable plasma nalmefene concentrations are observed at 2.5 minutes, and a dose-proportional increase in plasma levels is noted with two doses. Therefore, the study supports repeated dosing up to two doses administered without delay or up to 5 minutes of wait time.

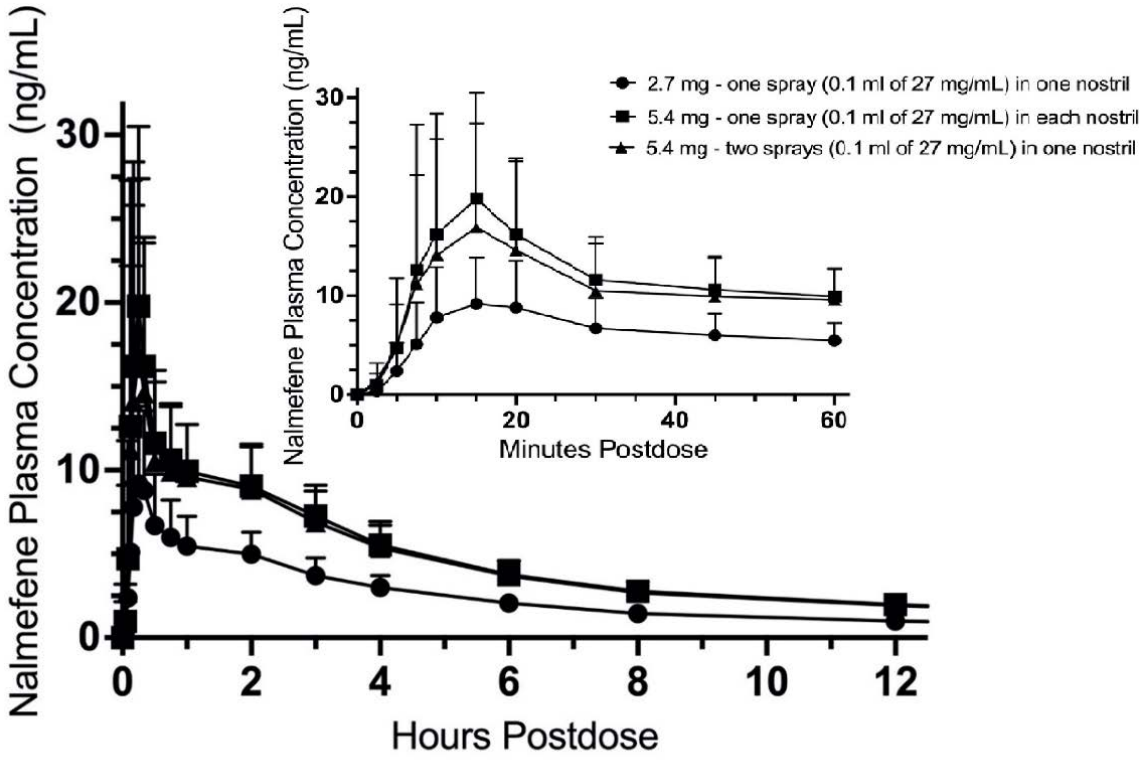


Figure 4: Plasma nalmefene profile (mean ± SD) over time truncated to 12 hours (inset up to 60 minutes) following single nalmefene nasal spray (3 mg nalmefene HCl or 2.7 mg nalmefene base), two doses (one in each nostril, and two doses (two in one nostril) in healthy volunteers.

Study OPNT003-OOD-001: Use of IV bolus nalmefene is indicated in the reversal of known or suspected opioid overdose. Should intravenous access be lost or not readily obtainable, a pharmacokinetic study has shown that a single dose of REVEX should be effective within 5-15 minutes after intramuscular or subcutaneous doses of 1.0 mg. Agency expressed concern that while 5-15 minutes of onset time may be acceptable in an emergency room where other resuscitative measures are available, such a delay in community setting may not be desirable. To address the Agency's concerns about the time to onset, and duration of action the applicant conducted the study OOD-001. Pharmacokinetics and pharmacodynamics of nalmefene were evaluated in opioid-experienced but non-dependent and otherwise healthy volunteers. Quantifiable plasma levels of nalmefene were noted within 2.5 minutes after single dose Opvee administration (Table 15). In addition, OCP's independent modeling & simulation using a previously developed systems pharmacology model (referred to as an opioid-effects

model [OEM]) support that nalmefene IN 3 mg has an adequate time to onset of action for reversal of opioid overdose in a community setting (**Figure 2** described above in Section 2.1, and **Figure 11** below in Appendix 4.3).

During initial development and validation of the opioid-effects model published by OCP [3], it was found that the onset of action of an opioid antagonist has a significant impact on two clinical endpoints: the antagonist's capability of preventing opioid-associated cardiac arrest, and its capability of shortening the brain hypoxia time. To translate the applicant's findings to a community setting, OCP's independent simulation of nalmefene IN 3 mg focused on these two endpoints. To better mimic community overdose situations, the opioids used in the simulations were fentanyl and carfentanil, using the medium overdose scenarios and virtual populations representing chronic opioid users (see **4.3.3 Methods**).

As shown in **Figure *5***, 1 dose of nalmefene IN 3 mg reduced the simulated percentage of patients experiencing fentanyl-associated cardiac arrest from 52% (median value without antagonist's administration) to 18% (median value with nalmefene), a 34% reduction. In contrast, 1 dose of naloxone IN 4 mg reduced the simulated cardiac arrest percentage from 52% to 28% (a 24% reduction). Similarly, after carfentanil overdose, nalmefene IN 3 mg reduced the simulated percentage of cardiac arrest by 38% (from 59% to 21%), compared to the 25% reduction (from 59% to 34%) when naloxone IN 4 mg was administered.

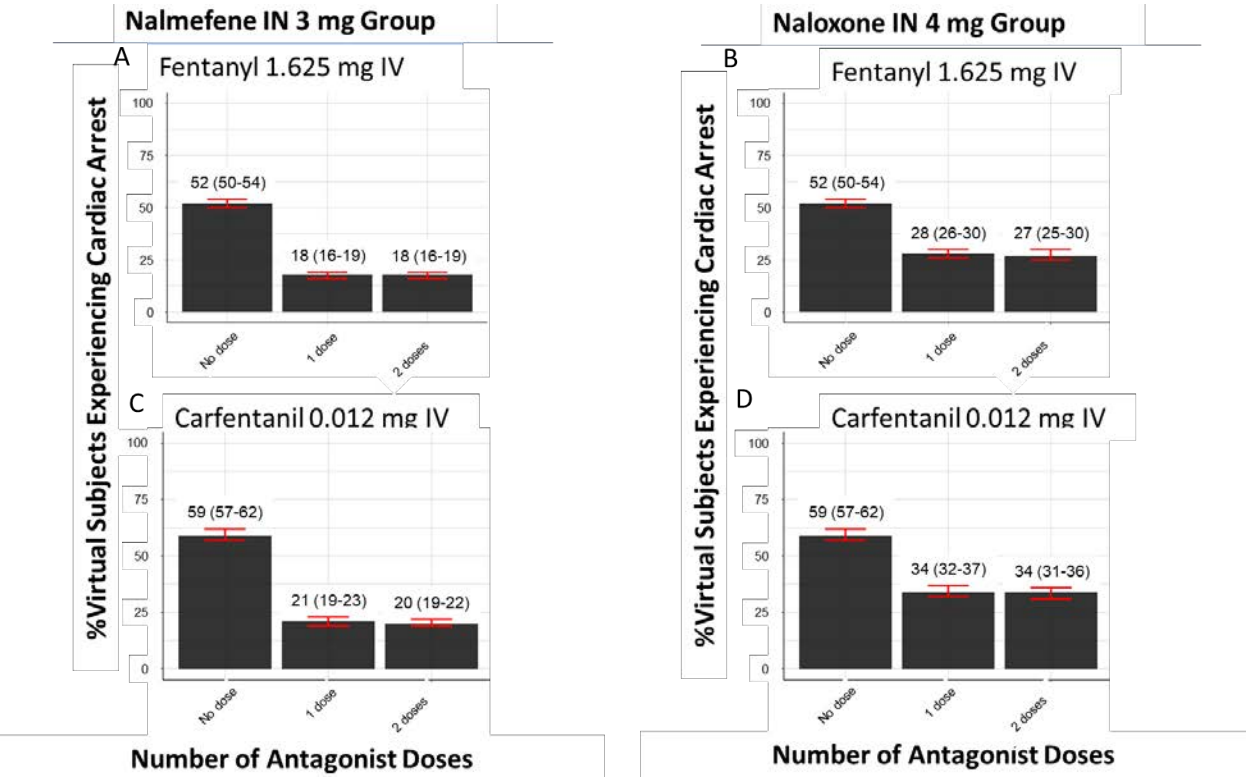


Figure 5: Percentage of virtual patients experiencing cardiac arrest after fentanyl (A and B) or carfentanil (C and D) overdose.

The opioid doses are based on the medium overdose scenarios previously estimated (1.625 mg intravenous bolus injection for fentanyl, and 0.012 mg for carfentanil). The 3 bars on each X axis represent no antagonist administration, 1 dose intranasal (IN) administration, and 2 doses IN administration (2.5 min apart, one dose into separate nostrils), respectively. The antagonist administered is nalmefene IN 3 mg (A and C) and naloxone IN 4 mg (B and D). The red error bars are the median and interquartile range of the estimated cardiac arrest percentages through repeated sampling of the virtual population (see Methods). The median and interquartile range values are also labeled on top of each error bar.

Finally, OCP's independent modeling & simulation suggests nalmefene's long duration of action, primarily due to its longer plasma half-life, would prevent re-narcotization up to 6 hours after antagonist administration in cases of delayed opioid absorption or prolonged exposure. The OCP opioid-effects model was used to simulate a high opioid dose (carfentanil 0.287 mg) that was slowly absorbed into the systemic circulation. Such a scenario may happen when opioid exposure is through routes such as inhalation (prolonged exposure) or oral (delayed gastrointestinal absorption). **Figure *6*** shows the simulated minute ventilation of a typical subject during such a slow opioid absorption with a single dose of either nalmefene IN 3 mg or naloxone IN 4 mg administered as the antagonist. As can be seen, both nalmefene and naloxone were able to recover minute ventilation initially. However, while nalmefene IN 3 mg administration restored minute ventilation for a relatively long time, naloxone IN 4 mg administration did not restore minute ventilation to baseline levels and minute ventilation gradually began to decline further. About 6 hours after naloxone IN 4 mg administration, minute ventilation decreased sufficiently to trigger cardiac arrest.

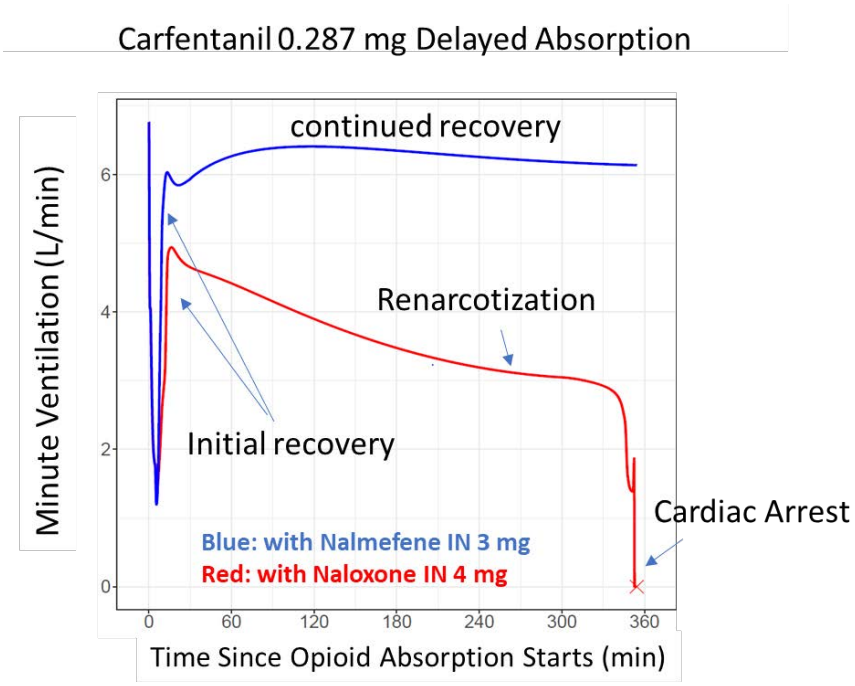


Figure 6: Comparison of nalmefene IN vs naloxone IN in preventing re-narcotization.

A large dose (0.287 mg) of carfentanil was simulated to be absorbed into the systemic circulation slowly. Both nalmefene IN 3 mg (blue) and naloxone IN 4 mg (red) were given 1 min after the minute ventilation dropped below 40% of baseline. This resulted in initial recovery from both antagonists. As time goes by,

the typical patient's minute ventilation after nalmefene IN administration remained at a high level. In contrast, the minute ventilation after naloxone IN administration decreased gradually, until it hit a critical point and triggered cardiac arrest about 6 hours after naloxone administration.

These simulations agree with the observations for nalmefene as noted in the Revex NDA 20459 label. For example, the label states "Pharmacodynamic studies have shown that nalmefene has a longer duration of action than naloxone at fully reversing doses. The duration of action of nalmefene is as long as most opioid analgesics. The apparent duration of action of nalmefene will vary, however, depending on the half-life and plasma concentration of the narcotic being reversed, the presence or absence of other drugs affecting the brain or muscles of respiration, and the dose of nalmefene administered."

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Does the clinical pharmacology evidence support the safe use in opioid use disorder patients?

It is expected that opioid use disorder patients may experience precipitated withdrawal when an opioid antagonist is used to prevent or reverse opioid overdose-induced respiratory and CNS depression.

The applicant proposes to market a two-pack presentation of Opvee nasal spray with the provision of repeated use two to five minutes later if no response is observed after first dose. The applicant responded to Agency's information request to address the safety of repeat dose administration in the context of previously approved REVEX injection and any available published data. Pharmacokinetic simulations were conducted to contextualize the impact of repeated doses of up to three doses of Opvee nasal spray compared to safety, in terms of precipitated withdrawal, known from intravenous use of nalmefene injection.

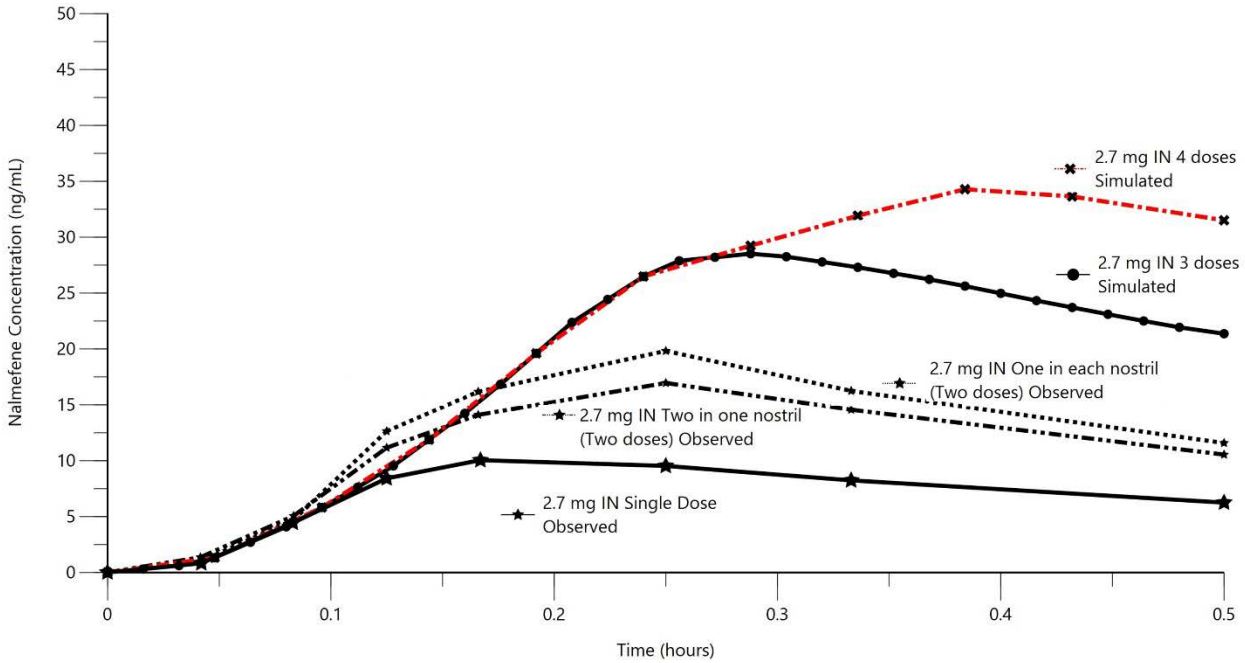


Figure 7: Mean profile of nalmefene observed and simulated following various doses of Opvee nasal spray (FDA analysis).

Observed: single dose (five-point star and solid line), two doses (one in each nostril, five-point star and dashed line); two doses (five-point star and long dash and dot), and
Simulated doses of three (circle and solid line) or four doses (X and long dash and dotted line in red color). Simulations were conducted with nalmefene nasal spray doses administered with a 5-minute gap between doses. Nonparametric superposition method was employed using Phoenix 32-bit version 8.3.4.295 to generate various PK parameters and profiles.

Safety with respect to AUC or overall exposure: The applicant proposes to market a two-pack presentation. We have used observed data and simulated additional one dose (total of three doses) to assess AUC. Safety of two doses is supported by the applicant's study PK-002 compared to label indicated AUC values for IV injection. Additionally, the applicant submitted two publications Kaplan 1993 and Kaplan 1999 where doses of up to 2 mg nalmefene IV injection were evaluated up to four doses administered five minutes apart. These publications offer supplementary support to safety. As shown in ***Table 1*** above, the AUC of up to three doses of Opvee nasal spray are expected to be lower than the highest safe regimen of nalmefene injection.

Safety with respect to Peak Plasma Concentrations: The applicant states that "While plasma concentrations following IV administration were not reported at earlier time points for REVEX, immediately (e.g., 1 minute) following IV administration plasma concentrations are likely to exceed Cmax concentrations following 1-2 doses of nalmefene nasal spray." In the Revex injection labeling, plasma drug concertation at 5 min following a 1 mg intravenous dose was reported, with a mean value of 3.7 ng/mL in young subjects and 5.8 ng/ml in elderly subjects. Additionally, a publication reported nalmefene plasma concentrations at 5 minutes after bolus dose of 2 mg nalmefene injection at an average of 17.3 ng/mL in healthy volunteers (Frye R.E. et al., Clin. Pharm. Ther. 1997, 61(1):15-23. For an intravenous injection product, the highest plasma drug concentration should be observed right after injection, and then drop quickly mainly due to drug distribution. Therefore, it is reasonable to assume that the drug concentration immediately after intravenous administration of nalmefene will be higher than the reported values at 5 min after injection. In addition, considering dose proportionality and accumulation after multiple-dose administration, the plasma concentration immediately after 4 repeated intravenous doses of 2 mg nalmefene injection, five minutes apart, will be even higher. Therefore, based on totality of evidence, the applicant's rationale is justified on a scientific basis. It is reasonable to conclude that the Cmax value after three doses of Opvee nasal spray (approximately 31.78 ng/mL) will be comparable or lower compared to 4 repeated intravenous administrations of 2 mg IV nalmefene injection.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

Does the population PK report support similar PK of nalmefene with Opvee nasal spray in adolescents and adults? Is there an effect of bodyweight on PK of Opvee?

Opvee nasal spray was not evaluated in any specific populations. As such no dosage adjustment is needed in elderly, renal impairment patients or hepatic impairment patients. The basis for the recommendation is reliance on label for nalmefene injection. Based on population PK simulations, compared to an adult population (mean weight 75.42 kg), 12-year-old virtual subjects with a median weight 50.6 kg (range 27.6 to 126.8 kg) are expected to have 7.6% higher mean C_{max} and 25.5% higher mean $AUC_{0-\infty}$. Since such anticipated differences in exposure may not adversely affect safety yet provide

effective plasma nalmefene concentrations, dosage adjustment of Opvee nasal spray in adolescent patients is not needed.

Geriatrics: In previous studies with nalmefene hydrochloride injection, dose proportionality was observed in nalmefene AUC following 0.5 to 2 mg intravenous administration to elderly male subjects. Following a 1 mg intravenous nalmefene dose, there were no significant differences between young (19-32 years) and elderly (62-80 years) adult male subjects with respect to plasma clearance, steady-state volume of distribution, or half-life. There was an apparent age-related decrease in the central volume of distribution (young: 3.9± 1.1 L/kg, elderly: 2.8 ± 1.1 L/kg) that resulted in a greater initial nalmefene concentration in the elderly group. While initial nalmefene plasma concentrations were transiently higher in the elderly, it would not be anticipated that this population would require dosing adjustment. No clinical adverse events were noted in the elderly following the 1 mg intravenous nalmefene dose.

Hepatic Impairment: In previous studies with nalmefene hydrochloride injection, subjects with hepatic disease, when compared to matched normal controls, had a 28.3% decrease in plasma clearance of nalmefene (0.56 ± 0.21 L/hr/kg versus 0.78 ± 0.24 L/hr/kg, respectively). Elimination half-life increased from 10.2 ± 2.2 hours to 11.9 ± 2.0 hours in the hepatically impaired. No dosage adjustment is recommended since Opvee nasal spray will be administered as an acute course of therapy.

Renal Impairment: In previous studies with nalmefene hydrochloride injection, there was a statistically significant 27% decrease in plasma clearance of nalmefene in the end-stage renal disease (ESRD) population during interdialysis (0.57± 0.20 L/hr/kg) and a 25% decreased plasma clearance in the ESRD population during intradialysis (0.59 ± 0.18 L/hr/kg) compared to normals (0.79±0.24 L/hr/kg). The elimination half-life was prolonged in ESRD patients from 10.2 ± 2.2 hours in normals to 26.1 ± 9.9 hours.

Weight: The effect of weight on nalmefene PK is assessed with population pharmacokinetic simulations. The PK of a single IN nalmefene 3 mg administration was assessed. Compared to the mean PK values across the full population in the PK dataset (median weight 74.70 kg), the 1st quartile of body weight (50.4 to 64.8 kg) had + 5.2% higher Cmax and + 15.7% and AUC0-∞ and the 4th quartile of body weight (91 to 106.8 kg) had – 4.4% lower Cmax and – 11.6% and AUC0-∞. A dose adjustment Weight values representing adolescent subjects were utilized in simulations to assess the effect of weight on PK in this age group. Based on the simulations, a 12 year old subjects (median wt 50.6 kg; 27.6 to 126.8 kg range), compared to the mean PK values across the full population in the PK dataset, have +7.6 higher Cmax and +25.5% higher AUC0-∞. The Applicant conducted PD simulations of a single 3 mg IN nalmefene administration to help assess the effect of weight on PD in adult and adolescent subjects. Weight does not affect the maximum PD effect (range 17.3 to 17.5 L/min), time to maximum effect (18.5 minutes), or time to achieve a concentration associated with half-maximum effect (4 to 4.05 minutes). The predicted effect duration is 6.92 hours in the full population, 6.18 hours for the 4^{th} weight quartile (91 to 106.8 kg), 8.03 hours for the 1^{st} weight quartile (50.4 to 64.8 kg), and 8.79 hours for 12-year old. Compared to the predicted effect duration in the 1^{st} weight quartile in adults (8.03 hours), the predicted effect duration in 12 year old (8.79 hours) is +10% longer. From a PK perspective, the proposed 3 mg IN nalmefene dose can be administered to adults and adolescents (≥ 12 years of age) without regard to weight.

3.3.4 Are the labeling claims supported by the clinical pharmacology submission?

Overall, the applicant proposed labeling is acceptable regarding the following:

a) Two-pack presentation of the product is acceptable.
b) Section 12.3 Pharmacokinetics: Description of pharmacokinetics of Opvee based on results from studies OPNT003-PK-001 and OPNT003-PK-002 as submitted in the proposed label is acceptable. The applicant needs to describe that the studies were conducted in subjects while they were supine and were instructed not to breath at the time of nasal spray administration.

The following revisions to the proposed label are necessary:

Section 1: Indication and Usage: Opvee nasal spray is indicated for the emergency treatment of known or suspected opioid overdose in adults and pediatric patients aged 12 years and older, as manifested by respiratory and/or central nervous system depression.

Opvee nasal spray is intended for immediate administration as emergency therapy in settings where opioids may be present.

Section 8.4: Pediatrics should describe the following: Use for this indication in this age group is supported by adult studies and pharmacokinetic simulation [see Clinical Pharmacology (12.3)]. There have been no studies conducted to evaluate the use of Opvee nasal spray in pediatric patients.

Section 12.3 Pediatric Patients should describe the following: No pharmacokinetic studies were conducted with Opvee nasal spray in pediatric patients. Based on population PK simulations, compared to an adult population (mean weight 75.42 kg), 12-year-old subjects with a median weight 50.6 kg, range 27.6 to 126.8 kg are expected to have 7.6% higher mean C_{max} and 25.5% higher mean $AUC_{0-\infty}$ [see Pediatric Use (8.4)].

After consultation with the clinical team and statistics team, clinical pharmacology team concluded that results of study OPNT003-OOD-001 are best described in Section 12.2 Pharmacodynamics (b) (4) The following labeling is proposed for description of results from the pharmacodynamic study.

Effect of nalmefene on remifentanil-induced respiratory depression was evaluated in an experimental ventilatory-response to hypercapnia model in sixty-one opioid-experienced, non-dependent subjects (Figure number to be decided). (b) (4)

Figure: (b) (4)

Nalmefene has no opioid agonist activity. Nalmefene is not known to produce respiratory depression, psychotomimetic effects, or pupillary constriction. No pharmacological activity was observed when nalmefene was administered in the absence of opioid agonists.

Nalmefene has not been shown to produce tolerance, physical dependence, or abuse potential.

Nalmefene can produce acute withdrawal symptoms in individuals who are opioid dependent.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Blood samples were collected from studies OPNT003-PK-001 and OPNT003-PK-002 at the clinical site Worldwide Clinical Trials Early Phase Services/ (b) (4)

Human plasma samples from study OPNT003-PK-001 were analyzed for nalmefene according to (b) (4) procedure ATM-2514, Original, effective 14 Apr 2020. The assay validation was finalized and reported under (b) (4) DCN 4009477. The method used in this study was validated for a range of 10.0 to 10,000 pg/mL based on the analysis of 0.200 mL of plasma by LC-MS-MS. The established long-term stability of 150 days at -20 °C for nalmefene in human K2-EDTA plasma covers the period of study sample storage (129 days). For PK-001 study, the incurred sample reproducibility analysis for nalmefene was acceptable (90%) with 162 out of 183 samples within 20% of their mean concentration.

Human plasma samples from study OPNT003-PK-002 were analyzed for nalmefene according to (b) (4) procedure ATM-2407, Original, effective 18 Oct 2018. The assay validation was finalized and reported under (b) (4) DCN 1004569. The method used in this study was validated for a range of 0.0500 to 25.0 ng/mL based on the analysis of 0.200 mL of plasma by LC-MS-MS. Nalmefene-D5 was utilized as an internal standard. The established long-term stability of 106 days at -20 °C for nalmefene in human K2-EDTA plasma covers the period of study sample storage (87 days). For PK-002 study, the incurred sample reproducibility analysis for nalmefene was acceptable (72.4%) with 84 out of 116 samples within 20% of their mean concentration.

Blood samples were collected from study OPNT003-OOD-001 at the clinical site ICON-EDS, Salt Lake City and analytical site (b) (4). The method used in this study was validated for a range of 10.0 to 10,000 pg/mL based on the analysis of 0.200 mL of plasma by LC-MS-MS (Triple Quad 6500).

Sensitivity, and specificity of nalmefene were acceptable, and quality control samples of nalmefene were acceptable regarding accuracy and precision. Quantitation was performed using a weighted $1/x^2$ linear least squares regression analysis generated from calibration standards of nalmefene.

The Office of Study Integrity and Surveillance determined that inspections are not needed for the Worldwide Clinical Trials Early Phase Services clinical site, and both the analytical sites (Review by Wendy Ng dated 2/2/2023) due to an acceptable inspection result in the recent past. At the time of composing this review, clinical site inspection by OSIS for study OPNT003-OOD-001 was pending. An amended review will be prepared based on findings from the OSIS inspection at a later date.

4.2 Clinical PK and/or PD Assessments

4.2.1 Synopsis of Study OPNT003-PK-001.

This was an open-label, randomized, two-period, two-treatment, two-sequence, crossover study comparing pharmacokinetics of nalmefene following administration of intranasal spray of Opvee (3 mg nalmefene HCl or 2.7 mg nalmefene base) and intramuscular injection of nalmefene (1 mg nalmefene base). Sixty-eight healthy volunteers received treatments in sequence AB or BA in the two periods, with four days (wash out) separating the treatments. There were 28 females and 40 males. Subjects' ages ranged from 21 to 55 years. Subjects' BMI ranged from 18.2 to 30.0 kg/m2. Subjects' height and weight ranged from 145.5 to 187.3 cm and 51.3 to 98.4 kg, respectively. Blood samples were collected for PK analysis at Pre-dose (within 15 mins), 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 for nalmefene were analyzed using noncompartmental methods in Phoenix™ WinNonlin® (Version 8.1, Certara, L.P.) in conjunction with the internet accessible implementation of Pharsight® Knowledgebase ServerTM (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 were treated as zero. Embedded (values between 2 quantifiable concentrations) and terminal BLQ concentrations were treated as missing. PK analysis was based on actual elapsed sample times, relative to time of dose.

Test Product, Dose and Mode of Administration, Lot Number (Treatment A): Intranasal spray 3 mg (0.1 mL nasal spray), Manufacturer: (b) (4) Lot: RNPA2003B, Retest Date: 31 May 2021.

Reference Product, Dose, and Mode of Administration, Lot Number (Treatment B): Intramuscular injection of 1.0 mL of 1.108 mg/ml nalmefene hydrochloride solution, Manufacturer: (b) (4) Lot: OPP-INJ-2011-01, Retest Date: 30 Nov 2021. CMC compliance for the comparator product (for IND 136851 submission) is documented in the review dated 2/4/2021 by Dr. Renishkumar Delvadia (CMC reviewer).

Subjects were given the IN formulation by administration of 0.1 mL spray of a 30 mg/mL solution into one nostril. The IN dose was administered with the subject in a fully supine position. Subjects were instructed to hold their breath during the administration of the nasal spray into the nose. The subject remained fully supine for approximately 1 hour (± 15 minutes) post-dose.

Subjects were given the IM injection by administration of a 1.0 mL of the 1.108 mg/mL nalmefene hydrochloride solution in the gluteal muscle. The dose was administered with the subject in a fully supine position, and the subject remained in a supine position for approximately 1 hour (± 15 minutes) post administration.

Determination of Sample Size: The number of subjects was determined based on the data from the pilot study (Krieter P. et al., 2019 JPET 371:409-415). The sample size was based on Geometric Means Ratio and Intrasubject Variability results obtained for partial AUC in the pilot study, covering the initial 30 minutes (described in protocol). Sample size of 60 subjects (68 recruited) was based on the non-inferiority t-test for log-normal distributed data and were performed for study designs: 2 x 2 x 2 (2

treatments x 2 sequences x 2 periods), using a target power of 80% and alpha level of 5%, sample size of 60 subjects was selected.

PK data from 68 subjects (n=66 in Treatment A, n=68 in Treatment B) were included in the analysis. Quantifiable plasma predose nalmefene concentrations were observed for several subjects (Treatment A (2), Treatment B (15)); however, they were all <5% of Cmax of the treatment. Two subjects discontinued from the study. Two subjects that did not receive Treatment A (nalmefene nasal spray).

Table 3: Descriptive Statistics for Plasma Concentration-Time Data of Nalmefene after Intranasal (IN) Administration of 3.0 mg of Nalmefene Hydrochloride (Treatment A) and Intramuscular (IM) Administration of 1.0 mg of Nalmefene Hydrochloride (Treatment B).

Treatment	Time (h)	n	Mean (ng/mL)	SD (ng/mL)	CV%	Min (ng/mL)	Median (ng/mL)	Max (ng/mL)
A	0.00	66	0.00146	0.0104	710	0.00	0.00	0.0833
	0.0420	61	0.818	1.31	159	0.0105	0.213	5.89
	0.0830	64	4.43	4.83	109	0.198	1.76	17.7
	0.125	64	8.41	7.04	83.7	0.821	6.20	27.1
	0.167	66	10.0	7.47	74.4	1.19	7.92	30.4
	0.250	65	9.53	5.70	59.9	1.57	8.11	24.8
	0.333	66	8.23	4.03	48.9	2.14	7.53	19.7
	0.500	66	6.25	2.38	38.1	0.549	5.86	12.9
	0.750	66	5.16	1.31	25.4	2.39	4.89	7.93
	1.00	66	4.64	0.998	21.5	2.30	4.68	6.67
	2.00	66	4.03	0.779	19.4	2.01	3.99	5.99
	3.00	66	3.17	0.679	21.4	1.55	3.13	5.39
	4.00	66	2.52	0.570	22.6	1.18	2.49	4.09
	6.00	66	1.69	0.452	26.7	0.627	1.65	2.99
	8.00	66	1.23	0.333	27.1	0.547	1.18	2.40
	12.0	66	0.870	0.208	23.9	0.445	0.832	1.59
	18.0	66	0.529	0.139	26.2	0.245	0.518	0.881
	24.0	66	0.366	0.114	31.1	0.168	0.341	0.770
	36.0	66	0.171	0.0626	36.7	0.0534	0.165	0.319
	48.0	66	0.0875	0.0380	43.4	0.0276	0.0843	0.194
B	0.00	68	0.00352	0.00712	202	0.00	0.00	0.0281
	0.0420	64	0.123	0.157	128	0.00	0.0721	0.905
	0.0830	64	0.599	0.852	142	0.0344	0.298	5.22
	0.125	66	1.01	1.15	114	0.0739	0.630	5.67
	0.167	68	1.23	1.18	96.4	0.124	0.835	6.43
	0.250	67	1.19	0.874	73.7	0.200	0.851	3.75
	0.333	68	1.20	0.694	58.1	0.244	0.984	2.91
	0.500	67	1.11	0.715	64.7	0.317	0.945	4.95
	0.750	68	0.990	0.431	43.5	0.350	0.879	2.17
	1.00	68	0.931	0.366	39.3	0.415	0.829	1.88
	2.00	68	0.972	0.397	40.9	0.482	0.858	1.93
	3.00	68	0.896	0.361	40.3	0.441	0.818	1.69
	4.00	68	0.824	0.320	38.8	0.346	0.770	1.47
	6.00	68	0.688	0.229	33.3	0.302	0.673	1.24
	8.00	68	0.670	0.240	35.9	0.244	0.629	1.47
	12.0	68	0.538	0.153	28.4	0.283	0.516	0.898
	18.0	68	0.360	0.129	36.0	0.162	0.341	0.721
	24.0	68	0.223	0.0777	34.8	0.103	0.203	0.449
	36.0	68	0.0968	0.0468	48.3	0.0304	0.0915	0.326
	48.0	68	0.0491	0.0236	48.1	0.0159	0.0436	0.132

Source: Table 14.4.1 Study report OPNT003-PK-001

Reference Treatment B (intramuscular injection of 1 mg nalmefene HCl): Plasma concentrations were observed at first sample collection time of 2.5 minutes in 64 out of 68 subjects. Plasma nalmefene concentrations at 5 minutes were an average of 0.599 ng/mL (range of 0.344 to 5.22 ng/mL), at 10 minutes were an average of 1.23 ng/mL (range of 0.124 – 6.43 ng/mL), and at 15 minutes they were an average of 1.19 ng/mL (range of 0.2 to 3.75 ng/mL). Peak plasma nalmefene levels were noted at 20 minutes (Tmax median of 20 minutes, range 7 minutes - 18 hours) at an average of 1.77 ng/mL (range 0.539 – 6.43 ng/mL). The mean and SD for Tmax were 1.9 and 3.75 hours, respectively (Source: Table 14.4.2a in study report). The reason for reporting mean is because the Revex label seems to describe mean Tmax instead of usual median and range. Additionally, it would contextualize and alleviate any misunderstanding of information across studies.

Treatment A (Intranasal spray of 3 mg nalmefene HCl): Sixty-one subjects out of 66 that received intranasal nalmefene had quantifiable concentrations (mean 0.818 ng/mL, range of 0.0105 to 5.89 ng/mL) at first sample collection time of 2.5 minutes. Plasma nalmefene concentrations at five minutes were an average of 4.43 ng/mL (range 0.198 to 17.7 ng/mL); at 8 hours the plasma levels decrease to an average of 1.23 ng/mL (range 0.547 – 2.4 ng/mL).

Descriptive statistics of pharmacokinetic parameters of nalmefene following both treatments are described in the ***Table 4*** below. The mean elimination half-life of nalmefene following IM injection (10.6 h) and intranasal (11.4 h) administration was similar.

Table 4: Pharmacokinetic Parameters of Nalmefene after Intranasal (IN) Administration of 3.0 mg of Nalmefene HCl (Treatment A) and Intramuscular (IM) injection of 1 mg Nalmefene HCl (Treatment B).

Parameter	Treatment A: Nalmefene HCl 3.0 mg (IN)				Treatment B: Nalmefene HCl 1.0 mg (IM)			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max}[a] (h)	66	0.250 (0.0833-2.00)			68	0.333 (0.117-18.0)		
C_{max} (ng/mL)	66	12.2	6.71	55.2	68	1.77	1.18	66.7
C_{max}/D (ng/mL/mg)	66	4.05	2.24	55.2	68	1.77	1.18	66.7
$AUC_{0\text{-}2.5min}$ (h*ng/mL)	66	0.0193	0.0305	158	68	0.00315	0.00416	132
$AUC_{0\text{-}5min}$ (h*ng/mL)	66	0.125	0.152	121	68	0.0181	0.0254	140
$AUC_{0\text{-}10min}$ (h*ng/mL)	66	0.787	0.666	84.6	68	0.0994	0.114	114
$AUC_{0\text{-}15min}$ (h*ng/mL)	66	1.60	1.15	71.8	68	0.200	0.192	96.0
$AUC_{0\text{-}20min}$ (h*ng/mL)	66	2.34	1.49	63.5	68	0.299	0.249	83.3
$AUC_{0\text{-}30min}$ (h*ng/mL)	66	3.55	1.93	54.2	68	0.491	0.337	68.6
AUC_{last} (h*ng/mL)	66	40.0	7.95	19.9	68	16.3	2.91	17.9
AUC_{last}/Dose (h*ng/mL/mg)	66	13.3	2.65	19.9	68	16.3	2.91	17.9
AUC_{inf} (h*ng/mL)	66	41.5	8.45	20.3	68	17.0	3.13	18.4
AUC_{inf}/Dose (h*ng/mL/mg)	66	13.8	2.82	20.3	68	17.0	3.13	18.4
AUC_{Extrap} (%)	66	3.56	1.91	53.8	68	4.50	2.45	54.5
λz (1/h)	66	0.0629	0.0104	16.5	68	0.0677	0.0112	16.6
$t_{1/2}$ (h)	66	11.4	2.37	20.8	68	10.6	1.95	18.5
T_{last} (h)	66	48.0	0.0459	0.0957	68	48.0	0.0226	0.0471
C_{last} (ng/mL)	66	0.0875	0.0380	43.4	68	0.0491	0.0236	48.1
CL/F (L/h)	66	75.7	18.0	23.8	68	60.7	11.5	18.9
V_z/F (L)	66	1230	305	24.9	68	916	211	23.0
F_{rel}	66	0.806	0.0880	10.9	NA	NA	NA	NA

[a] T_{max} presented as median (range)
Treatment A = 3.0 mg nalmefene hydrochloride IN dose (one 0.1 mL spray of a 30 mg/mL solution in one nostril)
Treatment B = 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)
NA = Not applicable
Source data: Table 14.4.2a, 14.4.2b, and 14.4.2c

Comparison of the log-transformed nalmefene PK parameters Cmax, AUC0-2.5min, AUC0-5min, AUC0-10min, AUC0-15min, AUC0-20min, and AUC0-30min, AUClast, and AUCinf across treatments was performed using an analysis of variance (ANOVA) model and the two one-sided t-tests procedure at the α =0.05 level of significance. The model included sequence, treatment, and period as fixed effects and subject nested within sequence as the random effect, to compare the Test Product (Treatment A) vs. Reference Product (Treatment B). The ratios of the geometric means (Test / Reference) and 90% confidence intervals were reported. Conclusions regarding the results of the statistical analysis (ANOVA) of PK parameters across treatments were based on the ratio of the geometric means (Test / Reference) and the 90% confidence interval about the ratio. No significant difference was demonstrated if the 90% confidence intervals were fully contained within the limits of 80.00% to 125.00%.

Based on the statistical analysis (***Table 5***) the partial AUCs at 2.5 to 30 minutes were all higher following intranasal spray compared to intramuscular injection. Maximum nalmefene exposure (Cmax) was approximately 6.86-fold higher, and total exposure was 2.4-fold higher with intranasal administration compared to intramuscular injection.

Table 5: 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).

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	p-value[d]	ANOVA
	Test	Ref	(Test/Ref)	Lower	Upper			CV%
C_{max}	10.3	1.50	685.98	609.14	772.51	0.9262	<0.0001	42.64
$AUC_{0\text{-}2.5min}$	0.008	0.002	456.58	331.53	628.80	0.3106	<0.0001	153.66
$AUC_{0\text{-}5min}$	0.060	0.010	584.17	458.02	745.06	0.4464	<0.0001	100.73
$AUC_{0\text{-}10min}$	0.514	0.064	803.98	682.79	946.68	0.7282	<0.0001	60.96
$AUC_{0\text{-}15min}$	1.19	0.142	837.01	724.57	966.91	0.8176	<0.0001	52.85
$AUC_{0\text{-}20min}$	1.87	0.228	821.20	722.79	933.00	0.8919	<0.0001	46.12
$AUC_{0\text{-}30min}$	3.04	0.405	752.66	671.80	843.27	0.9436	<0.0001	40.65
AUC_{last}	38.9	16.0	243.15	237.91	248.50	1.0000	<0.0001	7.50
AUC_{inf}	40.3	16.8	240.61	235.14	246.21	1.0000	<0.0001	7.92

[a] Geometric Mean for Treatment A, Test Product (Test) and Treatment B, Control Product (Ref) based on Least Squares Mean of log-transformed parameter values

[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

[c] 90% Confidence Interval

[d] p-value for the difference between treatments; Significant difference defined *a priori* as $p < 0.05$

Source data: Table 14.4.3 and Listing 16.2.6.5

4.2.2 Synopsis of Study OPNT003-PK-002

This was an open-label, randomized, 6-sequence, 3-treatment, 3-period crossover pilot study in which 24 healthy subjects received 3 separate administrations of IN nalmefene hydrochloride. Subjects were randomly assigned to 1 of 6 sequences (4 subjects per sequence). Each subject received one of the 3 treatments (Lot: RNPA2003C) in each of the 3 treatment periods:

Treatment 1 or A (T1): 3 mg (one 0.1 mL spray of 30 mg/mL nalmefene hydrochloride in one nostril).

Nalmefene HCl Nasal Spray 3mg; Dose = 3 mg (one 0.1 mL spray in left nostril); Manufactured by (b) (4) for Opiant Pharmaceuticals. Manufacture Date: 11 Nov 2020. Expiration Date: 30 Nov 2021 & 31 May 2022. Lot: RNPA2003C

Treatment 2 or B (T2): 6 mg (one 0.1 mL sprays of 30 mg/mL nalmefene hydrochloride in each nostril)

Nalmefene HCl Nasal Spray 3mg Dose = 6 mg (one 0.1 mL spray in each nostril); Manufactured by (b) (4) for Opiant Pharmaceuticals; Manufacture Date: 11 Nov 2020, Expiration Date: 30 Nov 2021 & 31 May 2022, Lot: RNPA2003C.

Treatment 3 or C (T3): 6 mg (two 0.1 mL sprays of 30 mg/mL nalmefene hydrochloride in one nostril)

Nalmefene HCl Nasal Spray 3mg Dose = 6 mg (two 0.1 mL sprays in right nostril); Manufactured by (b) (4) for Opiant Pharmaceuticals; Manufacture Date: 11 Nov 2020, Expiration Date: 30 Nov 2021 & 31 May 2022, Lot: RNPA2003C.

Subjects fasted from midnight the day before dosing sessions until at least 1 hour after the study drugs are administered. Water was provided ad libitum. Breakfast was provided approximately 1 hour after dosing, lunch approximately 4 hours after dosing, and all other meals were scheduled at appropriate times by the clinic.

The investigational product was administered in one or both nostrils, as scheduled, with the subject in a fully supine position. For administration, alternative nostrils were used to deliver treatment 1 and treatment 3. For treatments 2 and 3, the two sprays were administered in succession with no significant delay between doses. The subject remained fully supine for approximately 1 hour (± 15 minutes) post-dose. Subjects were instructed to hold their breath during administration of the nasal spray into the nose.

Washout period between treatments was 6 days. Volunteers were healthy, nonsmoking, adult male or female subjects, 18 to 55 years of age inclusive, with BMI ranging from 18 to 30 kg/m^2 inclusive. Female subjects were not pregnant or breastfeeding. Blood sampling (up to 48 hours), and PK analysis methodology were like that described above in PK-001 study above.

PK data from 24 subjects (n=23 in Treatment A, T1; n=23 in Treatment B, T2; and n=24 in Treatment C, T3) were included in the PK analysis; 23 subjects were included in the statistical analyses. Comparability between the nalmefene intranasal two sprays and nalmefene intranasal one spray was assessed from the geometric mean ratios and 90% CIs.

Table 6: Descriptive Statistics for Concentration-Time Data of Nalmefene after IN Administration of 3 mg Nalmefene HCl in One Nostril (Treatment A, T1), 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).

Treatment	Time (h)	n	Mean (ng/mL)	SD (ng/mL)	CV%	Min (ng/mL)	Median (ng/mL)	Max (ng/mL)
A	0.00	23	0.00	0.00	NC	0.00	0.00	0.00
	0.0416	22	0.353	0.232	65.7	0.00	0.362	0.766
	0.0833	22	2.38	2.86	120	0.319	1.29	12.3
	0.125	22	5.10	4.19	82.2	0.642	3.65	16.9
	0.166	22	7.78	5.12	65.8	1.09	6.28	20.4
	0.250	23	9.17	4.65	50.7	1.88	8.04	22.1
	0.333	22	8.79	4.75	54.0	1.97	8.07	20.2
	0.500	23	6.70	3.05	45.6	1.43	6.57	15.1
	0.750	23	5.99	2.23	37.2	2.52	5.85	10.9
	1.00	23	5.47	1.78	32.5	3.20	5.11	9.54
	2.00	23	4.99	1.31	26.4	3.28	4.62	7.64
	3.00	23	3.70	1.06	28.5	2.16	3.51	6.01
	4.00	23	2.99	0.724	24.2	1.97	2.78	4.86
	6.00	23	2.06	0.465	22.6	1.32	2.07	3.01
	8.00	23	1.44	0.328	22.8	1.00	1.34	2.19
	12.0	23	0.992	0.202	20.3	0.727	0.985	1.51
	18.0	23	0.591	0.141	23.9	0.370	0.581	0.851
	24.0	23	0.412	0.131	31.7	0.261	0.370	0.785
	48.0	23	0.0942	0.0460	48.8	0.00	0.0880	0.184
B	0.00	23	0.00	0.00	NC	0.00	0.00	0.00
	0.0416	20	0.981	1.17	119	0.0610	0.691	4.17
	0.0833	22	4.70	4.39	93.4	0.564	3.03	18.1
	0.125	22	12.6	14.7	116	2.39	6.85	60.1
	0.166	23	16.2	12.2	75.3	3.68	9.68	44.7
	0.250	21	19.8	10.7	54.2	6.08	19.4	42.8
	0.333	23	16.2	7.69	47.3	6.18	13.9	32.4
	0.500	23	11.6	4.36	37.6	6.21	10.7	21.6
	0.750	22	10.6	3.37	31.9	5.86	9.70	17.8
	1.00	23	9.93	2.79	28.1	6.33	8.93	16.6
	2.00	23	9.04	2.36	26.1	3.79	8.42	13.0
	3.00	23	7.27	1.49	20.5	4.84	7.26	10.2
	4.00	23	5.53	1.19	21.6	3.80	5.78	7.92
	6.00	23	3.76	0.799	21.2	2.65	3.48	5.54
	8.00	23	2.78	0.621	22.4	1.87	2.69	4.13
	12.0	23	1.97	0.418	21.2	1.30	1.92	2.95
	18.0	23	1.16	0.270	23.3	0.714	1.12	1.70
	24.0	23	0.827	0.215	26.0	0.447	0.793	1.33
	48.0	23	0.192	0.0749	39.0	0.0855	0.172	0.417
C	0.00	24	0.00	0.00	NC	0.00	0.00	0.00
	0.0416	23	1.35	1.83	135	0.102	0.746	8.54
	0.0833	22	5.05	6.71	133	0.630	2.58	28.9
	0.125	22	11.2	11.0	98.6	2.34	4.96	33.8
	0.166	23	14.1	11.7	82.9	3.37	8.55	41.3
	0.250	23	16.9	10.5	62.1	3.79	12.8	39.3
	0.333	24	14.6	8.96	61.6	5.09	11.2	41.3
	0.500	24	10.5	4.76	45.2	4.72	9.18	21.8
	0.750	22	9.92	3.87	39.0	4.33	9.69	16.7
	1.00	24	9.59	3.13	32.7	5.55	8.88	16.6
	2.00	24	8.86	2.69	30.4	5.33	8.60	15.8
	3.00	24	6.90	2.19	31.7	3.96	6.35	11.5
	4.00	24	5.37	1.57	29.3	3.29	4.89	8.96
	6.00	24	3.69	0.918	24.9	2.08	3.51	5.54
	8.00	24	2.69	0.658	24.5	1.86	2.46	4.01
	12.0	24	1.93	0.442	23.0	1.27	1.82	2.82
	18.0	24	1.11	0.240	21.5	0.696	1.12	1.61
	24.0	24	0.792	0.225	28.4	0.455	0.729	1.38
	48.0	23	0.182	0.0699	38.4	0.0712	0.176	0.346

Source Data: Table 14.4.1 and Listing 16.2.6.1 study report OPNT003-PK-002.

Quantifiable nalmefene concentrations were observed in 22 subjects at the first sample collection time (2.5 min) for each treatment.

Mean plasma concentrations (***Table 6***) at 2.5, 5, 7.5, 10-, and 15-minutes post-dose of single nasal spray were 0.353, 2.38, 5.1, 7.78, and 9.17 ng/mL, respectively.

Mean plasma concentrations noted following two sprays (Treatment B: one in each nostril) at 2.5, 5, 7.5, 10-, and 15-minutes post-dose were 0.981, 4.7, 12.6, 16.2, and 19.8 ng/mL, respectively. Since this observation anchors data to time, this observed mean peak plasma concentration, is technically not Cmax, which is best derived from noncompartmental analysis or compartmental PK analysis (See below).

Mean Plasma concentrations at 8 hours for Treatments A, B and C, were 1.44, 2.78, and 2.69 ng/mL, respectively.

Table 7: Plasma PK Parameters of Nalmefene after IN Administration of 3 mg Nalmefene HCl in One Nostril (Treatment A, T1), 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).

Parameter	Treatment A (T1): Nalmefene HCl 3 mg in One Nostril				Treatment B (T2): Nalmefene HCl 3 mg in Each Nostril				Treatment C (T3): Nalmefene HCl 6 mg in One Nostril			
	n	Mean	SD	CV%	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max}[a] (h)	23	0.267 (0.167-2.03)			23	0.250 (0.117-3.00)			24	0.250 (0.117-2.03)		
C_{max} (ng/mL)	23	10.8	4.87	45.2	23	22.2	13.5	60.8	24	18.9	11.2	59.2
AUC_{last} (h*ng/mL)	23	44.9	9.97	22.2	23	86.2	16.0	18.5	24	82.1	18.3	22.3
AUC_{inf} (h*ng/mL)	23	46.8	10.1	21.5	23	89.5	17.0	19.0	24	85.7	18.7	21.9
AUC_{Extrap} (%)	23	4.22	2.14	50.7	23	3.61	1.61	44.7	24	4.18	3.23	77.2
$t_{1/2}$ (h)	23	11.4	2.51	22.0	23	11.3	1.87	16.6	24	11.3	1.86	16.5
CL/F (L/h)	23	66.9	14.2	21.2	23	69.2	12.0	17.3	24	73.3	15.9	21.7
V_z/F (L)	23	1090	300	27.5	23	1120	228	20.3	24	1190	300	25.2
$AUC_{0\text{-}2.5min}$ (h*ng/mL)	23	0.00829	0.00573	69.2	23	0.0432	0.0924	214	24	0.0273	0.0337	124
$AUC_{0\text{-}5min}$ (h*ng/mL)	23	0.0618	0.0568	92.0	23	0.222	0.374	169	24	0.146	0.122	83.5
$AUC_{0\text{-}7.5min}$ (h*ng/mL)	23	0.219	0.185	84.7	23	0.638	0.854	134	24	0.482	0.432	89.7
$AUC_{0\text{-}10min}$ (h*ng/mL)	23	0.480	0.364	75.7	23	1.21	1.28	106	24	0.988	0.867	87.8
$AUC_{0\text{-}15min}$ (h*ng/mL)	23	1.18	0.713	60.5	23	2.67	2.03	76.0	24	2.24	1.70	75.9
$AUC_{0\text{-}20min}$ (h*ng/mL)	23	1.92	1.04	54.5	23	4.14	2.68	64.6	24	3.53	2.40	68.2
$AUC_{0\text{-}30min}$ (h*ng/mL)	23	3.19	1.57	49.4	23	6.46	3.52	54.6	24	5.58	3.28	58.7

[a]Tmax presented as median (range)
Treatment A: T1: 3 mg IN nalmefene dose (one 0.1 mL spray of a 30 mg/mL solution in one nostril)
Treatment B: T2: 6 mg IN nalmefene dose (one 0.1 mL spray of a 30 mg/mL solution in each nostril)
Treatment C: T3: 6 mg IN nalmefene dose (two 0.1 mL sprays of a 30 mg/mL solution in one nostril)
Source data: Table 14.4.2 and 14.4.3

Peak plasma concentrations of nalmefene were observed at approximately 0.250 h to 0.267 h (15 to 16 min) postdose for all treatments; median (range) Tmax values for Treatments A (T1), B (T2), and C (T3) were 0.267 h (0.167 – 2.03 h), 0.250 h (0.117 – 3.00 h), and 0.250 h (0.117 – 2.03), respectively. Mean Cmax, AUClast, and AUCinf values were approximately 2-fold higher after the 6.0 mg treatments (Treatment B, T2 and Treatment C, T3) compared to the 3.0 mg treatment (Treatment A, T1). Mean half-life (t1/2), clearance (CL/F), and volume of distribution (Vz/F) values were similar across treatments. For Treatments A (T1), B (T2), and C (T3), mean t1/2 values were similar at 11.4 h, 11.3 h, and 11.3 h, respectively; mean CL/F values were 66.9 L/h, 69.2 L/h, and 73.3 L/h, respectively; and mean Vz/F values were 1090 L, 1120 L, and 1190 L, respectively.

Table 8: Dose-Normalized Plasma PK Parameters of Nalmefene after IN Administration of 3 mg Nalmefene HCl in One Nostril (Treatment A, T1), 3 mg (6 mg Total Dose) Nalmefene HCl in Each Nostril (Treatment B, T2), and 6 mg Nalmefene HCl in One Nostril (Treatment C).

Parameter	Treatment A (T1): Nalmefene HCl 3 mg in One Nostril				Treatment B (T2): Nalmefene HCl 3 mg in Each Nostril				Treatment C (T3): Nalmefene HCl 6 mg in One Nostril			
	n	Mean	SD	CV%	n	Mean	SD	CV%	n	Mean	SD	CV%
C_{max}/D (ng/mL/mg)	23	3.59	1.62	45.2	23	3.70	2.25	60.8	24	3.15	1.87	59.2
AUC_{last}/D (h*ng/mL/mg)	23	15.0	3.32	22.2	23	14.4	2.66	18.5	24	13.7	3.06	22.3
AUC_{inf}/D (h*ng/mL/mg)	23	15.6	3.36	21.5	23	14.9	2.83	19.0	24	14.3	3.12	21.9
$AUC_{0\text{-}2.5min}$/D (h*ng/mL/mg)	23	0.00276	0.00191	69.2	23	0.00720	0.0154	214	24	0.00455	0.00562	124
$AUC_{0\text{-}5min}$/D (h*ng/mL/mg)	23	0.0206	0.0189	92.0	23	0.0369	0.0623	169	24	0.0244	0.0203	83.5
$AUC_{0\text{-}7.5min}$/D (h*ng/mL/mg)	23	0.0728	0.0617	84.7	23	0.106	0.142	134	24	0.0803	0.0720	89.7
$AUC_{0\text{-}10min}$/D (h*ng/mL/mg)	23	0.160	0.121	75.7	23	0.202	0.213	106	24	0.165	0.145	87.8
$AUC_{0\text{-}15min}$/D (h*ng/mL/mg)	23	0.393	0.238	60.5	23	0.445	0.338	76.0	24	0.374	0.284	75.9
$AUC_{0\text{-}20min}$/D (h*ng/mL/mg)	23	0.639	0.348	54.5	23	0.691	0.446	64.6	24	0.588	0.401	68.2
$AUC_{0\text{-}30min}$/D (h*ng/mL/mg)	23	1.06	0.525	49.4	23	1.08	0.587	54.6	24	0.931	0.546	58.7

Treatment A: T1: 3 mg IN nalmefene dose (one 0.1 mL spray of a 30 mg/mL solution in one nostril)
Treatment B: T2: 6 mg IN nalmefene dose (one 0.1 mL spray of a 30 mg/mL solution in each nostril)
Treatment C: T3: 6 mg IN nalmefene dose (two 0.1 mL sprays of a 30 mg/mL solution in one nostril)
Source data: Table 14.4.4 and 14.4.5

Based on dose-normalized parameter values (***Table 8***), mean Cmax, AUClast, and AUCinf were similar across treatments. Mean Cmax/D values for Treatments A (T1), B (T2), and C (T3) were 3.59, 3.70, and 3.15 ng/mL/mg, respectively. Dose-normalized systemic exposure based on AUClast and AUCinf were also comparable across treatments. Mean AUClast/D values for Treatments A (T1), B (T2), and C (T3) were 15.0, 14.4, and 13.7 h*ng/mL/mg, respectively. Mean AUCinf/D values for Treatments A (T1), B (T2), and C (T3) were 15.6, 14.9, and 14.3 h*ng/mL/mg, respectively.

Treatment C (T3, 6.0 mg in one nostril) vs. Treatment A (T1, 3.0 mg in one nostril) (***Table 9***): Based on dose-normalized ANOVA results, maximum nalmefene exposure (Cmax) was approximately 19% lower after 6.0 mg administered to one nostril (Treatment C, T3) compared to that after 3.0 mg administered to one nostril (Treatment A, T1). Dose-normalized total nalmefene exposure (AUClast and AUCinf) were similar for both treatments (geometric mean ratios were 91.77% and 91.19%, respectively).

Table 9: 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).

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	p-value[d]	ANOVA
	Test (C)	Ref (A)	(Test, C/Ref, A)	Lower	Upper			CV%
C_{max}/Dose	2.68	3.31	80.89	69.46	94.21	0.7803	0.0241	31.44
$AUC_{2.5min}$/Dose	0.00271	0.00202	134.62	86.89	208.57	0.2146	0.2598	108.46
AUC_{5min}/Dose	0.0172	0.0149	115.52	81.29	164.16	0.2757	0.4937	80.65
$AUC_{7.5min}$/Dose	0.0560	0.0582	96.28	75.12	123.39	0.4344	0.7983	53.28
AUC_{10min}/Dose	0.117	0.132	88.62	71.87	109.27	0.5440	0.3375	44.15
AUC_{15min}/Dose	0.284	0.340	83.67	69.87	100.18	0.6551	0.1034	37.52
AUC_{20min}/Dose	0.469	0.565	83.00	70.46	97.76	0.7277	0.0624	33.90
AUC_{30min}/Dose	0.791	0.959	82.42	71.48	95.04	0.8270	0.0275	29.29
AUC_{last}/Dose	13.5	14.7	91.77	87.68	96.06	1.0000	0.0029	9.21
AUC_{inf}/Dose	14.0	15.3	91.19	87.19	95.38	1.0000	0.0013	9.07

Treatment A: T1: 3 mg IN nalmefene dose (one 0.1 mL spray of a 30 mg/mL solution in one nostril) (Ref)
Treatment C: T3: 6 mg IN nalmefene dose (two 0.1 mL sprays of a 30 mg/mL solution in one nostril) (Test)

[a] Geometric Mean for Treatment C, T3 (Test) and Treatment A, T1 (Ref) based on Least Squares Mean of log-transformed parameter values

[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

[c] 90% Confidence Interval

[d] p-value for the difference between treatments; Significant difference defined *a priori* as $p < 0.05$

Source data: Table 14.4.6 and Listing 16.2.6.4

Treatment B (T2, 3.0 mg in each nostril) vs. Treatment A (T1, 3.0 mg in one nostril)(***Table 10***): Based on dose-normalized ANOVA results, maximum nalmefene exposure (Cmax) and total nalmefene exposure (AUClast and AUCinf) were similar after 3.0 mg administered to each nostril (Treatment B, T2) and 3.0 mg administered to one nostril (Treatment A, T1); geometric mean ratios were 98.15%, 96.87%, and 96.23%, respectively.

Table 10: 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).

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]				ANOVA
	Test (B)	Ref (A)	(Test, B/Ref, A)	Lower	Upper	Power	p-value[d]	CV%
C_{max}/Dose	3.25	3.31	98.15	84.27	114.31	0.7803	0.8374	31.44
$AUC_{2.5min}$/Dose	0.00280	0.00202	139.05	89.75	215.43	0.2146	0.2123	108.46
AUC_{5min}/Dose	0.0187	0.0149	125.35	88.21	178.13	0.2757	0.2857	80.65
$AUC_{7.5min}$/Dose	0.0666	0.0582	114.51	89.34	146.76	0.4344	0.3637	53.28
AUC_{10min}/Dose	0.143	0.132	108.32	87.84	133.56	0.5440	0.5248	44.15
AUC_{15min}/Dose	0.358	0.340	105.44	88.06	126.26	0.6551	0.6233	37.52
AUC_{20min}/Dose	0.588	0.565	104.11	88.39	122.63	0.7277	0.6809	33.90
AUC_{30min}/Dose	0.964	0.959	100.46	87.13	115.84	0.8270	0.9568	29.29
AUC_{last}/Dose	14.2	14.7	96.87	92.55	101.40	1.0000	0.2481	9.21
AUC_{inf}/Dose	14.8	15.3	96.23	92.00	100.65	1.0000	0.1576	9.07

Treatment A: T1: 3 mg IN nalmefene dose (one 0.1 mL spray of a 30 mg/mL solution in one nostril)
Treatment B: T2: 6 mg IN nalmefene dose (one 0.1 mL spray of a 30 mg/mL solution in each nostril)

[a] Geometric Mean for Treatment B, T2 (Test) and Treatment A, T1 (Ref) based on Least Squares Mean of log-transformed parameter values

[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

[c] 90% Confidence Interval

[d] p-value for the difference between treatments; Significant difference defined *a priori* as $p < 0.05$
Source data: Table 14.4.7 and Listing 16.2.6.4

Treatment B (T2, 3.0 mg in each nostril) vs. Treatment C (T3, 6.0 mg in one nostril)(***Table 11***): Based on dose-normalized ANOVA results, maximum nalmefene exposure (Cmax) was approximately 21% higher after 3.0 mg administered to each nostril (Treatment B, T2) compared to that after 6.0 mg administered to one nostril (Treatment C, T3). Dose-normalized total nalmefene exposure (AUClast and AUCinf) were similar for both treatments (geometric mean ratios were 105.56% and 105.53%, respectively).

Table 11: 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).

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]				ANOVA
	Test (B)	Ref (C)	(Test, B/Ref, C)	Lower	Upper	Power	p-value[d]	CV%
C_{max}/Dose	3.25	2.68	121.33	104.17	141.30	0.7803	0.0388	31.44
$AUC_{2.5min}$/Dose	0.00280	0.00271	103.29	66.67	160.02	0.2146	0.9017	108.46
AUC_{5min}/Dose	0.0187	0.0172	108.51	76.36	154.20	0.2757	0.6979	80.65
$AUC_{7.5min}$/Dose	0.0666	0.0560	118.94	92.80	152.44	0.4344	0.2464	53.28
AUC_{10min}/Dose	0.143	0.117	122.23	99.13	150.71	0.5440	0.1146	44.15
AUC_{15min}/Dose	0.358	0.284	126.03	105.25	150.91	0.6551	0.0366	37.52
AUC_{20min}/Dose	0.588	0.469	125.44	106.50	147.76	0.7277	0.0248	33.90
AUC_{30min}/Dose	0.964	0.791	121.89	105.71	140.56	0.8270	0.0242	29.29
AUC_{last}/Dose	14.2	13.5	105.56	100.85	110.49	1.0000	0.0528	9.21
AUC_{inf}/Dose	14.8	14.0	105.53	100.89	110.37	1.0000	0.0504	9.07

Treatment B: T2: 6 mg IN nalmefene dose (one 0.1 mL spray of a 30 mg/mL solution in each nostril) (Test)
Treatment C: T3: 6 mg IN nalmefene dose (two 0.1 mL sprays of a 30 mg/mL solution in one nostril) (Ref)

[a] Geometric Mean for Treatment B, T2 (Test) and Treatment C, T3 (Ref) based on Least Squares Mean of log-transformed parameter values

[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

[c] 90% Confidence Interval

[d] p-value for the difference between treatments; Significant difference defined *a priori* as $p < 0.05$
Source data: Table 14.4.8 and Listing 16.2.6.4

4.2.3 Synopsis of Study OPNT003-OOD-001

This is a two-part open-label study of the pharmacodynamic effects of intranasal nalmefene compared to intranasal naloxone in healthy volunteers under steady-state opioid agonism. This was a single-center, open-label, 2-part study. Part 1 and the 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 (See Figure below). Key experimental, study design, and observations are reported here, while results and analyses are results are discussed within DARS review and pharmacometrics review. Safety observations are reviewed by medical officer Dr. Tanya Brescia-Oddo.

Subjects started receiving a hypercapnic gas mixture using a ventilatory response to hypercapnia (VRH) face mask at Time 0 mins, which was removed at Time 45 mins and then reapplied for 10 mins at Time 75 mins, 105 mins, and at 135 mins (Part 2), respectively. VRH was monitored with the subjects breathing through a tightly sealed face mask while lying on a bed at 45° recumbent position. VRH data was collected at 0. 15, 20, 25, 27.5, 30, 32.5, 35, 40, and 45 mins. Minute ventilation was determined prior to the start of the hypercapnic gas mixture and following the start of the hypercapnic gas mixture at Time 0, 5, 10, 15, 20, 25, 27.5, 30, 32.5, 35, 40, 45, 55, 70, 85, 115, 125, 135, 145, 155, 165, and 175 minutes (i.e., at -25, -20, -15, -10, -5, 0, 2.5, 5, 7.5, 10, 15, 20, 30, 45, 60, 90, 100, 110, 120, 130, 140, and 150 minutes in relation to study drug administration), using the ExSpiron® device.

Blood samples for PK analysis were collected predose (within 15 minutes) and approximately 2.5, 5, 7.5, 10, 15, 20, 30, 45, 60, 90, and 120 mins after study drug administration.

Study Drug Administration: Subjects received either a 3 mg nalmefene hydrochloride IN dose or a 4 mg naloxone hydrochloride IN dose at Time 25 minutes.

Identity of Investigational Products (Study Drug): Test preparation Nalmefene hydrochloride nasal spray (3 mg, one spray in one nostril delivers 0.1 mL of 30 mg/mL nalmefene hydrochloride); Manufacturer: Opiant Pharmaceuticals, Inc; Batch numbers: RNAPA2003B.

Reference medication (Narcan® nasal spray, 4 mg (one spray in one nostril delivers 0.1 mL of 40 mg/mL naloxone hydrochloride); Manufacturer: Adapt Pharma, Inc.; sourced by pharmacy at (b) (4) Batch number: 201617, 211853, and 211834.

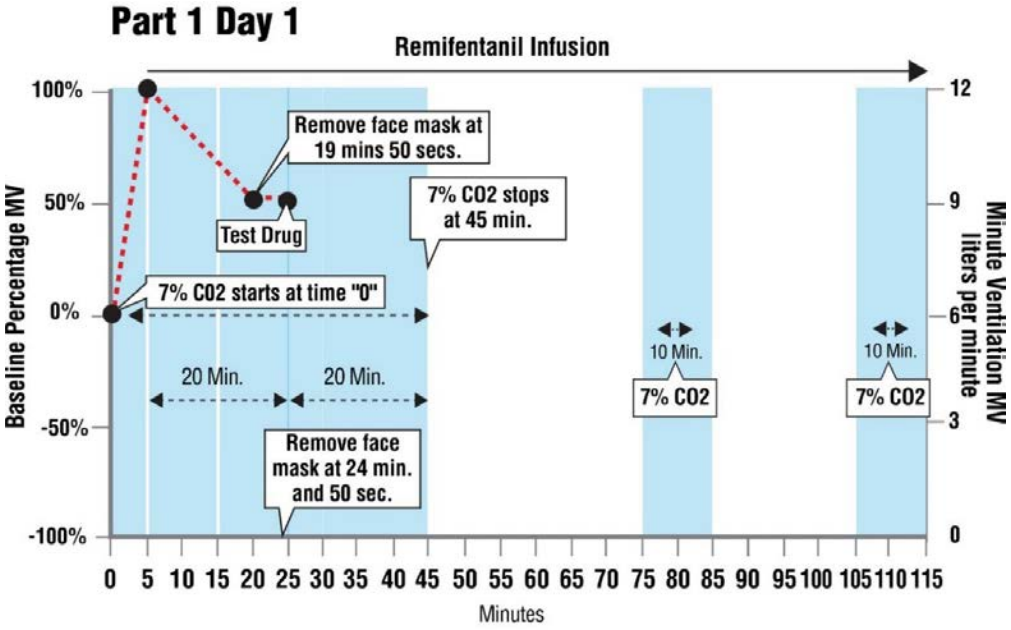
Healthy subjects who were nondependent opioid experienced users were recruited in this study. Opioid experience defined as exposure to an opioid on at least 1 occasion prior to screening. Naloxone Challenge Test was administered prior to treatment parts 1 and 2 to confirm the subjects were not opioid-dependent. Naloxone hydrochloride (0.2 mg IV) was administered first. If there were no signs of withdrawal apparent within 30 seconds after administration, another 0.6 mg naloxone hydrochloride IV was administered. Vital signs were recorded at predose (first naloxone hydrochloride dose) and at 5 minutes, 0.25, 0.5, 1, 1.5, and 2 hours following the second dose of naloxone. Vital signs were recorded at nominal time points ± 5 minutes. COWS was collected and recorded at predose, and at 30 seconds following the first naloxone hydrochloride dose and 5 minutes after the second dose was administered. Symptoms of withdrawal following naloxone hydrochloride administration (Naloxone Challenge Test)

were not collected as adverse events unless they met the criteria for a new adverse event or a serious adverse event.

Male or female; female subjects could be of childbearing potential, of nonchildbearing potential, or postmenopausal. Age range: 18 to 55 years, inclusive, at screening. Body mass index (BMI): 18.0 to 32.0 kg/m2, inclusive, at screening. Weight: ≥50 kg, inclusive, at screening.

Subjects were excluded if they were taking prescription or over the counter (OTC) medications, dietary supplements, herbal products, vitamins or recent use of opioid analgesics for pain relief within 14 days prior to the first dose of study drug and throughout the duration of the study. An exception was made for acetaminophen, which was allowed up to admission to the clinical research unit and for treatment of adverse events (AEs) during the study.

Figure 8: Study Design for Part 1 Day 1 of study OPNT003-OOD-001.



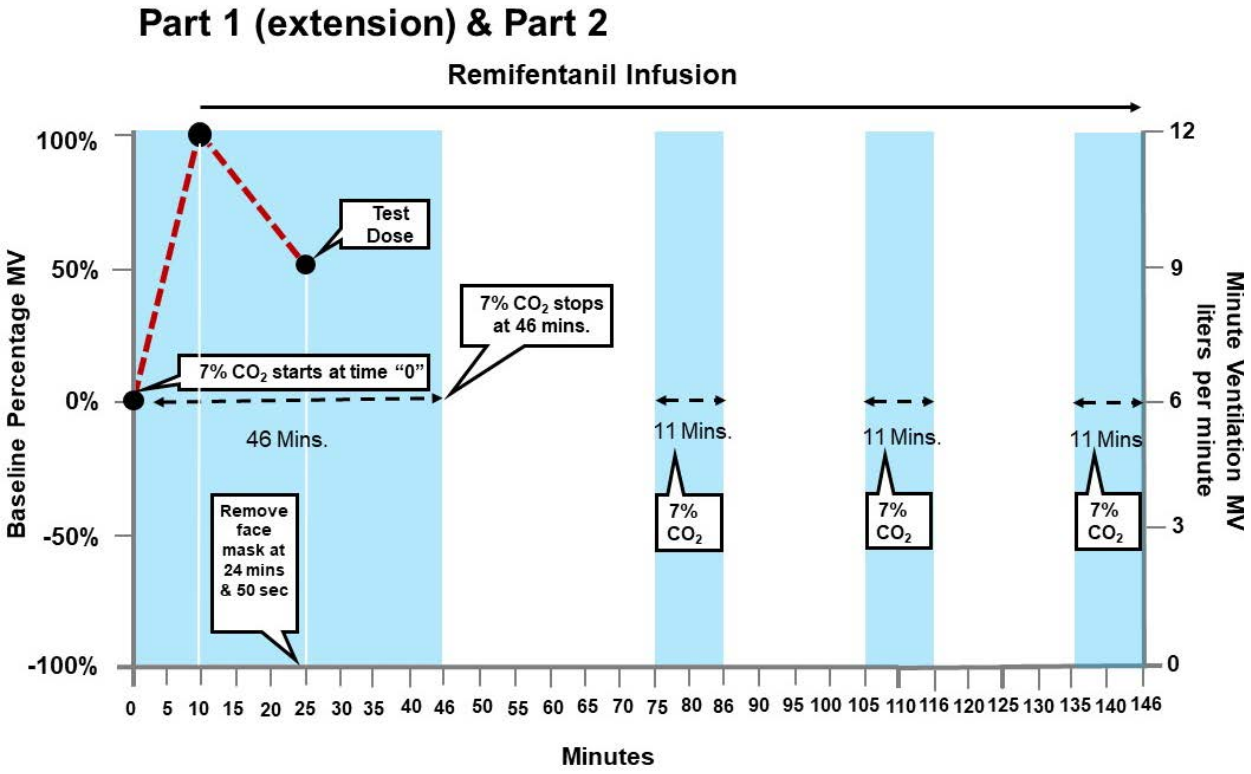
Objectives of Part 1 of the study was to primarily determine the relationship between remifentanil dose and suppression of CO2-induced increases in minute ventilation. Additionally, it served its purpose in determining the effect of brief mask removal on minute ventilation, tolerability of IV remifentanil, and the effects of IN naloxone on minute ventilation during steady-state remifentanil infusion.

Part 2 was a randomized, 2-period, 2-treatment, crossover study to evaluate the 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 1 and Part 2, subjects 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), followed by a remifentanil hydrochloride infusion with minute ventilation measured in the presence of elevated CO2

as a continuous assessment. Subjects received 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 steady-state. On Dose Day 1 of Part 1, each subject received 4 mg IN naloxone hydrochloride. In part 2, each subject received a single dose of either 3 mg IN nalmefene hydrochloride or 4 mg IN naloxone hydrochloride in a randomized 2-period crossover manner, in accordance with the randomization schedule, with an approximately 4-day washout period between doses.

Figure 9: Study Design for Part 1 extension, and Part 2 of study OPNT003-OOD-001.



In Part 2, 69 subjects received remifentanil at a rate of 0.175 µg/kg/min. Naloxone hydrochloride nasal spray (4 mg) was administered to 60 subjects and nalmefene hydrochloride (3 mg) nasal spray was administered to 61 subjects (data from 56 - 61 subjects were derived for each data point).

Part 2 of the study primarily evaluated the change in minute ventilation from remifentanil-induced nadir to 5 minutes after study drug administration. Additionally, the following were also observed (See ***Table 12*** below):

• Change in minute ventilation from remifentanil-induced nadir to 2.5, 7.5, 10, 15, 20, 60, 90, and 120 minutes after study drug administration (***Table 12***).

• Maximum change in minute ventilation from remifentanil-induced nadir after study drug administration (***Table 13***).

• Time to maximum change in minute ventilation from remifentanil-induced nadir after study drug administration (***Table 13***).

• Change in minute ventilation from the maximum change in minute ventilation from remifentanil-induced nadir to 120 minutes after study drug administration (**Table 14**).

Table 12: Descriptive Statistics of ExSpiron Device pharmacodynamic measurements at various timepoints.

Minutes in Relation to Study Drug Administration	Naloxone hydrochloride Nasal Spray Minute Ventilation (MV) & Mean Change in MV from Nadir Baseline (n=60)		Nalmefene hydrochloride Nasal Spray Minute Ventilation (MV) & Mean Change in MV from Nadir Baseline (n=61)	
	Mean MV ± SD (L/min)	Mean Change ± SD (L/min)	Mean MV ± SD (L/min)	Mean Change ± SD (L/min)
-25 (Gas Baseline)	10.15 ± 2.42		10.12 ± 2.16	
-15 (Remifentanil baseline)	17.29 ± 5.97	-	16.63 ± 4.99	-
0 (Nadir baseline)	10.55 ± 4.65	-	10.63 ± 4.02	-
2.5	12.25 ± 3.26	1.71 ± 4.05	13.24 ± 4.05	2.55 ± 2.97
5	13.98 ± 4.53	3.43 ± 4.69	16.44 ± 5.27	5.74 ± 4.83
7.5	14.56 ± 4.39	4.01 ± 4.82	17.01 ± 6.26	6.3 ± 5.5
10	15.51 ± 4.91	4.96 ± 5.3	17.21 ± 5.22	6.58 ± 5.17
15	16.05 ± 5.22	5.55 ± 4.94	17.75 ± 5.89	7.12 ± 6
20	16.44 ± 5.55	5.93 ± 5.24	17.46 ± 5.55	6.79 ± 5.53
60	12.99 ± 4.22	2.52 ± 4.39	13.60 ± 4.55	2.92 ± 4.36
90	12.67 ± 3.93	2.14 ± 4.66	13.42 ± 4.38	2.71 ± 4.56
120	12.49 ± 3.91	2.02 ± 3.86	13.59 ± 4.59	2.877 ± 4.59

MV=minute ventilation
Mean change of minute ventilation for each timepoint after the study drug is presented. Source: Study Report OPNT003-OOD-001, Table S3.

Table 13: Maximum change and Time to maximum change in minute ventilation from remifentanil-induced nadir after study drug administration.

PD Parameter	Statistic	Hypercapnic Gas Mixture +Remifentanil +Naloxone	Hypercapnic Gas Mixture +Remifentanil +Nalmefene
TE_{max} (min)	n	59	61
	Median	40.0	40.0
	Min, Max	28, 145	28, 120
VE E_{max}	n	59	61
	Mean	7.237	9.307
	SD	5.3971	5.4774
	SE	0.703	0.701
	%CV	74.6	58.9
	Median	6.550	9.300
	Min, Max	-1.76, 28.73	-1.04, 24.74
	Q1, Q3	3.490, 9.330	5.590, 12.170

Table 14: Change in minute ventilation from the maximum change in minute ventilation from remifentanil-induced nadir to 120 minutes after study drug administration.

		Treatment	
		Hypercapnic Gas Mixture+Remifentanil+Naloxone (N=60)	**Hypercapnic Gas Mixture+Remifentanil+Nalmefene (N=61)**
Timepoint	Statistic	Result	Result
Baseline (E_{max})	N	59	61
	Mean	7.237	9.307
	SD	5.3971	5.4774
	SE	0.703	0.701
	%CV	74.6	58.9
	Median	6.550	9.300
	Min, Max	-1.76, 28.73	-1.04, 24.74
	Q1, Q3	3.490, 9.330	5.590, 12.170
VE Change (120 Minutes from nadir baseline)	N	56	59
	Mean	-2.32	-2.61
	SD	6.165	4.262
	SE	0.824	0.555
	%CV	-265.6	-163.4
	Median	-2.70	-2.03
	Min, Max	-18.5, 27.0	-12.6, 4.9
	Q1, Q3	-5.62, -0.26	-6.23, 0.44

Following intranasal spray administration of 3 mg dose, nalmefene plasma concentrations were first quantifiable in 98.4% of subjects by 2.5 minutes post dose and remained quantifiable until 2 hours post dose in all subjects. Mean plasma concentrations and other descriptive statistics noted at different timepoints are listed in the ***Table 15*** below.

Table 15: Mean plasma concentrations of nalmefene and naloxone following intranasal spray of 3 mg Nalmefene IN spray and Narcan (4 mg naloxone HCl spray) in part 2.

Time (h)	N	Mean	SD	CV%	Min	Median	Max
Nalmefene Nasal Spray (3 mg nalmefene HCl)							
0	67	0	0	.	0	0	0
0.042	61	1.46	1.78	122.61	0	0.654	6.42
0.083	60	2.66	2.15	80.89	0.16	2.09	8.29
0.125	59	3.73	2.88	77.18	0.45	2.63	13.1
0.167	60	3.97	2.84	71.39	0.81	3.11	13.6
0.25	59	4.70	2.57	54.68	1.42	3.94	12
0.333	58	5.37	2.58	48.12	1.8	4.815	13.1
0.5	58	5.57	2.30	41.33	2.23	4.96	13.8
0.75	58	5.19	1.63	31.42	1.85	5.2	8.58
1	58	4.92	1.34	27.27	1.96	4.94	8
1.5	58	4.23	1.08	25.53	1.66	4.13	6.49

2	58	3.78	0.91	24.20	1.45	3.79	6.05
Narcan (4 mg Naloxone HCl Nasal Spray)							
0	61	0	0	.	0	0	0
0.042	59	0.73	1.06	145.12	0	0.21	5.46
0.083	58	1.71	1.79	105.06	0.03	0.94	6.7
0.125	58	2.41	2.15	89.29	0.06	1.52	8.1
0.167	58	2.56	2.32	90.51	0.11	1.85	10.7
0.25	58	3.13	2.31	73.61	0.49	2.36	10.9
0.333	59	3.73	2.81	75.50	0.81	3.05	17.9
0.5	58	4.84	2.78	57.37	1.51	4.18	17.7
0.75	58	4.83	1.82	37.62	1.5	4.60	9.76
1	58	3.92	1.40	35.62	1.35	3.77	8.07
1.5	58	2.83	1.01	35.64	0.98	2.66	5.69
2	59	2.17	0.81	37.50	0.74	2.02	4.43

During filing, it was noted that the plasma concentrations of nalmefene in this study were lower than that observed following single spray dose in PK-001 and PK-002 studies. The applicant explained as follows: "The mean absorption rate of nalmefene in the pharmacodynamic study appeared to be slower than that observed in the two pharmacokinetic studies. It is hypothesized that this could be related to the drying of the nasal passages, resulting from the hypercapnic mask breathing. As this effect would be present in both the nalmefene and naloxone treatments, the direct comparison offered by the crossover study design would not be compromised." The other difference between this PD study and the previous two PK studies is the position of healthy volunteers. Whereas subjects were in supine (on their back) position in PK studies PK-001, and PK-002 study, subjects were in 45^{o} angle recumbent position in PD study OOD-001. The applicant responded to an information request with CMC data and states that "The reliability data demonstrates that device orientation does not influence performance of the Aptar Unidose Nasal Spray (UDSTM) device." Additionally, it is not clear if the ongoing infusion of remifentanil played any role in reducing the absorption of naloxone or nalmefene via the intranasal route. For example, remifentanil product label lists nasal congestion as an adverse event, without much description or details. See additional discussion on impact of experimental conditions on Opvee nasal spray PK and Narcan nasal spray PK in DARS review below (***Figure 13***). Overall, the impact of this observation is limited because any PD observations made with relatively lower systemic levels in this study would only support pharmacological effect of higher exposure data in other studies.

Observations from this study and other studies, and additional analyses are presented in DARS review and Population PK/PK-PD analysis below.

4.3 DARS Review

Independent Mechanistic PK-PD Modeling of

NDA 217470 Nalmefene Hydrochloride Intranasal Spray 3 mg

Division of Applied Regulatory Science, Office of Clinical Pharmacology

4.3.1 Executive Summary

The objective of this review was to perform independent modeling & simulation to translate findings from the Applicant's healthy volunteer PK-PD study into labeling for community opioid overdose scenarios, focusing on three key aspects:

1) that the onset of action of nalmefene intranasal (IN) 3 mg was appropriate for opioid reversal in a community setting
2) the need for dose titration or re-administration of nalmefene IN 3 mg in a community setting
3) the capacity of nalmefene IN 3 mg to prevent re-narcotization

OCP's independent modeling & simulation using a previously developed systems pharmacology model (referred to as an opioid-effects model [OEM]) support that nalmefene IN 3 mg has an onset of action at least as rapid as naloxone IN 4 mg, which is an approved opioid antagonist formulation for reversal of opioid overdose in a community setting. OCP's evaluation also supports that the proposed dose of nalmefene IN 3 mg is unlikely to require titration or re-administration to significantly decrease the incidence of opioid-associated cardiac arrest or brain hypoxia in a community setting, as long as the 1st dose of nalmefene was administered early enough. Finally, OCP's independent modeling & simulation suggests nalmefene's long duration of action, primarily due to its longer plasma half-life, would prevent re-narcotization up to 6 hours after antagonist administration in cases of delayed opioid absorption or prolonged exposure.

4.3.2 Background

The opioid antagonist nalmefene has been shown to reverse the respiratory depression effects of opioids. Nalmefene (Revex, nalmefene hydrochloride injection) was approved by the US Food and Drug Administration (FDA) in 1995 for the management of known or suspected opioid overdose [1]. The product was removed from the market in 2008, and FDA responded to a Citizen Petition in 2017 concluding that the product was not discontinued or withdrawn for safety or effectiveness reasons. The first nalmefene generic formulation was approved in 2022 [2]. (b) (4)

The FDA nalmefene product label [1, 2] states that nalmefene hydrochloride injection has a longer duration of action than naloxone. The labeling also states that for IM and subcutaneous (SC) routes, "therapeutic plasma concentrations are likely to be reached within 5 to 15 minutes after a 1 mg dose", and "great care should be taken if repeated doses must be given by these routes". Since development of

new nalmefene formulations would rely on safety and effectiveness findings from the original NDA and since the original evaluations were mostly performed with the intravenous formulation, the FDA issued an IND advice letter to all sponsors developing nalmefene products for community use on November 7th, 2019. In the letter, the sponsors were advised to address the following three (3) questions in their development program: 1) whether the intended route of administration (b) (4) provided fast enough onset of action to reverse respiratory depression in a community setting; 2) whether the intended dose for community use would rely on titration using incremental doses or re-administration; 3) whether the prolonged duration of action may result in protracted opioid withdrawal symptoms in those who are opioid dependent.

In March 2020 in response to the FDA advice letter, the sponsor, Opiant Pharmaceuticals (hereafter referred to as the Applicant), proposed to conduct a pharmacokinetic/pharmacodynamic (PK-PD) study for their nalmefene IN 3 mg product to address the above questions. The Applicant also proposed that the longer duration of action for nalmefene reduces the likelihood of a re-narcotization that may occur with high potency, longer-acting opioids.

On November 22nd, 2022, the applicant submitted NDA 217470 to the FDA, which included results of the pharmacodynamic study (OPNT003-OOD-001). A detailed review of the clinical data and PK/PD model developed by the Applicant will be covered in other parts of the OCP review. This section of the review instead focused on how a translational PK/PD model developed by OCP [3] was used to evaluate the Applicant's nalmefene product and address the three question related to: 1) the onset of action; 2) the potential need for repeat dosing; 3) the capacity to preventing re-narcotization.

4.3.3 Methods

The OCP opioid-effects model was developed to translate the systemic exposure of different opioid agonists and antagonists into clinically interpretable outcome such as minute ventilation, blood gas tensions, and cardiac output [3]. The goal of using the model is to evaluate the nalmefene IN product under scenarios different from the settings of the Applicant's PK/PD study OPNT003-OOD-001 that are closer to real-world community overdose situations (see **Table 16** for details).

To apply the OCP opioid-effects model to the review of NDA 217470, various components of the previously developed model were updated. The PK components of the opioid antagonists were updated based on the PK data of nalmefene IN 3 mg and naloxone IN 4 mg from study OPNT003-OOD-001 (**Figure 10**). The receptor binding component for nalmefene was updated using internal data from in vitro receptor binding kinetic experiments. The physiological component and PK/PD component for remifentanil were updated based on study OPNT003-OOD-001 (**Figure 11**). The receptor binding component for naloxone, the physiological component for healthy subjects and chronic opioid users, and the PK/PD component for fentanyl and carfentanil, were all from the published manuscript describing the OCP model [3].

To simulate community overdose scenarios, 2000 virtual subjects representing chronic opioid users were simulated. Medium overdose scenarios for fentanyl and carfentanil were estimated based on a large dataset of community fatal overdose cases. The first dose of nalmefene IN 3 mg or naloxone IN 4

mg was administered 1 min after the minute ventilation volume of virtual subjects dropped below 40% of the baseline. If nalmefene or naloxone dosing was repeated, the second dose was assumed to be given 2.5 min after the first and into the other nostril. Cardiac arrest was defined as a precipitous decline of cardiac output (cardiovascular collapse) followed by a cessation of circulation (cardiac output < 0.01 L/min). Brain hypoxia time was defined as the time brain tissue oxygen partial pressure was below 20 mm Hg. To capture the uncertainty in the estimates of the cardiac arrest percentage, 10% of the virtual population (200 out of 2000 subjects) were repeatedly (2500 times) sampled to form subpopulations, from which the median and interquartile range of cardiac arrest percentage were calculated.

To simulate re-narcotization, we modified an opioid aerosol PK model, which the team had previously developed and used to evaluate another naloxone product [4], to simulate a situation where a large dose of carfentanil (0.287 mg) was absorbed into the systemic circulation slowly. A single dose of nalmefene IN 3 mg or naloxone IN 4 mg was administered early in the procedure (1 min after the minute ventilation of the typical virtual subject dropped to 40% of the baseline). Simulations continued for about 6 hours to monitor changes in minute ventilation and cardiac output.

Table 16: Key differences between the scenarios evaluated using OCP's opioid-effects model and the Applicant's study OPNT003-OOD-001.

	Scenarios evaluated in OCP's independent analysis	**Settings of OPNT003-OOD-001**
Inspired air	Room air (21% O_2, 0% CO_2)	Hyperoxic and hypercapnic (~50% O_2 and ~7% CO_2)
Baseline minute ventilation (before opioid administration)	6.7 L/min (within physiological range)	~18 L/min (baseline is elevated under hypercapnic conditions)
Clinical outcome	Cardiac arrest; Brain hypoxia; Minute ventilation; End-tidal CO_2; Blood gas tensions.	Minute ventilation; End-tidal CO_2
Study participants	Chronic opioid users	Healthy subjects
Opioids used	Fentanyl and carfentanil	Remifentanil
Repeated dosing evaluated?	Yes	No

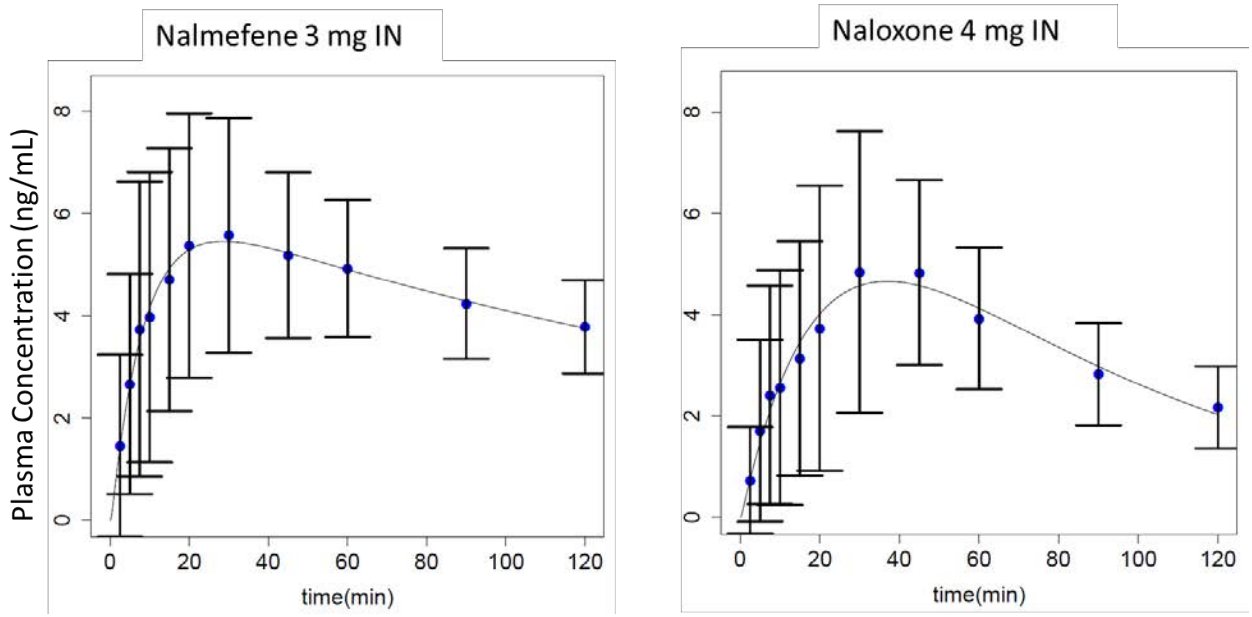


Figure 10: Plasma profiles of nalmefene IN 3 mg and naloxone IN 4 mg in OPNT003-OOD-001.

Plasma profiles of nalmefene IN 3 mg (left) and naloxone IN 4 mg (right) were obtained from the study OPNT003-OOD-001. The blue dots and error bars represent the mean and standard deviation of measured plasma concentration, respectively. The black line represents OCP's model simulation of a typical subject. Note that nalmefene IN 3 mg plasma concentrations rise faster and decline slower than naloxone IN 4 mg, consistent with more rapid absorption and slower elimination, respectively.

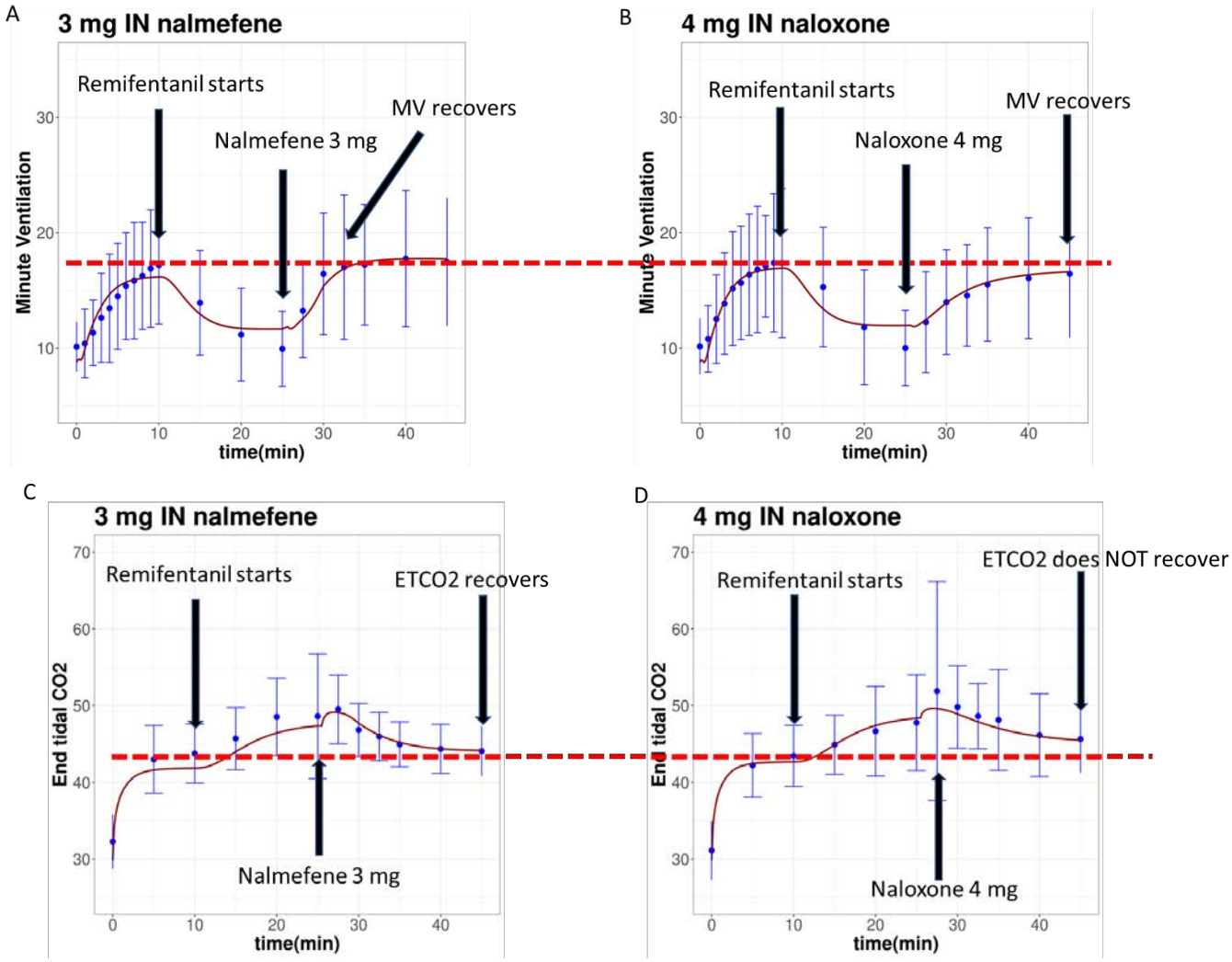


Figure 11: Pharmacologic effects on minute ventilation (MV) and end-tidal CO2 (ETCO2) from nalmefene IN 3 mg (A & C) and naloxone IN 4 mg (B & D) in OPNT003-OOD-001.

A and B: effects on MV. Starting from time 0, subjects breathed in a hyperoxic and hypercapnic gas mixture (see **Table 16** for details). This resulted in an increase of MV. Starting from 10 min, the remifentanil (0.175 ug/kg/min) infusion began, resulting in a decrease of MV. At the 25th minute, IN nalmefene (A) or naloxone (B) was administered, leading to a recovery (increase) of MV. For the nalmefene group (A), it took less than 10 min for MV to recover to the pre-opioid level (thick horizontal red dash line). For the naloxone group (B), it took at least 20 min. C and D: the same study but showing effects on $ETCO_2$. For the nalmefene group (C), 20 min after the IN administration, $ETCO_2$ has recovered (decreased) to the pre-opioid level (thick horizontal red dash line). For the naloxone group (D), 20 min after the IN administration, $ETCO_2$ has not fully recovered (still above the pre-opioid level). Blue error bars: mean and standard deviation from the study OPNT003-OOD-001. Thin red lines: model simulation of a typical subject.

4.3.4 Results (Question Based Review)

1) Does OCP's independent modeling & simulation support that nalmefene IN 3 mg has an onset of action appropriate for opioid reversal in a community setting?

OCP's opioid-effects model recapitulated the observations from the applicant's study OPNT003-OOD-001, that the nalmefene IN 3 mg group had both the minute ventilation (MV) and end-tidal CO2 (ETCO2) values return to the pre-remifentanil levels faster than the naloxone IN 4 mg group did (**Figure 11**). While this suggests that the onset of action for nalmefene IN 3 mg is at least as fast as that for naloxone IN 4 mg in a healthy population under hypercapnic situations, an open question is if these results would translate to a community overdose situation, where subjects are typically chronic opioid users breathing room air. Another question is if the recovery of MV and ETCO2 can be translated to more clinically interpretable endpoints, such as recovery from the overdose (i.e., survival of an overdosed subject) with high potent opioids such as fentanyl and its derivatives.

During initial development and validation of the opioid-effects model published by OCP [3], it was found that the onset of action of an opioid antagonist has a significant impact on two clinical endpoints: the antagonist's capability of preventing opioid-associated cardiac arrest, and its capability of shortening the brain hypoxia time. To translate the applicant's findings to a community setting, OCP's independent simulation of nalmefene IN 3 mg focused on these two endpoints. To better mimic community overdose situations, the opioids used in the simulations were fentanyl and carfentanil, using the medium overdose scenarios and virtual populations representing chronic opioid users (see Methods).

As shown in **Figure *12***, 1 dose of nalmefene IN 3 mg reduced the simulated percentage of patients experiencing fentanyl-associated cardiac arrest from 52% (median value without antagonist's administration) to 18% (median value with nalmefene), a 34% reduction. In contrast, 1 dose of naloxone IN 4 mg reduced the simulated cardiac arrest percentage from 52% to 28% (a 24% reduction). Similarly, after carfentanil overdose, nalmefene IN 3 mg reduced the simulated percentage of cardiac arrest by 38% (from 59% to 21%), compared to the 25% reduction (from 59% to 34%) when naloxone IN 4 mg was administered.

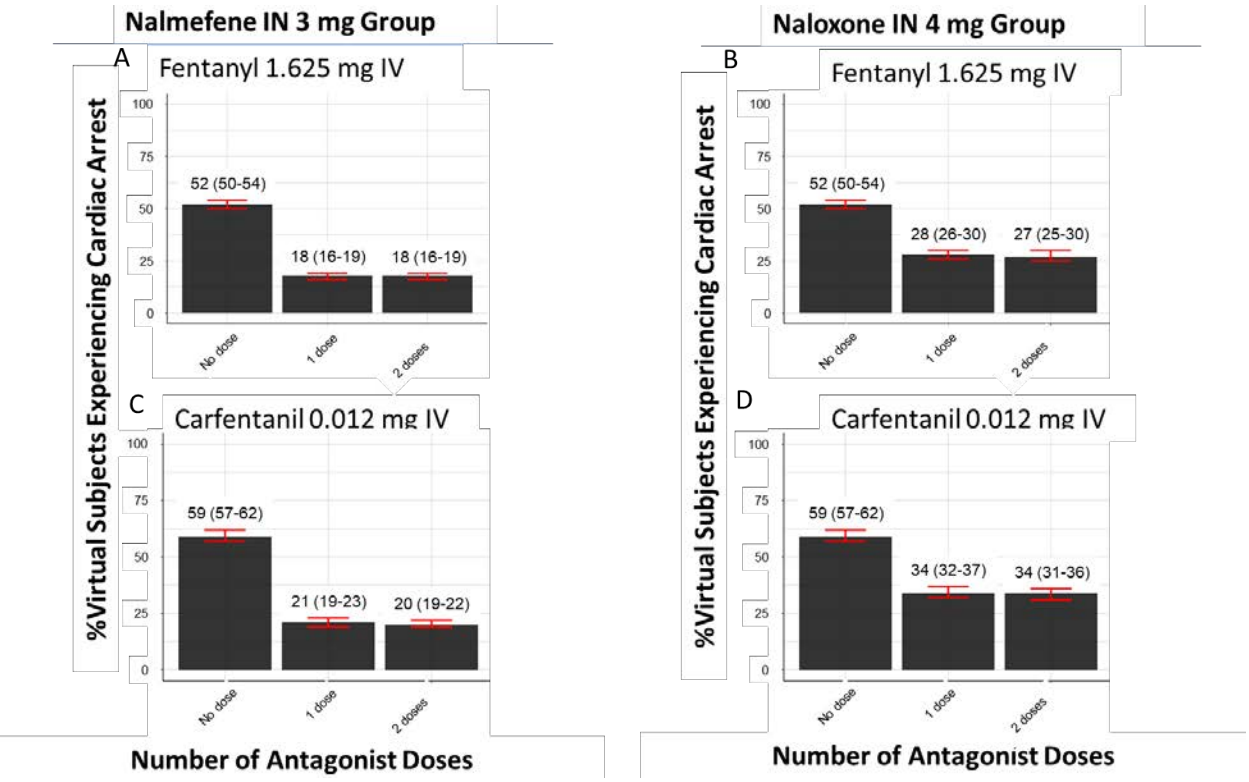


Figure 12: Percentage of virtual patients experiencing cardiac arrest after fentanyl (A and B) or carfentanil (C and D) overdose.

The opioid doses are based on the medium overdose scenarios previously estimated (1.625 mg intravenous bolus injection for fentanyl, and 0.012 mg for carfentanil). The 3 bars on each X axis represent no antagonist administration, 1 dose intranasal (IN) administration, and 2 doses IN administration (2.5 min apart, one dose into separate nostrils), respectively. The antagonist administered is nalmefene IN 3 mg (A and C) and naloxone IN 4 mg (B and D). The red error bars are the median and interquartile range of the estimated cardiac arrest percentages through repeated sampling of the virtual population (see Methods). The median and interquartile range values are also labeled on top of each error bar.

As shown in **Table *17***, for opioid (fentanyl or carfentanil) overdose without an antagonist administration, the median value of brain hypoxia time could not be calculated because more than half of the virtual subjects developed cardiac arrest (and hence no meaningful recovery expected). One dose of nalmefene IN 3 mg had a median brain hypoxia time of 1.8 and 1.7 min, after fentanyl and carfentanil overdose respectively. In contrast, 1 dose of naloxone IN 4 mg had a median brain hypoxia time 2.3 and 2.6 min respectively, both longer than when nalmefene IN 3 mg was administered. Taken together, these simulated results comparing nalmefene IN 3 mg with a naloxone formulation already approved for community use support that the onset of action for nalmefene is appropriate for community use.

Nalmefene IN 3 mg				
		Median value	Lower bound of IQR	Higher bound of IQR
Fentanyl 1.625 mg	Without Nalmefene	CA	0 min	CA
	With Nalmefene	1.8 min	0 min	3.9 min
	2 dose Nalmefene	1.8 min	0 min	3.9 min
Carfentanil 0.012 mg	Without Nalmefene	CA	0 min	CA
	With Nalmefene	1.7 min	0 min	4.3 min
	2 dose Nalmefene	1.7 min	0 min	4.2 min

Naloxone IN 4 mg				
		Median value	Lower bound of IQR	Higher bound of IQR
Fentanyl 1.625 mg	Without Naloxone	CA	0 min	CA
	With Naloxone	2.3 min	0 min	CA
	2 dose Naloxone	2.3 min	0 min	CA
Carfentanil 0.012 mg	Without Naloxone	CA	0 min	CA
	With Naloxone	2.6 min	0 min	CA
	2 dose Naloxone	2.5 min	0 min	CA

CA: subjects experienced cardiac arrest so brain hypoxia time not calculated
IQR: inter-quartile range in the virtual population

Table 17: Brain hypoxia time experienced by virtual subjects after fentanyl or carfentanil overdose.

Brain hypoxia time is defined as the time brain oxygen partial pressure is below the critical threshold 20 mm Hg. The median and interquartile range of brain hypoxia time are based on the total population of 2000 virtual subjects. The median value of brain hypoxia time for nalmefene (left) and naloxone (right) are marked as red.

During the review, a question was raised regarding the Applicant's nalmefene PK profile in study OPNT003-OOD-001. The plasma concentration in this study rises slower compared to previous PK studies using the same product. Consequently, the review team questioned whether this could impact evaluation of onset time from the OPNT003-OOD-001. The review team also wanted to know whether the slower absorption was a study-specific factor (that affects both nalmefene and naloxone in the study), or drug-specific effect (only one of the drugs was affected). OCP compared the naloxone profile from study OPNT003-OOD-001 to those from the naloxone IN 4 mg product label and from a separate FDA-led PK study (referred to as SCR-011 in **Figure 13**) using the same naloxone product. As shown in **Figure 13**, the naloxone plasma concentration from study OPNT003-OOD-001 rises slower than previous studies, similar to what was observed for the nalmefene profile in OPNT003-OOD-001. This suggests a study-specific factor from OPNT003-OOD-001 slowed down the absorption of both nalmefene and naloxone through nasal mucous membranes. While the root cause for this systemic effect is unknown, this is not expected to compromise the comparison between nalmefene and naloxone since the data from both drugs was from the same study OPNT003-OOD-001.

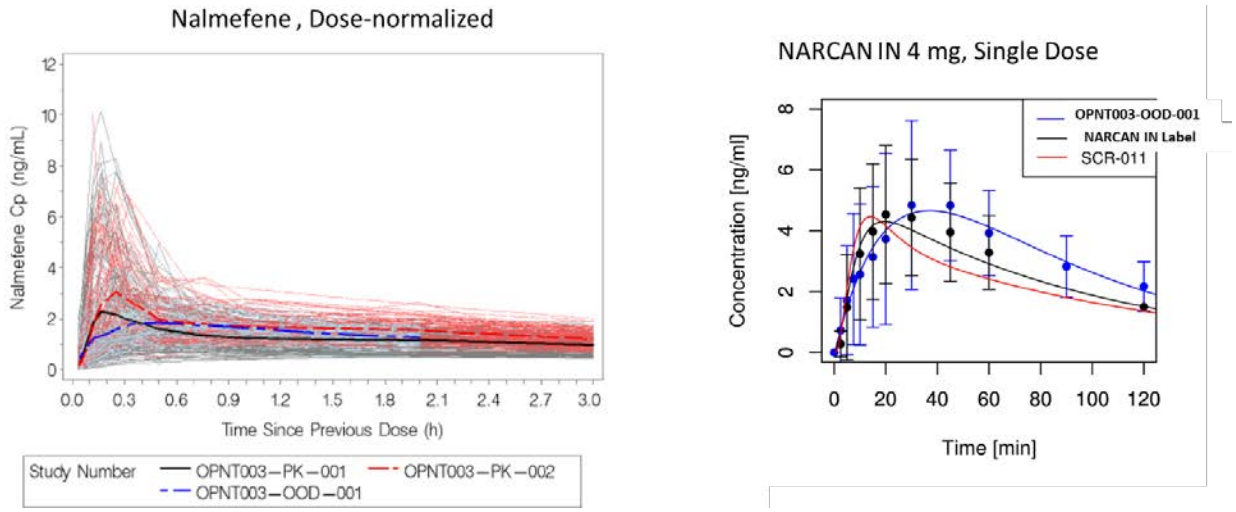


Figure 13: Comparison of the nalmefene and naloxone plasma profiles in OPNT003-OOD-001 to previous studies.

Left: Nalmefene plasma profiles across three of the Applicant's studies. Because different studies used different doses, the dose-normalized plasma concentrations were shown on the Y axis. Thin lines are individual patient's profiles while the three thick lines represent the geometric mean from each study. Note that OPNT003-OOD-001, the blue line, rises slower and reaches a lower peak compared to the other two studies. Right: Naloxone plasma profiles from the Applicant's study OPNT003-OOD-001 (blue), the NARCAN IN product label (black), and a clinical pharmacokinetic study SCR-011 conducted by the FDA (red). Error bars are mean and standard deviation from each study while solid lines are PK model simulations. All studies used a single dose of naloxone IN 4 mg except SCR-011, which used repeated dosing of naloxone IN 4 mg. Consequently, only model simulation of single dose was shown for SCR-011. Note that OPNT003-OOD-001, the blue line, rises slower than the other two studies.

2) Does OCP's independent modeling & simulation support the proposed nalmefene dose for community use is unlikely to require dose titration or re-administration for effectiveness?

The OCP opioid-effects model was used to simulate two dosing schemes of the nalmefene IN product: a single administration of nalmefene IN 3 mg, or two doses of nalmefene IN 3 mg into each nostril, with a 2.5 min delay between the doses. As shown in **Figure *12***, this 2-dose nalmefene scheme did not significantly change the cardiac arrest percentage in the virtual populations after fentanyl or carfentanil overdose, in comparison to the 1-dose nalmefene scheme. Similarly, shows that the 2-dose nalmefene scheme had the same median brain hypoxia time as the 1-dose nalmefene scheme in the virtual populations after fentanyl or carfentanil overdose.

While it is conceivable that under certain scenarios (e.g., with rescue breathing or cardiopulmonary resuscitation) re-administration of IN nalmefene after the 1st dose may have benefits, the results in **Figure *12*** and **Table *17*** suggested that the proposed dose (IN 3 mg) would not require titration or re-administration to achieve significant protection against opioid-associated cardiac arrest and brain hypoxia.

3) Does OCP's independent modeling & simulation support the Applicant's hypothesis that the longer duration of action for nalmefene reduces the likelihood of re-narcotization?

The OCP opioid-effects model was used to simulate a high opioid dose (carfentanil 0.287 mg) that was slowly absorbed into the systemic circulation. Such a scenario may happen when opioid exposure is through routes such as inhalation (prolonged exposure) or oral (delayed gastrointestinal absorption). **Figure 14** shows the simulated minute ventilation of a typical subject during such a slow opioid absorption with a single dose of either nalmefene IN 3 mg or naloxone IN 4 mg administered as the antagonist. As can be seen, both nalmefene and naloxone were able to recover minute ventilation initially. However, while nalmefene IN 3 mg administration restored minute ventilation for a relatively long time, naloxone IN 4 mg administration did not restore minute ventilation to baseline levels and minute ventilation gradually began to decline further. About 6 hours after naloxone IN 4 mg administration, minute ventilation decreased sufficiently to trigger cardiac arrest.

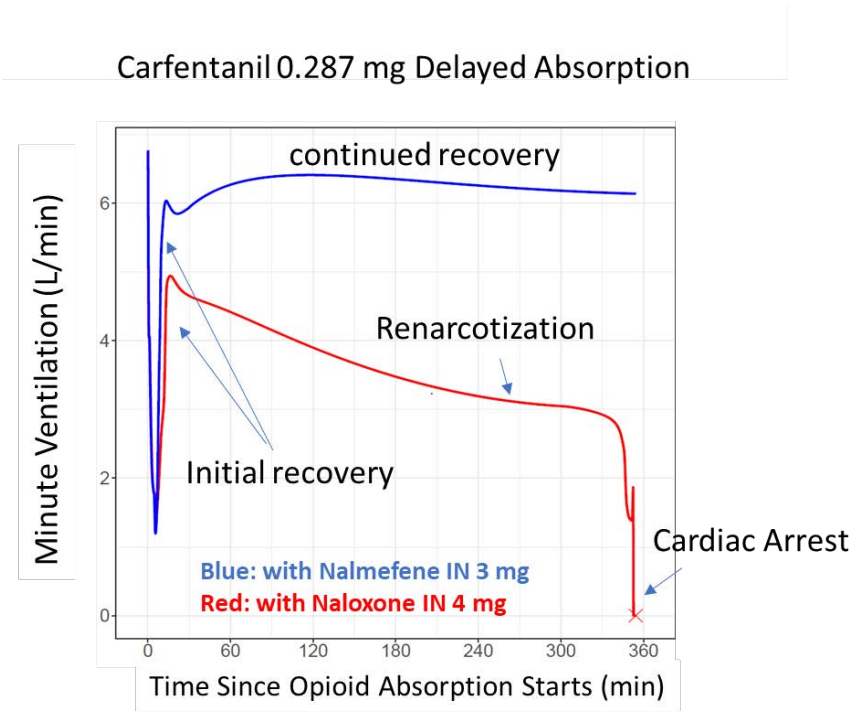


Figure 14: Comparison of nalmefene IN vs naloxone IN in preventing re-narcotization.

A large dose (0.287 mg) of carfentanil was simulated to be absorbed into the systemic circulation slowly. Both nalmefene IN 3 mg (blue) and naloxone IN 4 mg (red) were given 1 min after the minute ventilation dropped below 40% of baseline. This resulted in initial recovery from both antagonists. As time goes by, the typical patient's minute ventilation after nalmefene IN administration remained at a high level. In contrast, the minute ventilation after naloxone IN administration decreased gradually, until it hit a critical point and triggered cardiac arrest about 6 hours after naloxone administration.

4.3.5 Limitations

These results are based on modeling & simulation and have limitations associated with the following assumptions.

First of all, while the capability of this model to predict various clinical endpoints (minute ventilation, blood gas tensions, etc.) after opioid exposure were objectively assessed during model development by comparing the model prediction to a series of clinical data [3], most of the data were from fentanyl. It was assumed that a similar level of model credibility can be attributed to carfentanil, which has very little clinical data available. This assumption is partially supported by the validation studies during model development, where the model was used to predict various physiological variables (minute ventilation, PaO2, PaCO2, CO2 response slope) from independent clinical studies involving different opioids (fentanyl, alfentanil, and remifentanil) [3]. The overlap between predictions and vast majority of observed data points suggests that applying the model to structurally similar fentanyl analogues like carfentanil may have acceptable credibility.

Second, the relationship between respiratory depression (more specifically the decrease of arterial O2 partial pressure PaO2) and cardiovascular collapse/cardiac arrest is derived from animal data. The OCP opioid-effects model assumes this relationship can be approximately applied to humans as well. This assumption is necessary because no human data are available to assess such relationship. Multiple species (dogs, pigs, horses) were used to calibrate and validate this relationship in the model [3]. The fact that such a quantitative relationship (between the degree of hypoxia and the occurrence of cardiac arrest) appeared to be consistent among different animal species suggests that it may be reasonable to assume the relationship can be applied to humans. The use of an endpoint, such as cardiac arrest, instead of minute ventilation imposes a more restricted time for the naloxone intervention to be successful in reversing the opioid exposure. As such, the predictions using cardiac arrest can be considered as both a more realistic representation of outcome and more conservative than simulations focusing on changes in baseline ventilation.

Third, there is a lack of clinical PK data for carfentanil. The OCP opioid-effects model assumes carfentanil PK is similar to fentanyl PK, with the plasma half-life prolonged according to limited human carfentanil PK data [3]. While there are multiple ways to adjust the model to reproduce the observed long half-life of carfentanil [6], we chose a parameter set that would give the highest maximum plasma concentration and slowest clearance. As such, the carfentanil PK model we used could be considered a “worst case” scenario.

Last, the OCP opioid-effects model assumes the 1st dose of antagonist would be given 1 min after some signs of respiratory depression, defined as minute ventilation reducing to 40% of baseline. It is difficult to estimate how soon naloxone or nalmefene can be given after opioid exposure. If the administration of antagonist is further delayed, more patients will be predicted to experience opioid-associated cardiac arrest. On the other hand, since the same dosing time was applied to naloxone and nalmefene, such an uncertainty is not expected to interfere with the comparison of the two antagonists.

4.3.6 Conclusions

OCP's conducted independent modeling & simulation using a previously developed opioid-effects model to evaluate the onset of action of nalmefene IN 3 mg compared to naloxone IN 4 mg. The analyses support that the onset of action for nalmefene IN 3 mg was at least as rapid as naloxone IN 4 mg, an approved product for reversing opioid overdose in a community setting, supporting that this nalmefene product is also appropriate for use in a community setting. OCP's evaluation also supports that the proposed dose of nalmefene IN 3 mg is unlikely to require titration or re-administration to significantly decrease the incidence of opioid-associated cardiac arrest or brain hypoxia in a community setting, as long as the 1st dose of nalmefene was administered early enough. Finally, OCP's independent modeling & simulation suggests that nalmefene's long duration of action, primarily due to its longer plasma half-life, would not result in re-narcotization under certain opioid exposure scenarios whereas a single dose of naloxone would lead to initial recovery but delayed re-narcotization.

4.3.7 References

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4.4 Population PK and Population PKPD Analyses

The Applicant submitted report opnt003-poppk-001.pdf titled "*Development of Population Pharmacokinetic Model for Nalmefene Following Intranasal and Intramuscular Administration*" and report opnt003-pkpd-001.pdf titled "*Development of Pharmacokinetic/Pharmacodynamic Model for Comparison of Nalmefene and Naloxone Reversal of Minute Ventilation Depression Following Opioid Exposure*" to modules 5335 and 5354 of sequence 0004. Report opnt003-pkpd-001.pdf describes the PPK analyses of nalmefene and naloxone. Report opnt003-pkpd-001 discussed the PKPD analyses for naloxone and nalmefene. These studies analyzed data from three phase 1 studies; OPNT003-PK-001, OPNT003-PK-002, and OPNT003-OOD-001. Study design details are found in **Table 18** and **Table 19**.

Table 18: Design of Studies Included in the PPK and PKPD Analyses

Study Number/ Phase	Study Title	Participants	Duration of Dosing	Use in Analysis/ Major Exclusions
OPNT003-PK-001/ Phase 1	A two-period, two-treatment, randomized crossover study of the pharmacokinetics of nalmefene by intranasal and intramuscular administration in healthy volunteers	Planned 68 subjects; n = 66 completed IN treatment, n = 68 completed IM treatment	Single dose administration of each formulation; separated by a washout period	Nalmefene PK model
OPNT003-PK-002/ Phase 1	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	Planned 24 subjects; n = 23 in 3 mg IN (in 1 nostril), n = 23 in 6 mg IN (3 mg in each nostril), and n = 24 in 6 mg IN (2 × 3 mg in 1 nostril)	Single dose administration of each dose; separated by a washout period	Nalmefene PK model
OPNT003-OOD-001/ Phase 1	A two-part open-label study of the pharmacodynamic effects of intranasal nalmefene compared to intranasal naloxone in healthy volunteers under steady-state opioid agonism	Planned 68 subjects in Part 2; n = 52 both IN nalmefene hydrochloride and naloxone treatments, n = 8 naloxone treatment only, n = 9 nalmefene treatment only	IN nalmefene hydrochloride: single dose administration IN naloxone: single dose administration	Part 1: naloxone test doses not included in analysis Part 2: PK for naloxone and nalmefene PK models

Abbreviations: IM, intramuscular; IN, intranasal; n, number of subjects; PK, pharmacokinetic.
Source: sequence 0004, module 5335, optn003-poppk-001-pk.pdf, page 49

Table 19: Dosing and PK sampling in Studies Included in the PPK and PKPD Analyses

Study Number/ Phase	Dosing Regimen	Pharmacokinetic Sampling Plan
OPNT003-PK-001/ Phase 1	Nalmefene hydrochloride, single dose 2-way crossover • 1 mg IM • 3 mg IN	Day 1: predose (within 15 minutes) and 2.5, 5, 7.5, 10, 15, 20, 30, and 45 minutes, and 1, 2, 3, 4, 6, 8, 12, and 18 hours postdose Day 2: 24 and 36 (±5 minutes) hours postdose Day 3: 48 hours (±5 minutes) postdose
OPNT003-PK-002/ Phase 1	Nalmefene hydrochloride, single dose, 3-way crossover • 3 mg IN (3 mg in 1 nostril) • 6 mg IN (3 mg in each nostril) • 6 mg IN (2 × 3 mg in 1 nostril)	Day 1: predose (within 15 minutes) and 2.5, 5, 7.5, 10, 15, 20, 30, and 45 minutes, and 1, 2, 3, 4, 6, 8, 12, and 18 hours postdose Day 2: 24 (±5 minutes) hours postdose Day 3: 48 hours (±5 minutes) postdose
OPNT003-OOD-001/ Phase 1	Nalmefene hydrochloride, single dose • 3 mg IN Naloxone, single dose • 4 mg IN	Predose (within 15 minutes) and approximately 2.5, 5, 7.5, 10, 15, 20, 30, 45, 60, 90, and 120 minutes postdose

Abbreviations: IM, intramuscular; IN, intranasal;.
Source: sequence 0004, module 5335, optn003-poppk-001-pk.pdf, page 50

4.4.1 PPK Analyses: Nalmefene

The Applicant submitted report opnt003-poppk-001.pdf which describes the nalmefene PPK analyses. The objectives of these analyses are to develop a nalmefene population PK model using pooled plasma drug concentration data from 3 clinical studies of IN nalmefene hydrochloride and evaluate the impact of intrinsic and extrinsic subject factors on nalmefene PK variability.

The final dataset includes 4401 nalmefene plasma concentrations from a total of 153 subjects. Data used in these analyses came from studies OPNT003-PK-001, OPNT003-PK-002, and OPNT003-OOD-001. Study details are found in **Table 18** and **Table 19**.

The final model includes two compartments with disposition processes parameterized in terms of CL, Vc, Q, and Vp. Absorption was characterized by parallel zero-order and first-order processes for both intranasal (IN) and intramuscular (IM) administration. Separate estimates for the fraction of dose absorbed via the zero-order process and first-order absorption rate parameters were determined for IN and IM administration. The same zero-order absorption duration is used for IM and IN routes. The first order absorption process for IN and IM included time lag. The IN route has relative bioavailability with respect to the IM route. Clearance is related to weight as an allometric effect using a power model. Study OPNT003-OOD-001 as a binary variable is a covariate on the IN first order absorption rate. BSV estimated for CL, Vc, IN first order absorption, and IM first order absorption. A proportional model is used to describe residual error. Parameter estimates for the final nalmefene PPK model (nmf-final-model-01.ctl) are found in **Table 20**.

Table 20: Parameter Estimates for the final nalmefene PPK model

Parameter		Final Parameter Estimate		Magnitude of Variability	
		Population Mean	%RSE	Final Estimate	%RSE
CL	Central Clearance (L/h)	63.7	2.10	15.4 %CV	19.3
	Exponent of (WTKG/74.7) for CL	0.572	16.6		
V_c	Central Volume of Distribution (L)	15.2	11.8	211 %CV	10.3
Q	Distribution Clearance (L/h)	81.3	7.23	NE	NA
V_p	Peripheral Volume of Distribution (L)	522	3.05	NE	NA
INKA	Intranasal First-Order Absorption Rate Constant (1/h)	0.497	9.09	39.8 %CV	18.4
IMKA	Intramuscular First-Order Absorption Rate Constant (1/h)	0.156	5.45	50.4 %CV	18.4
D2	Zero-Order Absorption Duration (h)	0.302	7.33	NE	NA
INFK0	Fraction Intranasal Dose With Zero-Order Absorption (fraction)	0.0485	13.3	NE	NA
IMFK0	Fraction Intramuscular Dose With Zero-Order Absorption (fraction)	0.0170	10.9	NE	NA
ALAG1	Lag-time of First-Order Absorption (h)	0.0615	7.58	NE	NA
FR	Relative Bioavailability of Intranasal Dose (fraction)	0.834	2.23	NE	NA
STDEFF	Proportional Shift in INKA (fraction)	-0.349	17.7	NE	NA
Residual Variability		0.111	4.48	33.3 %CV	NA
Minimum Value of the Objective Function = 239.523					

Abbreviations: %CV, coefficient of variation expressed as a percent; IIV, interindividual variability; NA, not applicable; NE, not estimated; %RSE, relative standard error expressed as a percent; WTKG, body weight (kg). Shrinkage estimates: 23.7% for IIV in CL, 5.7% for IIV in Vc, 16.5% for IIV in INKA, and 9.4% for IIV in IMKA.
Source: sequence 0004, module 5335, optn003-poppk-001-pk.pdf, page 60

Key diagnostic plots are presented below.

Figure 15: Diagnostic plots for the final nalmefene PPK model – Intranasal Route

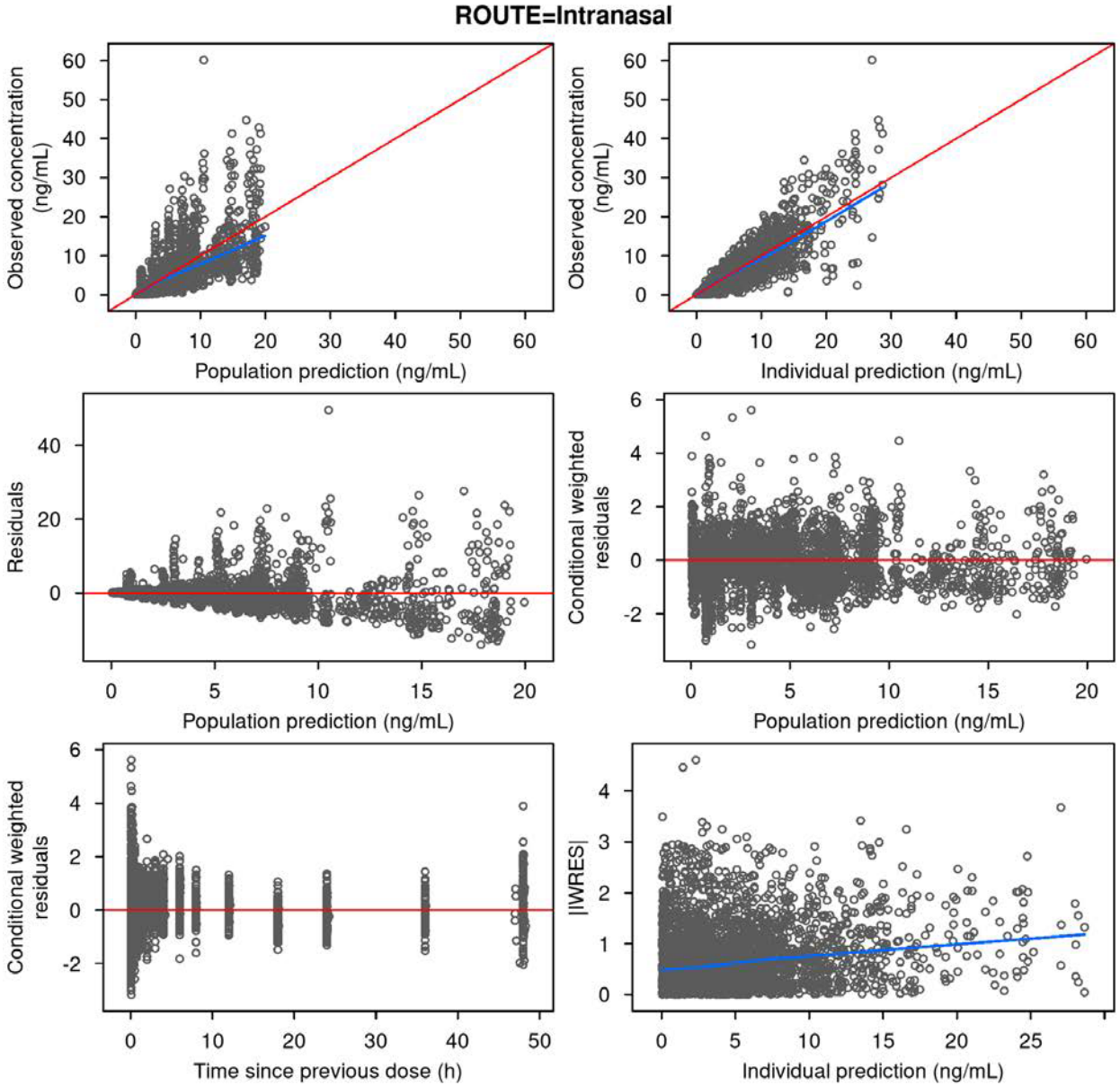

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Figure 16: Diagnostic plots for the final nalmefene PPK model – Intramuscular Route

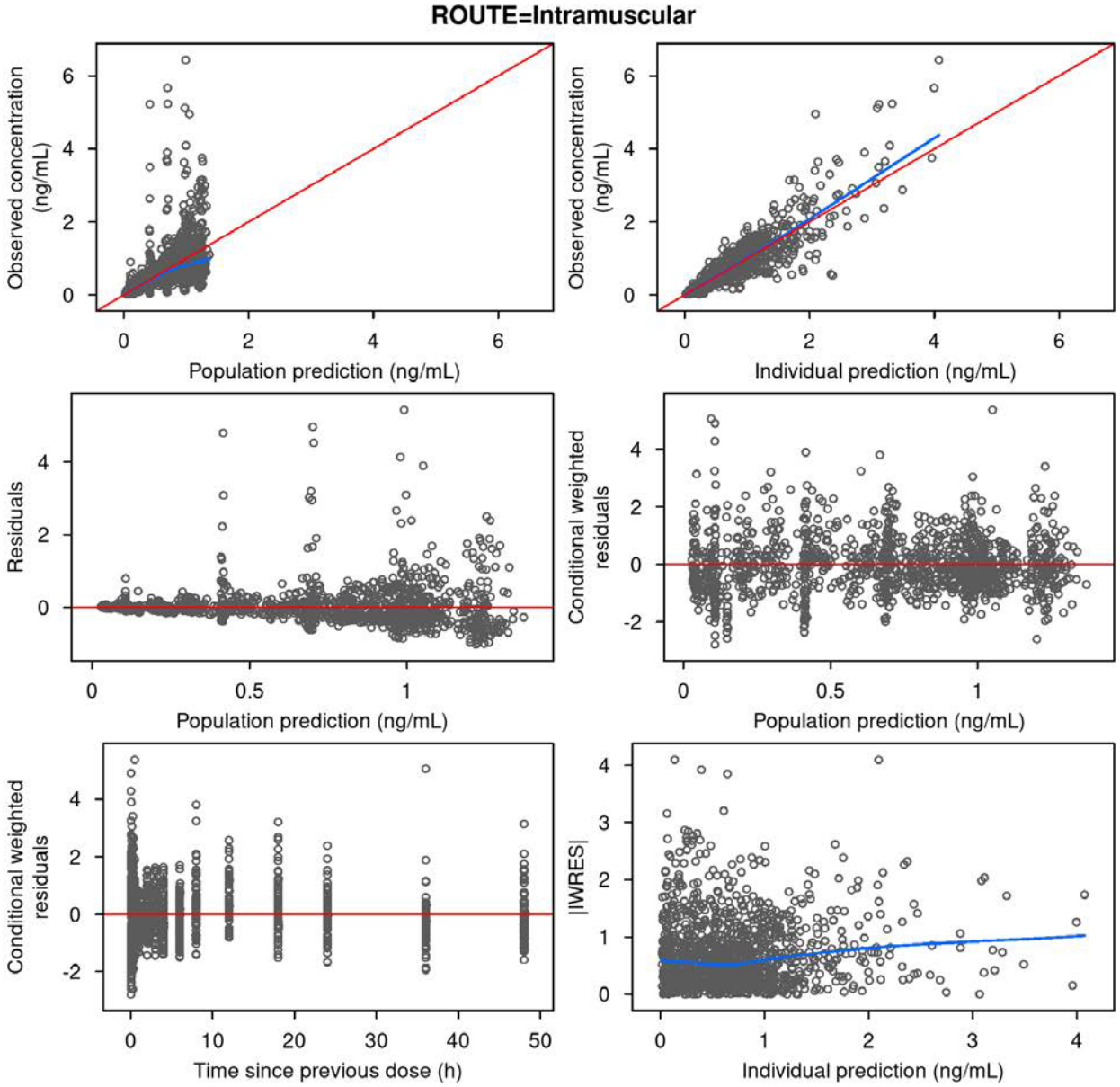

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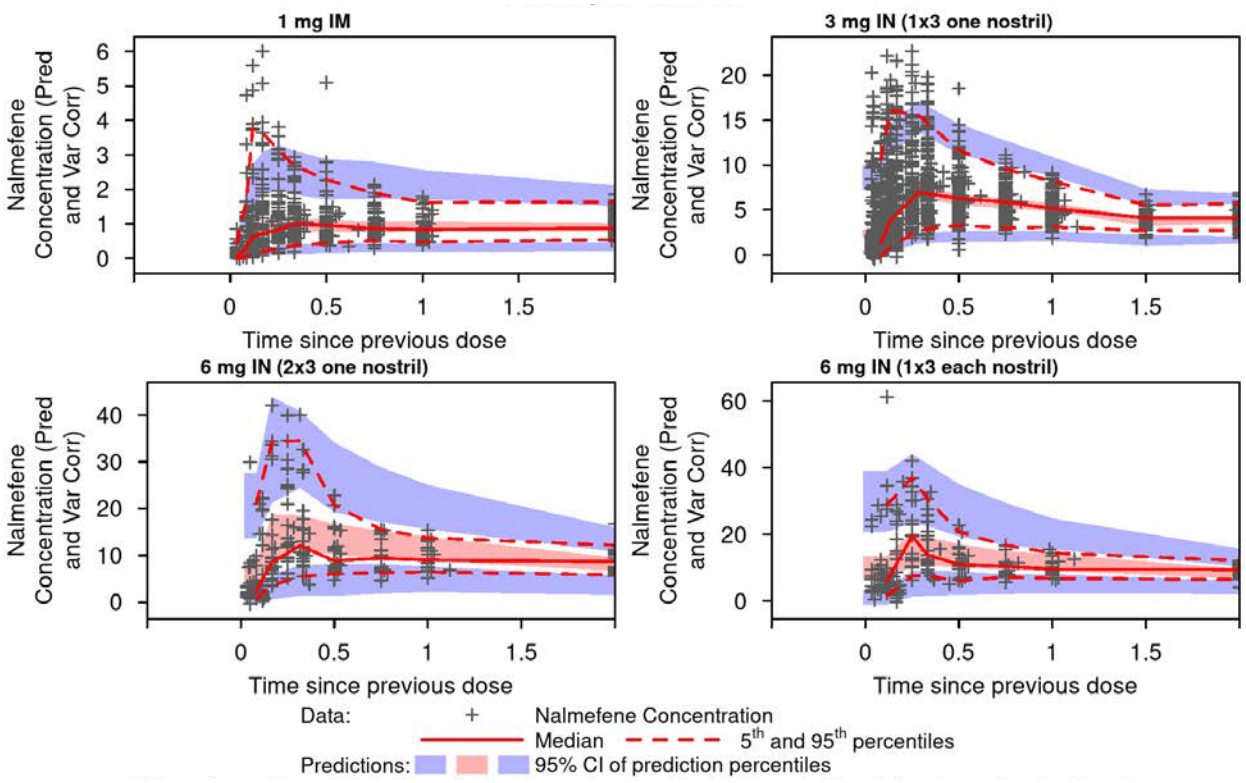
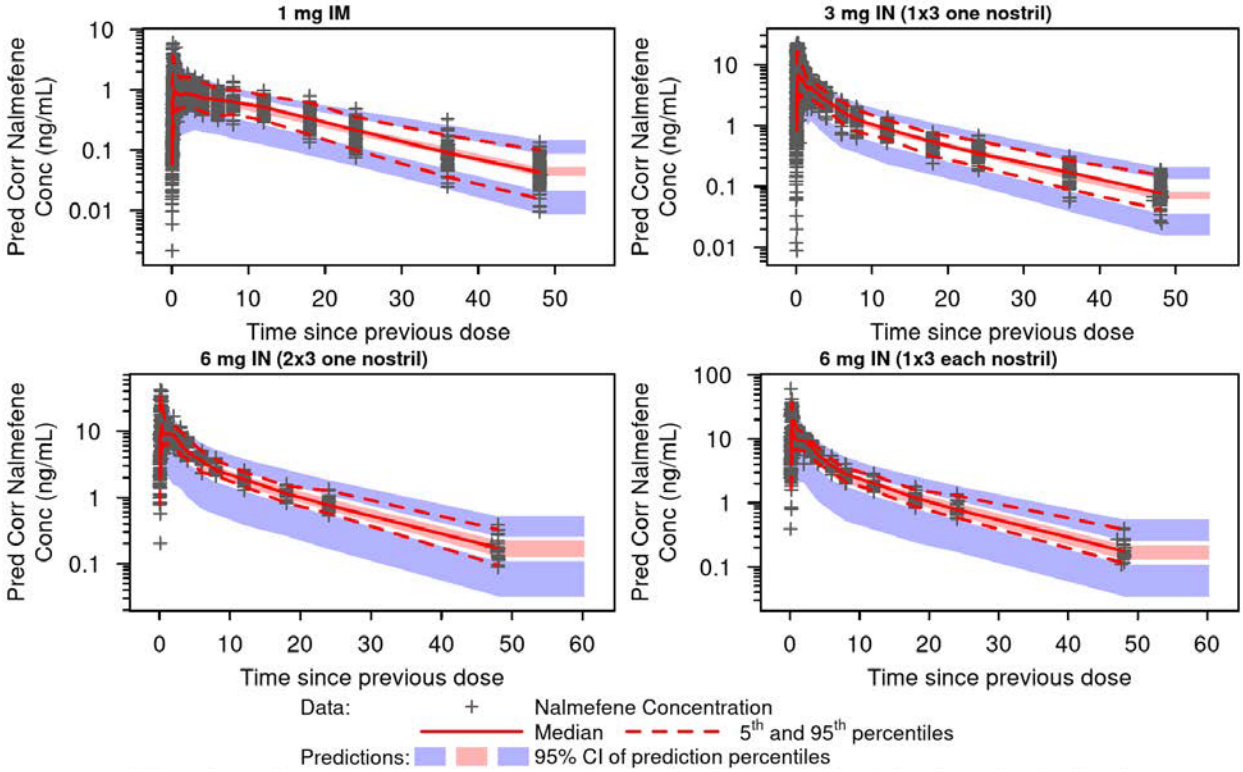
Figure 17: VPC for final nalmefene PPK model – Absorption Phase



Source: sequence 0004, module 5335, optn003-poppk-001-pk.pdf, page 84

Figure 18: VPC for final nalmefene PPK model – Full Time Frame



Source: sequence 0004, module 5335, optn003-poppk-001-pk.pdf, page 83

[*Reviewer comment: The eta shrinkage is low (23.7% for IIV in CL, 5.7% for IIV in Vc, 16.5% for IIV in INKA, and 9.4% for IIV in IMKA).*

*The diagnostic plots in **Figure 15** and **Figure 16** do not suggest bias with respect to time after administration nor concentration magnitude. The majority of the CWRES values are within ± 2 standard deviations in **Figure 15** and **Figure 16** . The VPCs (**Figure 17** and **Figure 18**) indicates that the model performs best at times near Tmax. The correlation matrix indicates low correlation among parameters. The residual squared errors for fixed effect as well as random effects are acceptable. The condition number is 85 which does not suggest overparameterization. **Overall, the nalmefene PPK model is acceptable**.*]

4.4.2 PPK Analyses: Naloxone

The Applicant submitted report opnt003-poppk-001.pdf which describes the PPK analyses of naloxone. The objective of these analyses is to develop a naloxone population PK model using plasma drug concentration data from Clinical Study OPNT003-OOD-001 of IN naloxone to obtain post hoc PK parameter estimates for individual subjects suitable for use in the pharmacokinetic/pharmacodynamic modeling.

The final dataset includes 632 naloxone plasma concentrations from a total of 60 subjects. Data used in these analyses came from study OPNT003-OOD-001. Study details are found in **Table 18** and **Table 19**.

The final model utilizes two-compartments and the disposition processes are parameterized in terms of apparent clearance (CL/F), central volume of distribution (Vc), distribution clearance (Q), and apparent volume of distribution (Vp). The applicant utilized Cl/F with a fixed CL to estimate the IN naloxone bioavailability. The value of Cl was fixed to an estimate determined after intravascular naloxone administration from a publication by Yassen et al. (2007) [1]. The values of Q and Vp were also fixed to the values from the Yassen et al. (2007) publication. Absorption is described by parallel zero-order and first-order processes with time lag on the first-order process. No covariates were included in final model. Between subject variability was estimated for Cl/F, Vc, and fraction of dose undergoing zero-order absorption. A proportional model describes the residual error.

Parameter estimates for the final naloxone PPK model (nlx-final-model-01.ctl) are found in **Table 21**.

[1] Yassen A, Olofsen E, van Dorp E, Sarton E, Teppema L, Danhof M, et al. Mechanism-based pharmacokinetic-pharmacodynamic modelling of the reversal of buprenorphine-induced respiratory depression by naloxone.

Table 21: Parameter Estimates for the final naloxone PPK model

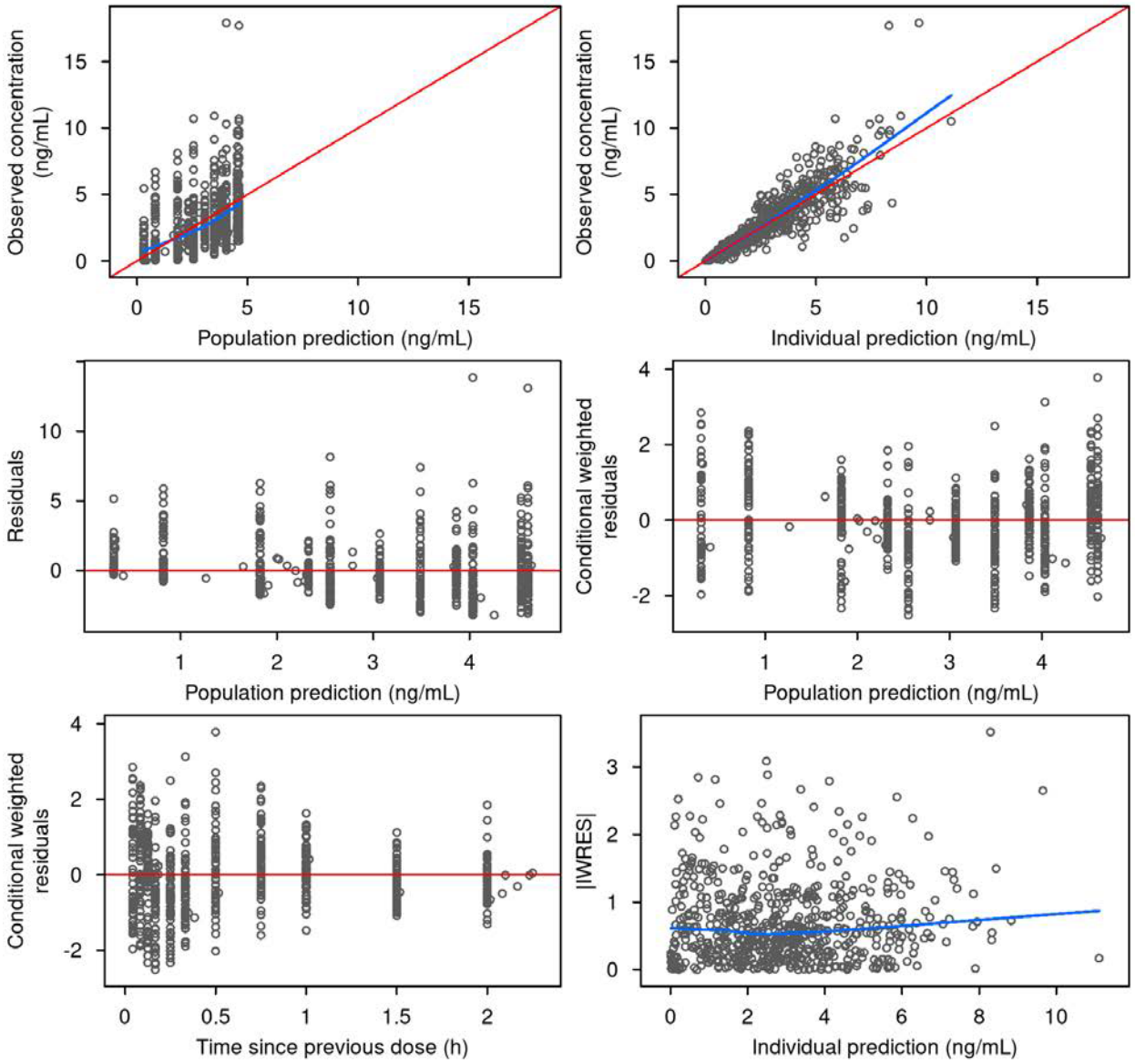
Parameter		Final Parameter Estimate		Magnitude of Variability	
		Population Mean	%RSE	Final Estimate	%RSE
CL/F	Apparent Clearance (L/h)	396	5.50	39.1 %CV	22.4
V_c	Central Volume of Distribution (L)	65.7	24.0	240 %CV	22.6
Q	Distribution Clearance (L/h)	284	FIXED	NE	NA
V_p	Peripheral Volume of Distribution (L)	102	FIXED	NE	NA
k_a	First-Order Absorption Rate Constant (1/h)	0.998	10.6	NE	NA
D2	Zero-Order Absorption Duration (h)	0.689	3.67	NE	NA
FK0	Fraction Dose with Zero-Order Absorption (fraction)	0.183	23.1	151 %CV[a]	30.1
ALAG1	Lag Time of First-Order Absorption (h)	0.0717	1.82	NE	NA
Residual Variability		0.104	12.2	32.3 %CV	NA
Minimum Value of the Objective Function = 594.507					

Abbreviations: %CV, coefficient of variation expressed as a percent; IIV, interindividual variability; NA, not applicable; NE, not estimated; %RSE, relative standard error expressed as a percent. The magnitude of interindividual variability (%CV) of Fraction Dose with Zero-Order Absorption (fraction) was calculated using the following equation: 100 × (1-0.183) × SQRT(3.42).

Source: sequence 0004, module 5335, optn003-poppk-001-pk.pdf, page 58

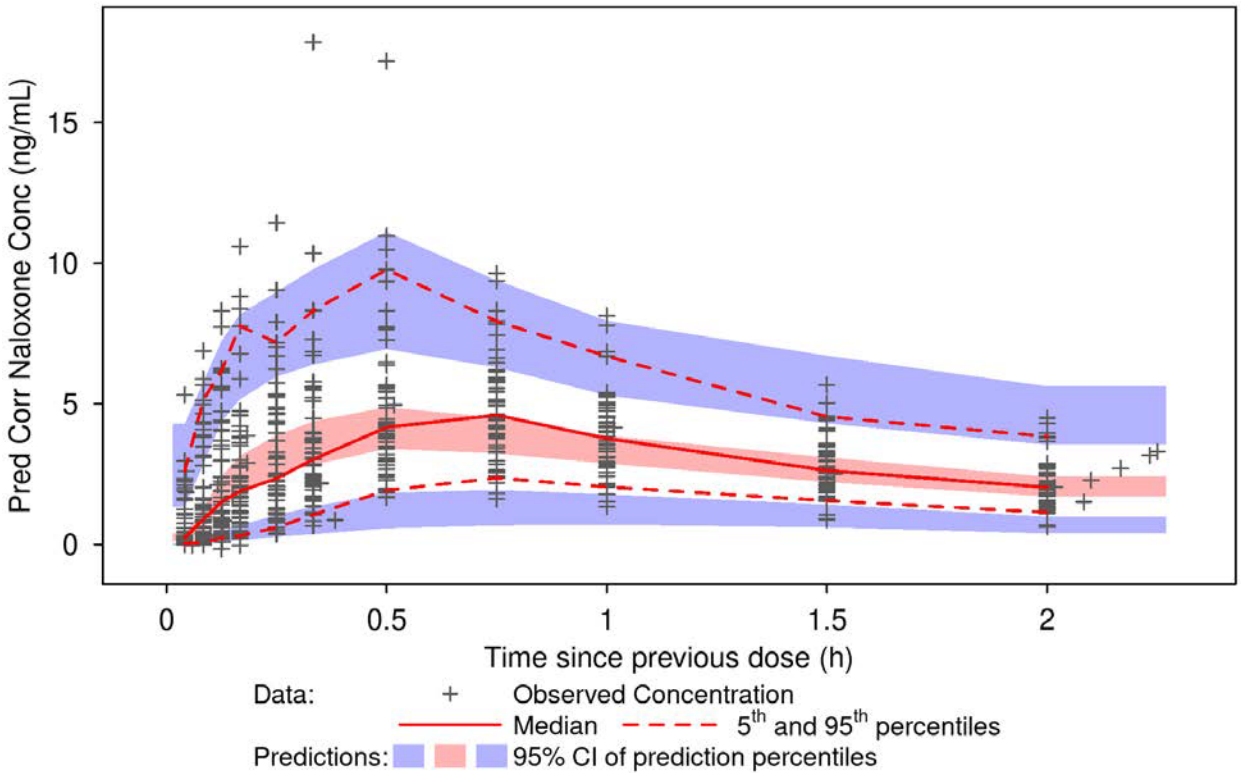
Key diagnostic plots are presented below.

Figure 19: Diagnostic plots for the final naloxone PPK model



Source: sequence 0004, module 5335, optn003-poppk-001-pk.pdf, page 101

Figure 20: VPC for final naloxone PPK model



Abbreviations: CI, confidence interval; Conc, concentration; Pred Corr, prediction corrected.
Source: sequence 0004, module 5335, optn003-poppk-001-pk.pdf, page 100

[*Reviewer comment: Eta shrinkage is low (12.7% for IIV in CL/F, 8.7% for IIV in Vc, and 16.7% for IIV in FK0).*

The Applicant's approach of fixing the values of Cl, Q, and Vp to the values in the Yassen article is reasonable. The estimation of Cl/F value of 396 when using a fixed Cl value of 3.45 L/min (207 L/h) indicates an F estimate of 207/396 = 0.52, or 52% absolute bioavailability for the intranasal naloxone spray.

The % RSE values are acceptable for all fixed and random effects. The diagnostic plots in ***Figure 19*** *do not indicate systematic bias with respect to time or concentration magnitude. The CWRES values in* ***Figure 19*** *are within ± 2 standard deviations. The VPC (****Figure 20****) does not indicate any obvious problems with model performance. The correlation matrix indicates that correlation among PK parameters is low. The condition number is 22 which does suggest overparameterization.* ***Overall, the PPK model for IN naloxone is acceptable.***]

4.4.3 PKPD Analyses

The PKPD analyses are described in report opnt003-pkpd-001.pdf which was submitted to module 5354 of sequence 0004. The objectives of these analyses are to A) develop a population PK/PD model describing the reversal of remifentanil-induced minute ventilation depression following the administration of IN nalmefene hydrochloride or IN naloxone hydrochloride; and B) simulate individual PD response profiles and calculate parameters describing the onset and duration of action.

The final PKPD dataset includes 2648 observation records from n=69 individuals. These data originated from Part 2 of PKPD study OPNT003-OOD-001. Study details are found in **Table 18** and **Table 19**.

Development of the naloxone PPK model and nalmefene PPK model included generation of the individual empiric Bayesian PK parameter estimates for each subject (see sections **4.4.1** PPK Analyses: Nalmefene and **4.4.2** PPK Analyses: Naloxone). The individual PK parameter estimates for subjects in the PKPD study OPNT003-OOD-001 are used to predict PK concentrations at the time of PD measurements for use in developing the PKPD model of minute ventilation response.

The final PKPD model includes an Emax model with separate EC50 values for nalmefene and naloxone. Each subject is assigned the same Emax values and baseline minute ventilation response (Base; L/min) for both the nalmefene period and the naloxone period of PKPD study OPNT003-OOD-001. The final model did not include any of the factors (age, body weight, body mass index, racial classification, and sex) assessed as covariates. Between subject variability is estimated for the baseline response (Base; L/min) and the magnitude of change in response (Emax; L/min). An additive error model describes residual PD variability. The parameter estimates for the final PKPD model (mv_de_emax1.ctl) are shown in **Table 22**.

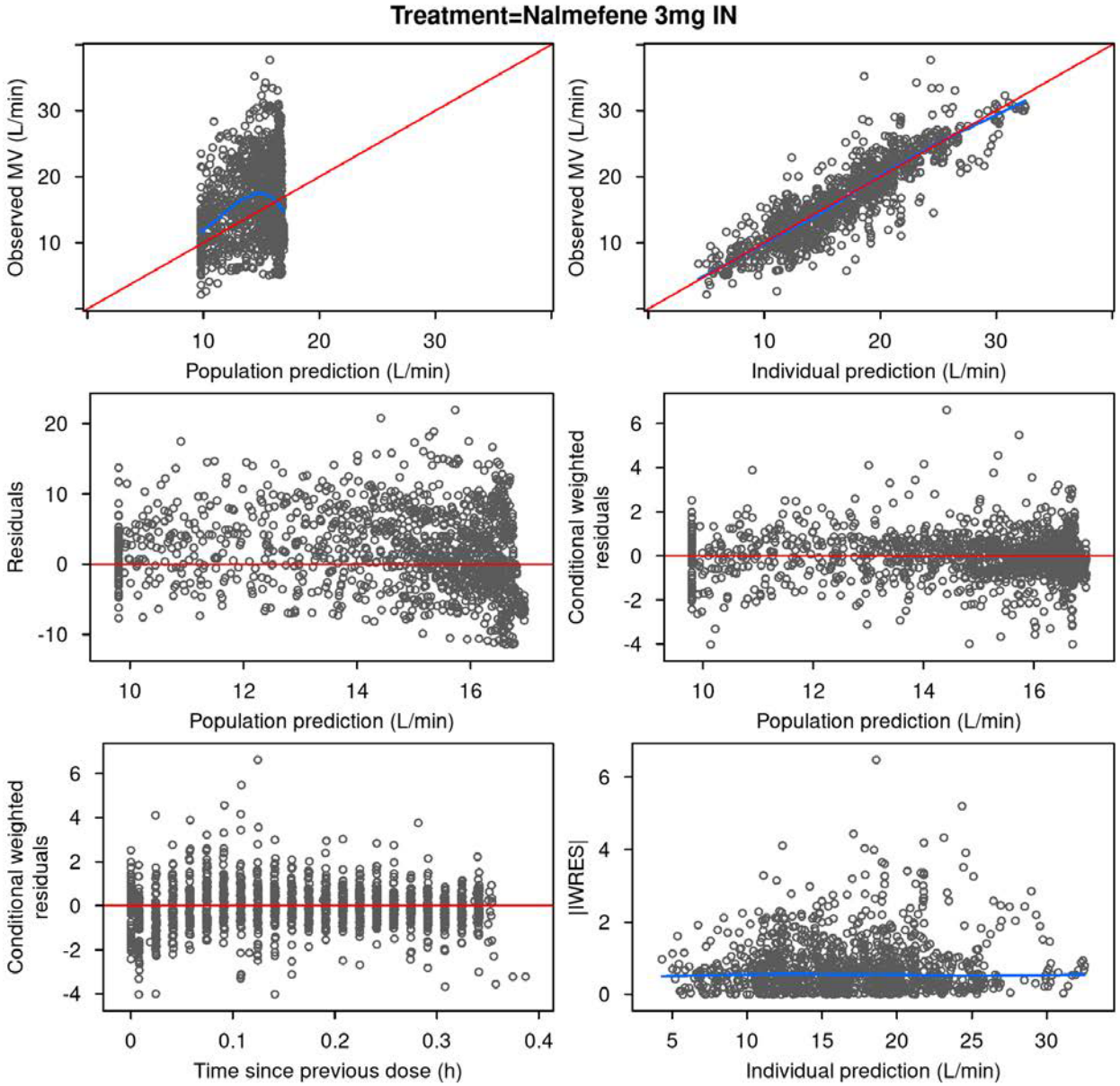
Table 22: Parameter Estimates for the final PKPD model for nalmefene and naloxone

Parameter		**Final Parameter Estimate**		**Magnitude of Variability**	
		Population Mean	**%RSE**	**Final Estimate**	**%RSE**
BASE	Baseline Response (L/min)	9.80	5.07	41.7 %CV	17.7
EMAX	Magnitude of Change in Response (L/min)	8.11	12.4	84.5 %CV	27.1
EC50F	Half-Stimulatory Nalmefene Concentration (ng/mL)	1.50	25.9	NE	NA
EC50X	Half-Stimulatory Naloxone Concentration (ng/mL)	3.32	20.5	NE	NA
Residual Variability for Pharmacokinetics		NA	NA	NA	NA
Residual Variability for Pharmacodynamics		6.58	13.7	2.56 SD	NA
Minimum Value of the Objective Function = 8127.17					

Abbreviations: %CV, coefficient of variation expressed as a percent; NA, not applicable; NE, not estimated; %RSE, relative standard error expressed as a percent; SD, standard deviation.
Source: sequence 0004, module 5354, opnt003-pkpd-001.pdf, page 42

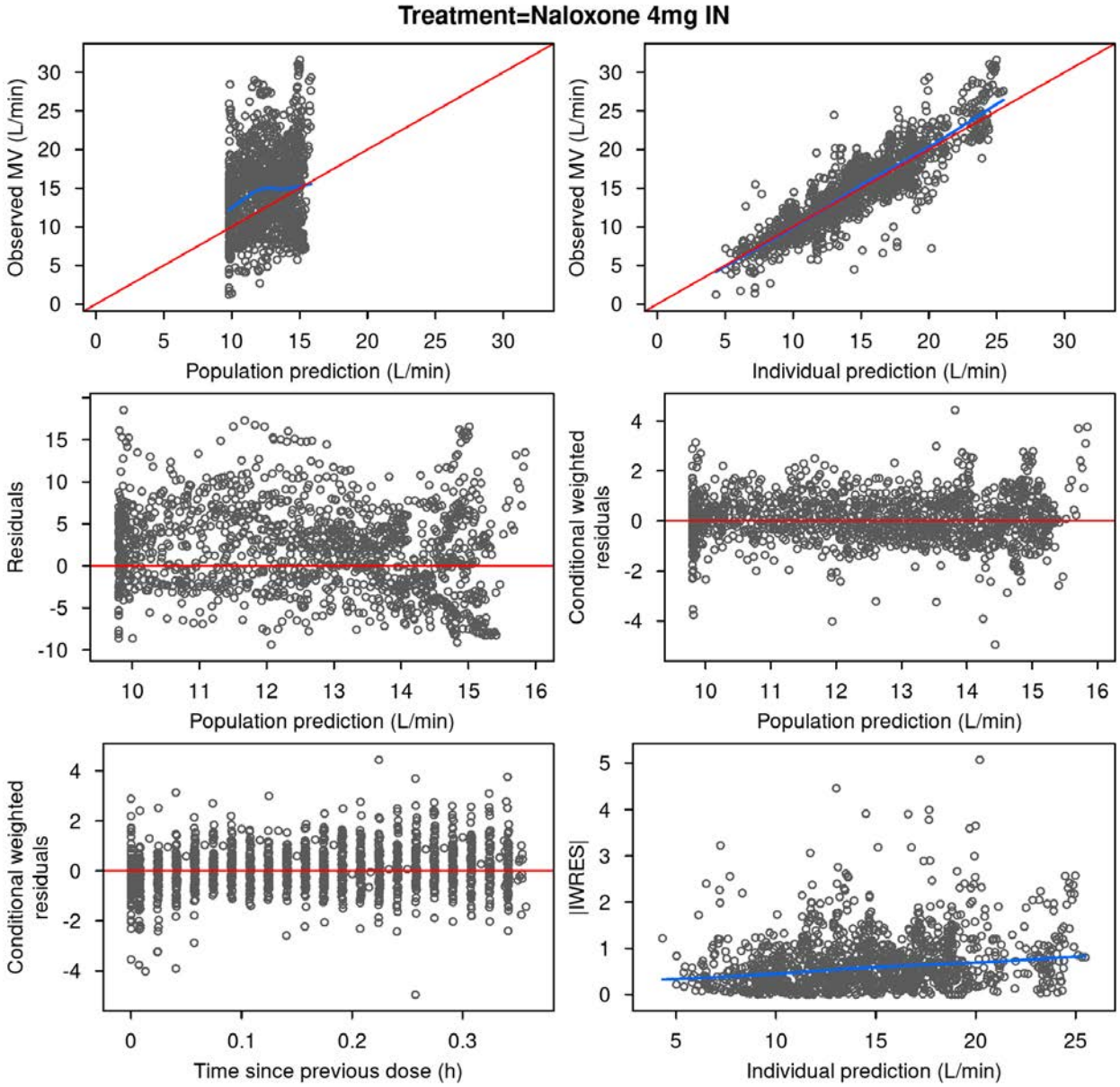
Key diagnostic plots are presented below.

Figure 21: Diagnostic plots for the final PKPD model - Nalmefene



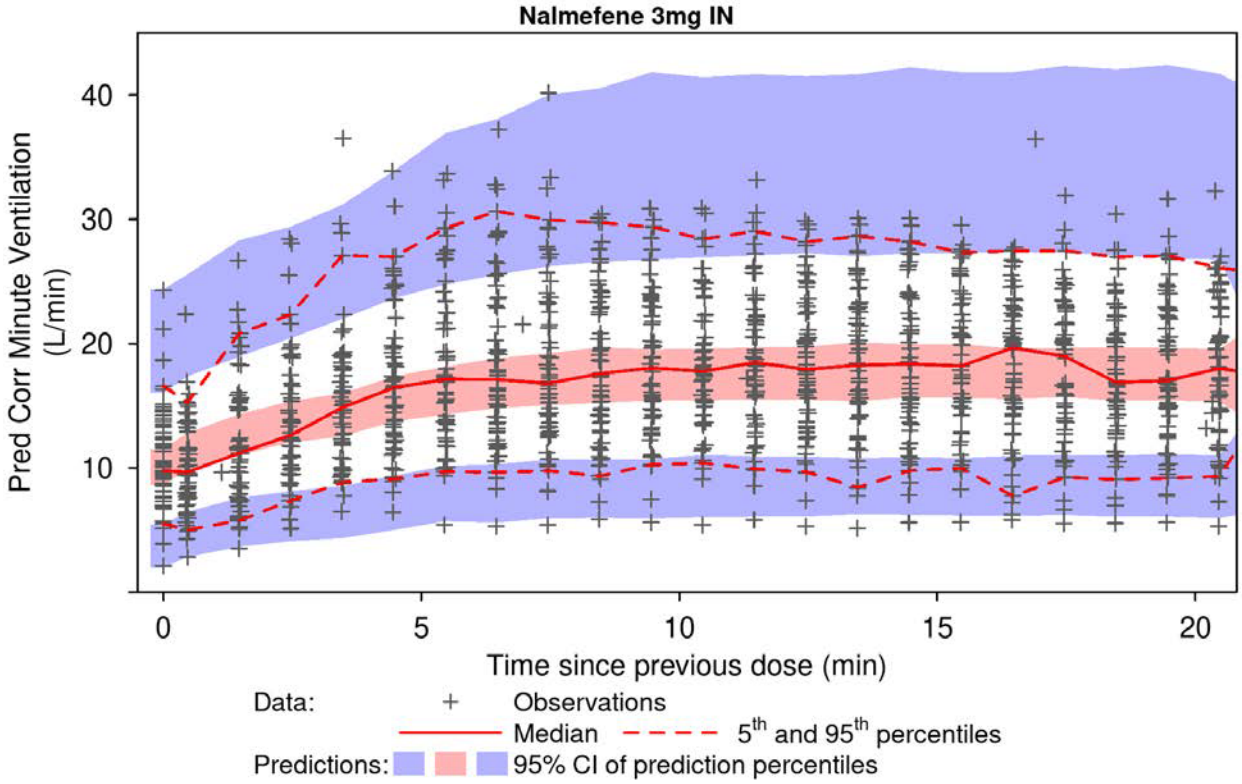
Source: sequence 0004, module 5354, opnt003-pkpd-001.pdf, page 71

Figure 22: Diagnostic plots for the final PKPD model - Naloxone



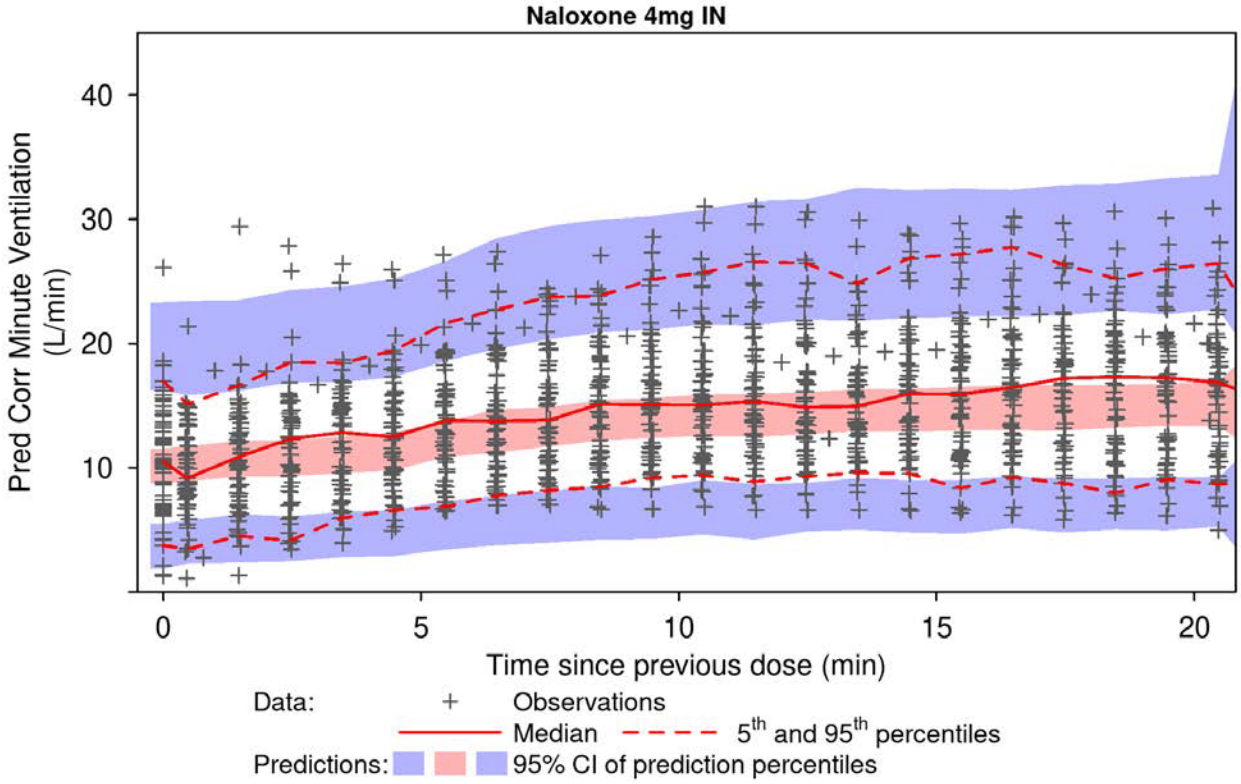
Source: sequence 0004, module 5354, opnt003-pkpd-001.pdf, page 71

Figure 23: VPC for final PKPD Model - Nalmefene



Source: sequence 0004, module 5354, opnt003-pkpd-001.pdf, page 77

Figure 24: VPC for final PKPD Model - Naloxone



Source: sequence 0004, module 5354, opnt003-pkpd-001.pdf, page 77

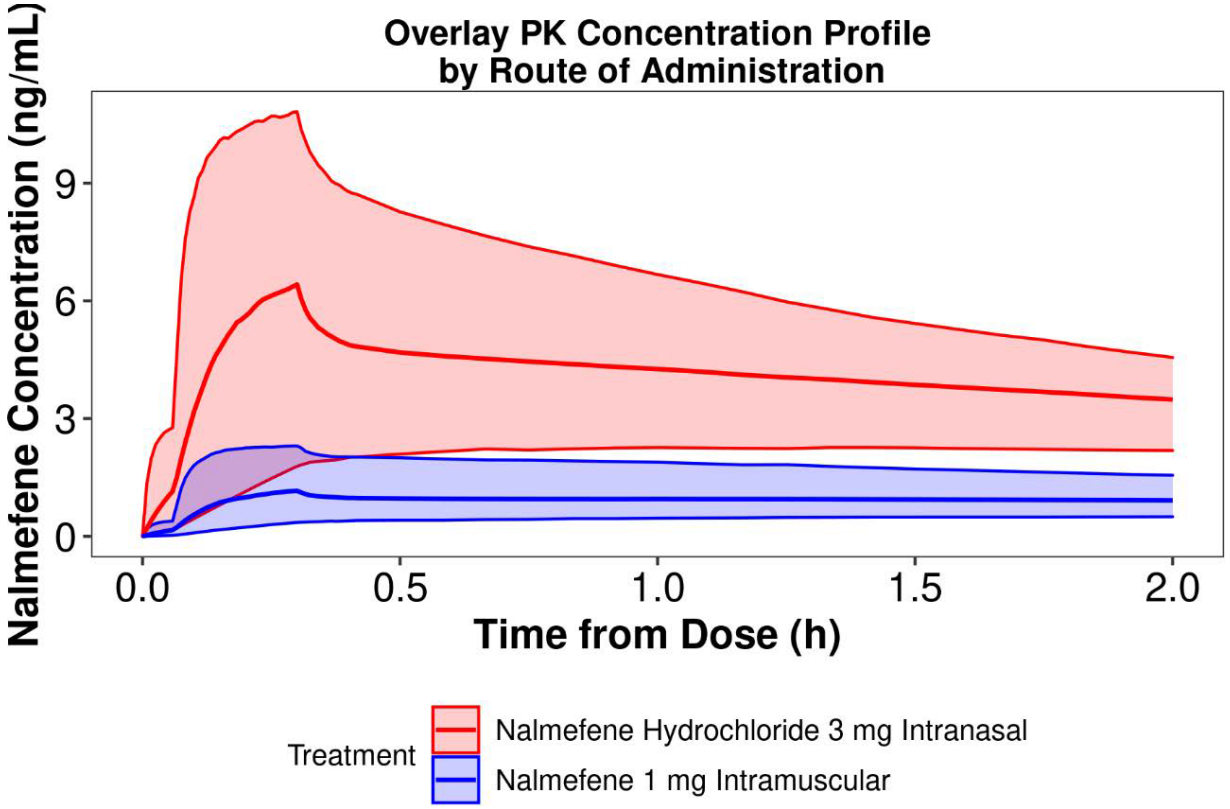
[*Reviewer comments: The eta shrinkage values are low (4.1% for IIV in BASE and 8.4% for IIV in EMAX).*

*The diagnostic plots (**Figure 21** and **Figure 22**) do not suggest any signs of bias for nalmefene or naloxone. The majority of the CWRES points are within ± 2 standard deviations in **Figure 21** and **Figure 22**. The VPCs (**Figure 23** and **Figure 24**) do not suggest any concerns with model performance. The correlation matrix values indicate low correlation among parameters. The condition number is 10 which does not suggest the model is overparameterized. The residual squared errors are acceptable for all fixed effects and random effects. Overall, the PKPD model is acceptable.*]

4.4.4 PPK Simulations

The Applicant conducted PK simulations to assess the PK profile for naloxone and nalmefene. **Figure 25** shows the PK simulation of the population PK profile for a single administration of 3 mg IN nalmefene or 1 mg IN naloxone.

Figure 25: PK Simulation of IN and IM Administration



The lines and shaded boxes represent the median and 90% prediction interval.

Source: sequence 0004, module 5335, optn003-poppk-001-pk.pdf, page 99

The Applicant conducted PK simulations to assess the effect of weight on nalmefene PK. The simulation methodology is to simulate PK for each subject in the population PK dataset and use the mean PK parameters for the full dataset (median weight 74.7 kg) as a reference for comparison to the PK parameters in the first quartile of body weight (50 kg to 64.8 kg) as well as the fourth quartile of body weight (91 to 106.8 kg). The Applicant also assessed the predicted PK in weights associated with 12-year old subjects (median wt 50.6 kg; 27.6 to 126.8 kg range). The PK simulation results are presented in **Table 23**.

Table 23: Simulated Effect of Weight on Nalmefene PK

Simulation Scenario	Geometric Mean (%CV)	
	C_{max} (ng/mL)	$AUC_{0\text{-}inf}$ (ng × h/mL)
Nalmefene 3 mg IN (full body weight distribution and PD study IN k_a)	6.17 (42)	38.8 (19)
Nalmefene 3 mg IN (low body weight subjects – first quartile and PD study IN k_a)	6.49 (43)	44.9 (16)
Nalmefene 3 mg IN (high body weight subjects – last quartile and PD study IN k_a)	5.90 (42)	34.3 (16)
Nalmefene 3 mg IN (12-year-old subjects – body weight distribution and PD study IN k_a)	6.64 (43)	48.7 (23)

Abbreviations: AUC0-inf, area under the plasma concentration-time curve from the time of drug administration (time 0) extrapolated to infinity; Cmax, maximum plasma concentration; %CV, coefficient of variation expressed as a percent; IN, intranasal; ka, first-order absorption rate constant; PD, pharmacodynamic.

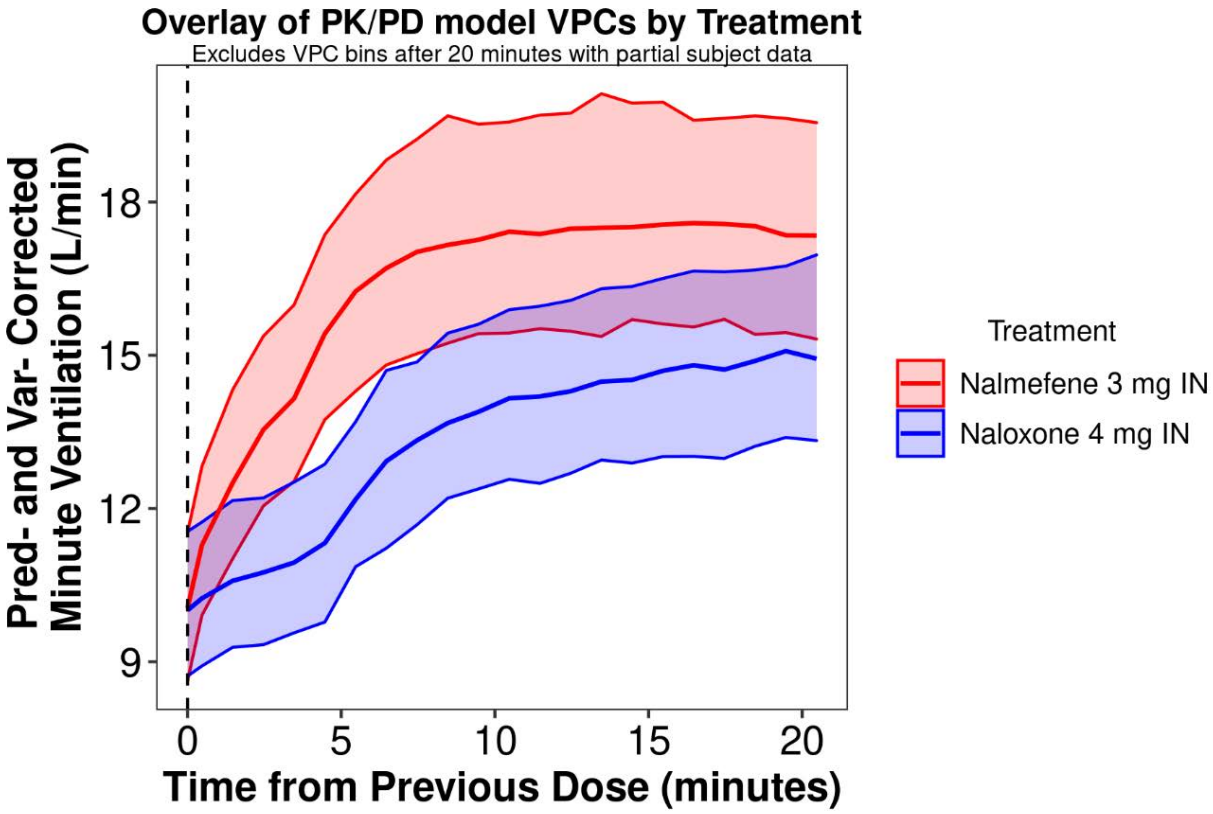
Source: sequence 0004, module 5335, optn003-poppk-001-pk.pdf, page 61

Based on **Table 23**, compared to the mean PK values across the full population in the PK dataset (median weight 74.70 kg), the 1st quartile of body weight (50.4 to 64.8 kg) had + 5.2% higher Cmax and + 15.7% and AUC0-∞ and the 4th quartile of body weight (91 to 106.8 kg) had – 4.4% lower Cmax and – 11.6% and AUC0-∞. The virtual 12 year old subjects (median weight 50.6 kg; 27.6 to 126.8 kg range), compared to the mean PK values across the full population in the PK dataset, have +7.6 higher Cmax and +25.5% higher AUC0-∞. These results are discussed in section **3.3.3** Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?. The effect of weight on PD is assessed in section 4.4.5 PKPD Simulations**.**

4.4.5 PKPD Simulations

The Applicant conducted PD simulations to assess the PD profile for naloxone and nalmefene. **Figure 26** shows simulated PD profiles following a single administration of 3 mg IN nalmefene or 1 mg IN naloxone.

Figure 26: PD Simulation of IN and IM Administration



The lines and shaded boxes represent the median and 90% prediction interval.

Source: sequence 0004, module 5354, opnt003-pkpd-001.pdf, page 78

The Applicant conducted simulations of the effect of weight on nalmefene PD. The simulation methodology is to simulate PD for each subject in the population PKPD dataset and use the mean PD parameters for the full dataset (median weight 74.7 kg) as a reference for comparison with the PD parameters in the first quartile of body weight (50 kg to 64.8 kg) and the fourth quartile of body weight (91 to 106.8 kg). The Applicant also assessed the predicted PD for weights associated with 12-year old subjects (median weight 50.6 kg; 27.6 to 126.8 kg range). The results of the PD simulations are presented in **Table 24**.

Table 24: Simulated Effect of Weight on Nalmefene PD

Simulation Scenario	Median (5th to 95th Percentile)			
	R_{max} (L/min)	TR_{max} (minutes)	Time to EC_{50} (minutes)	Time Above EC_{50} (hours)
Nalmefene 3 mg IN (full body weight distribution and PD study IN k_a)	17.4 (9.56 – 33.9)	18.5 (8.22 – 105)	4.00[a] (1.00 – 15.0)	6.92[a] (4.88 – 10.4)
Nalmefene 3 mg IN (low body weight subjects – first quartile and PD study IN k_a)	17.5 (9.59 – 34.0)	18.5 (8.64 – 109)	4.00[b] (1.00 – 14.9)	8.03[b] (5.63 – 11.5)
Nalmefene 3 mg IN (high body weight subjects – last quartile and PD study IN k_a)	17.3 (9.54 – 33.9)	18.5 (8.10 – 100)	4.05[c] (1.00 – 15.0)	6.18[c] (4.44 – 8.5)
Nalmefene 3 mg IN (12-year-old subjects – body weight distribution and PD study IN k_a)	17.4 (9.60 – 34.3)	18.5 (8.88 – 110.4)	4.00[d] (1.00 – 15.1)	8.79[d] (5.71 – 13.9)

Simulation Scenario	Median (5th to 95th Percentile)			
	AUEC (0 to 5 min) (L)	AUEC (0 to 10 min) (L)	AUEC (0 to 15 min) (L)	AUEC (0 to 20 min) (L)
Nalmefene 3 mg IN (full body weight distribution and PD study IN k_a)	12.6 (2.07 – 52.5)	39.8 (8.66 –142)	70.6 (17.2 – 240)	103 (26.5 – 337)
Nalmefene 3 mg IN (low body weight subjects – first quartile and PD study IN k_a)	12.8 (2.08 – 53)	40.0 (8.66 –141)	71.0 (17.2 – 240)	104 (26.5 – 339)
Nalmefene 3 mg IN (high body weight subjects – last quartile and PD study IN k_a)	12.6 (2.07 – 51.9)	39.6 (8.62 –139)	70.1 (17.0 – 239)	102 (26.3 – 335)
Nalmefene 3 mg IN (12-year-old subjects – body weight distribution and PD study IN k_a)	12.8 (2.09 – 52.9)	40.1 (8.68 –142)	71.3 (17.2 – 240)	104 (26.7 – 340)

Abbreviations: AUEC, area under the effect curve; EC50, concentration at which pharmacologic effect is half maximum; IN, intranasal; ka, first-order absorption rate; min, minutes; PD, pharmacodynamic; PK, pharmacokinetic; Rmax, maximal effect above baseline; TRmax, time of Rmax.

Source: sequence 0004, module 5354, opnt003-pkpd-001.pdf, page 43

According to the results in **Table 24**, weight does not affect the maximum PD effect (range 17.3 to 17.5 L/min), time to maximum effect (18.5 minutes), or time to achieve a concentration associated with half-maximum effect (4 to 4.05 minutes). The predicted effect duration of concentrations above the EC50 is 6.92 hours in the full population, 6.18 hours for the 4th weight quartile (91 to 106.8 kg), 8.03 hours for the 1st weight quartile (50.4 to 64.8 kg), and 8.79 hours for 12-year old subjects. Compared to the predicted effect duration in the 1st weight quartile in adults (8.03 hours), the predicted effect duration in 12 year old (8.79 hours) is +10% longer. These results are discussed in section **3.3.3** Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?.

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