Office of Clinical Pharmacology Review

NDA or BLA Number	218590
Link to EDR	\\CDSESUB1\evsprod\NDA218590
Submission Date	2/7/2024
Submission Type	*[Priority Review]*
Brand Name	Zurnai (b) (4)
Generic Name	Nalmefene Autoinjector
Dosage Form and Strength	Autoinjector delivers 1.5 mg nalmefene (equivalent to 1.7 mg nalmefene hydrochloride) in 0.5 mL solution.
Route of Administration	IM Injection
Proposed Indication	Opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose induced by natural or synthetic opioids in adults and pediatric patients aged 12 years and older, (b) (4) (b) (4)
Applicant	Purdue Pharma LLC
Associated IND	*[IND 137597]*
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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 dose with the autoinjector, 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	Described 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) prior to the submission of this NDA, as follows: "Conduct a Pediatric Pharmacokinetic, Pharmacodynamic and Safety Study in Children 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.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

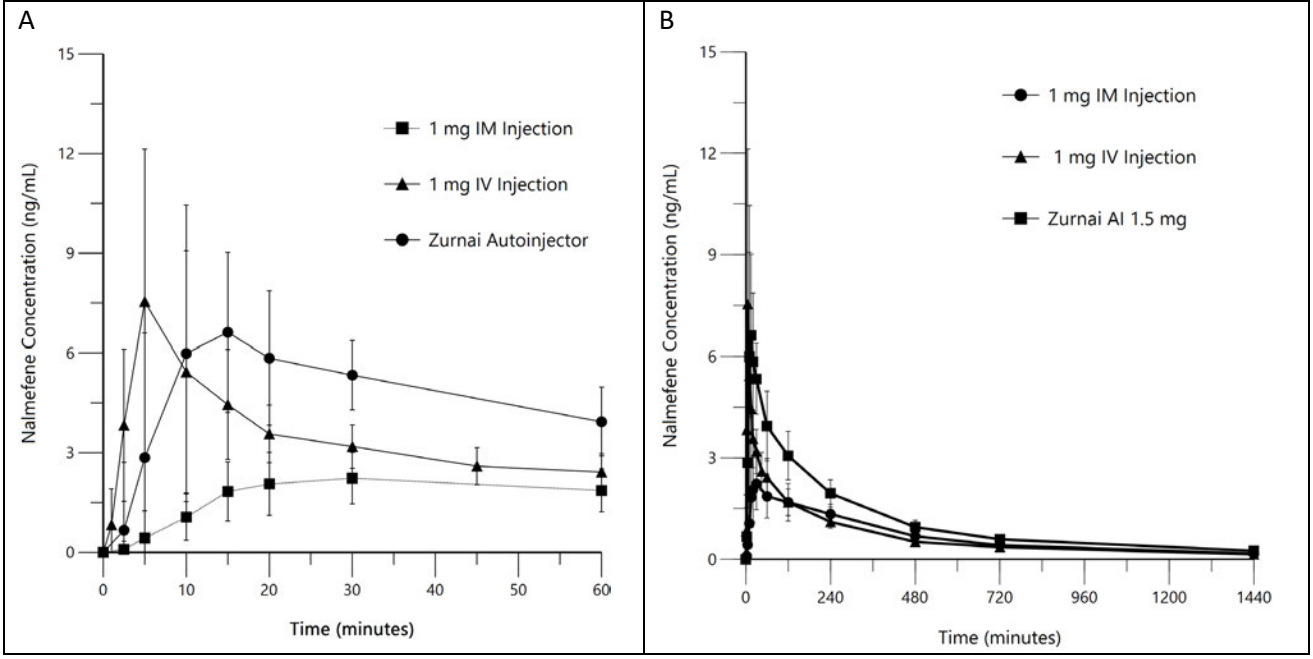
2.1 Pharmacology and Clinical Pharmacokinetics

This is a 505(b)(2) NDA application for Zurnai Autoinjector, which relies on the previous Agency findings of safety and efficacy for the reference listed drug REVEX (nalmefene hydrochloride injection), NDA 020459. Zurnai (b) (4) is the brand name for the nalmefene hydrochloride (HCl) intramuscular (IM) autoinjector that delivers 1.5 mg nalmefene base which is equivalent to 1.7 mg nalmefene HCL in 0.5 mL solution. REVEX, nalmefene HCl injection, 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 pharmacokinetics (PK) and pharmacodynamics (PD) of Zurnai Autoinjector following IM administration have been characterized in one relative bioavailability study (NAL1005) and one pharmacokinetic-pharmacodynamic (PK-PD) study (NAL1004) as well as a population PK report investigating the effect of body weight and height effect on PK of Zurnai. Additional dose-selection studies (NAL1002 and NAL1003) and simulations of multiple dose administrations were also submitted to the NDA.

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 Zurnai: Following single IM dose administration of Zurnai Autoinjector, quantifiable plasma nalmefene levels were observed at the first time point of blood collection at 2.5 minutes (**Figure 1**).

Figure 1: Pharmacokinetics of nalmefene (mean ± SD) following Zurnai Autoinjector administration from relative bioavailability study NAL1005 (A – Left) truncated to the first 60 minutes; (B – Right) displayed to 24 hours (1440 minutes).



Plasma levels of single IM injection of Zurnai were higher at all time points compared to 1 mg IM injection of nalmefene (generic nalmefene injection ANDA 212955) in healthy volunteers (n=24). In

addition, the applicant evaluated PK of 1 mg nalmefene HCl following intravenous administration (generic nalmefene injection ANDA 212955) in a subset (n=12) of the healthy volunteers. Dose-normalized peak plasma levels (Cmax) of nalmefene Zurnai Autoinjector were higher compared to IM injection and lower compared to IV bolus in study NAL1005 (See **Table 2** and **Table 3**). Based on dose-normalized area under the curve to infinity (AUCinf), bioavailability of Zurnai Autoinjector was 113% relative to IM injection and 115% relative to IV bolus of nalmefene (See **Table 2** and **Table 3**).

It is anticipated that if the patient does not respond to the first dose, opioid overdose reversal products may be administered repeatedly until emergency services arrive. The applicant conducted pharmacokinetic simulations of various scenarios comparing exposure (Cmax and AUC) following repeat dose administration of Zurnai autoinjector, IM injection of nalmefene or IV bolus of nalmefene. Based on Revex injection (NDA 20459) label, nalmefene exhibited dose proportional pharmacokinetics following intravenous administration of 0.5 mg to 2.0 mg. Kaplan J.L. et al., (1999) evaluated safety of up to four doses of nalmefene following 1 mg and 2 mg IV injections administered every five minutes. Since the Kaplan 1999 publication did not evaluate pharmacokinetics, the pharmacokinetic simulations helped provide an understanding of the bracket for safety. As described in section 4.4.3, many scenarios of repeated dose administration were simulated; however, PK parameters from one pertinent scenario are presented in the **Table 1** below. The PK data from repeat dose simulations suggests that following administration of two doses of Zurnai Autoinjector administered 2 minutes apart, the systemic exposure (both Cmax and AUC) will be below two doses of 2 mg IV administered 5 minutes apart.

Table 1: Mean ± SD systemic exposure of nalmefene simulated with Zurnai autoinjector and nalmefene 2 mg IV injection.

Parameter	**Zurnai Autoinjector 1.5 mg Observed** Single Dose	**Nalmefene IM Injection 1 mg Observed** Single Dose	**Nalmefene IV Injection 1 mg Observed** Single Dose	**Zurnai Autoinjector 1.5 mg Simulated** Repeat doses 2-minute interval			**Nalmefene 2mg IV Bolus (Kaplan 1999) Simulated** Repeat doses 5-minute interval		
				2 doses	3 doses	4 doses	2 doses	3 doses	4 doses
Cmax (ng/mL)	8.14 ± 3.86	2.51 ± 0.82	7.81 ± 4.35	15.5 ± 6.9	22.3 ± 9.34	28.62 ± 11.5	26.5 ± 15.3	35.6 ± 18.1	42.6 ± 19.1
AUCt (ng.hr/mL)	28.76 ± 4.99	16.46 ± 3.66	16.42 ± 2.46	60.1 ± 9.4	90.2 ± 14.1	120.3 ± 18.8	65.7 ± 10.1	98.5 ± 15.1	131.3 ±20.1
AUC0-∞ (ng.hr/mL)	30.91 ± 4.95	18.37 ± 3.86	18.42 ± 2.82	61.9 ±10.3	92.9 ± 15.4	123.91 ± 20.6	71.3 ± 11	107 ± 16.5	142.6 ± 22

Source: Adapted from Table 20 from repeated dose simulations report. Data is Arithmetic Mean ± Standard deviation.

Pharmacodynamics: Onset of reversal of fentanyl-induced respiratory depression with Zurnai Autoinjector was observed within 2.5 to 5 minutes in the experimental clinical pharmacology study NAL1004 conducted in opioid-experienced, non-dependent healthy volunteers. Naloxone (Narcan nasal spray) was included as a positive-control or validity measure. Maximum reversal effect of nalmefene in reversing respiratory depression was noted in 15 minutes. OCP's independent modeling & simulation using a previously developed systems pharmacology model further support the applicant's claim that

nalmefene IM 1.5 mg has an onset of action at least as fast as naloxone IN 4 mg which is an approved opioid antagonist formulation for reversal of opioid overdose in a community setting.

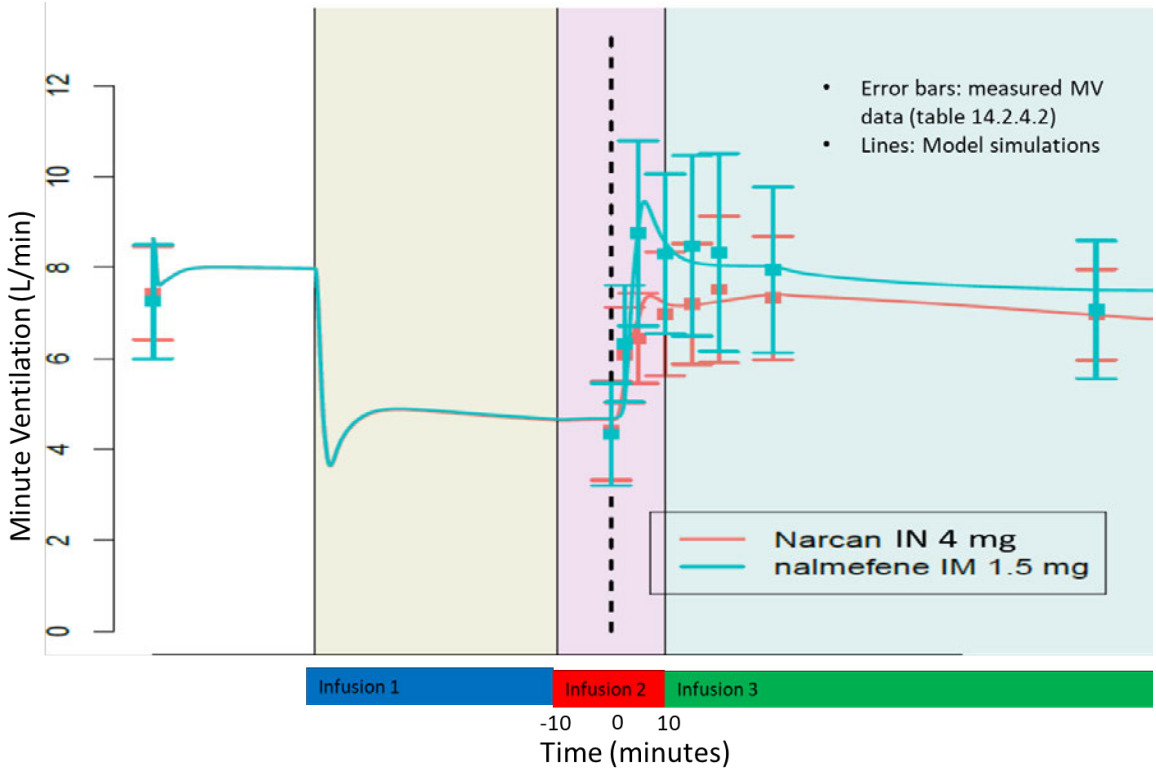


Figure 2: Comparison of the pharmacologic effects on minute ventilation (MV) from nalmefene IM 1.5 mg and naloxone IN 4 mg in NAL1004.

Error bars: mean and standard deviation of minute ventilation in the naloxone IN 4 mg group (red) and nalmefene IM 1.5 mg group (blue) from the study NAL1004. Solid lines: OCP systems pharmacology model simulation of a typical subject. During "infusion 1", fentanyl IV infusion was started at a rate of 5 mcg/min and was stopped when there was a 50% decrease in MV for the individual subject. The duration of infusion 1 was adjusted for each individual subject. After "infusion 1", "infusion 2" started at a rate lower than infusion 1. The rate for fentanyl infusion in "infusion 2" was calculated according to the Applicant's prespecified table so that the predicted plasma concentration of fentanyl at the end of infusion 1 would be maintained during the course of infusion 2. During the study, subjects were breathing air with supplemental oxygen at a rate of at least 2 L/min. Ten minutes after the initiation of infusion 2, IM nalmefene 1.5 mg (blue) or IN naloxone 4 mg (red) was administered (reported as time 0 in the **Figure 2**), leading to a recovery (increase) of MV. Twenty minutes after the initiation of "infusion 2", the fentanyl infusion at the "infusion 2" rate was stopped and "infusion 3" initiated, which had an even lower infusion rate according to the Applicant's prespecified dosing table (not shown in this review).

OCP's evaluation also supports that the proposed dose of 1.5 mg nalmefene IM may not 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 is administered early enough (See DARS review appended in 4.3 DARS review:).

Zurnai Autoinjector was not evaluated in any specific populations. Considering the acute course of therapy, no dosage adjustment is needed 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, 12- to 17-year-old virtual subjects with a median weight of 62 kg are expected to have 8% to 27% higher Cmax and 4% to 15% higher AUC0-inf. Such anticipated exposures may not adversely affect safety while providing effective plasma nalmefene concentrations and hence Zurnai Autoinjector can be administered in adolescent patients without dose adjustment.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

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

2.2.2 Therapeutic individualization

General dosing recommendations apply to patients 12 years and older. Adolescent patients (median bodyweight 62 kg) are expected to have 8% to 27% higher Cmax and 4% to 15% higher AUC0-inf than adults. Titration or dosage adjustment regarding age, sex, bodyweight, hepatic impairment, and renal impairment is not necessary.

2.3 Outstanding Issues

None

2.4 Summary of Labeling Recommendations

A single (b) (4) in patients over 12 years and older is recommended for reversal of known or suspected opioid overdose. If necessary, an additional dose of Zurnai Autoinjector two to five minutes after the first dose is adequate.

Descriptive observations regarding time to onset, and time to peak effect of nalmefene in reversing opioid-induced respiratory depression following Zurnai Autoinjector administration from study NAL1004 should be described in Section 12.2 Pharmacodynamics.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Purdue Pharma LLC submitted 505(b)(2) NDA 218590 for nalmefene IM autoinjector (Brand name Zurnai) which relies on the previous Agency findings of safety and efficacy for the reference listed drug Revex (nalmefene HCl 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. Zurnai Autoinjector comprises a single use IM injection device which delivers 1.5 mg nalmefene (equivalent to 1.7 mg nalmefene HCl) in 0.5 mL solution.

The data submitted to the NDA consists of two clinical studies that utilized the to-be-marketed Zurnai Autoinjector. A bioavailability study NAL1005 that forms the scientific bridge between Zurnai Autoinjector and Revex injection and a pharmacokinetic-pharmacodynamic study NAL1004 that evaluated the time to onset of action and maximum effect of reversal of opioid overdose reversal in an experimental clinical pharmacology study. As previously mentioned, the reference drug Revex is effective in reversing known or suspected opioid overdose-induced respiratory depression and central nervous system depression. The study NAL1004 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 similar studies that 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 fentanyl-induced opioid agonism or 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 study, and use of naloxone (Narcan nasal spray) served as a positive-control or validity measure.

From a product development perspective, the applicant conducted various Phase 1 PK and PK-PD investigations prior to selection of the proposed 1.5 mg nalmefene dose for the IM injection with the autoinjector.

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 injection following fentanyl-induced respiratory depression model in adult volunteers.	
Time onset	After single IM injection with Zurnai Autoinjector 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 IM injection with Zurnai Autoinjector.
Pharmacokinetics	
Dose-proportionality	Nalmefene exhibited dose proportional pharmacokinetics following intravenous administration of 0.5 mg to 2.0 mg.
Absorption	Quantifiable levels of nalmefene are noted in 2.5 minutes following Zurnai Autoinjector administration. Plasma nalmefene concentration with single Zurnai Autoinjector are higher than 1 mg IM injection at all time points. Nalmefene IM and subcutaneous (SC) Injection: As per REVEX label, Therapeutic plasma concentrations are likely to be reached within 5-15 minutes after a 1 mg dose in an emergency.
Bioavailability	After dose normalization, mean bioavailability (Frel) of NAI was 1.13 relative to IM administration of nalmefene 1 mg; and mean absolute bioavailability (Fabs) of NAI was 1.15 relative to IV administration of nalmefene 1 mg.

Characteristic	Drug Information
Tmax	Peak plasma levels of nalmefene are noted at a median of 15 minutes (Range 5 – 60 minutes) following IM administration of Zurnai Autoinjector.
Distribution	Nalmefene distributes into brain. Following a 1 mg parenteral dose, nalmefene was rapidly distributed. In a study of brain receptor occupancy, a 1 mg dose of nalmefene blocked over 80% of brain opioid receptors within 5 minutes after administration. The apparent volumes of distribution centrally (Vc) and at steady-state (Vdss) are 3.9 ± 1.1 L/kg and 8.6 ± 1.7 L/kg, respectively.
Elimination	After administration of Zurnai Autoinjector to healthy adult subjects, plasma concentrations have a terminal elimination half-life of 9.07 (%CV 26.2) hours. Following a 1 mg parenteral dose, the apparent clearance of nalmefene is 55.46 (%CV 8.41) L/hr.
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	Population pharmacokinetic analyses identified weight as a covariate on nalmefene PK. However, no dosage adjustment is needed for adolescents and adults with regard to bodyweight. Pharmacokinetics of Zurnai Autoinjector were not evaluated in pediatric patients.
Age	No dosage adjustment is needed for elderly patients or adolescent patients. Pharmacokinetics of Zurnai Autoinjector were not evaluated in elderly patients or pediatric 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 Zurnai Autoinjector 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 Zurnai Autoinjector 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. Bioavailability study NAL1005 provides the scientific bridge between Zurnai Autoinjector and listed drug Revex (IM nalmefene Injection). PK-PD study NAL1004 addresses the clinical concerns raised during the drug development regarding the time to onset of effect.

NAL1005: Plasma levels of nalmefene were observed starting at 2.5 minutes (earliest sampling timepoint) and partial AUCs for time points starting at 5 minutes up to 30 minutes were higher following Zurnai Autoinjector (1.5 mg nalmefene base of 1.7 mg nalmefene HCl) compared to IM nalmefene injection (1 mg nalmefene base) (See **Figure 1** above). Maximum nalmefene exposure (Cmax) was approximately 3-fold higher and partial AUCs were approximately 3.5 to 7-fold higher and total exposure (AUClast or AUCt and AUCinfinity or AUCinf) were 1.7-fold higher with Zurnai Autoinjector compared to IM nalmefene injection (**Table 2**).

***T*able 2:** Statistical analysis comparing 1.5 mg Zurnai Autoinjector to 1 mg IM injection of nalmefene.

Parameters	N	Zurnai Autoinjector 1.5 mg IM	Nalmefene HCl 1.0 mg IM	Ratio %	90% Confidence Interval
Cmax	24	7.512	2.387	314.7	258.71, 382.89
AUC0-2.5	14	0.009	0.002	383.9	68.65, 2147.15
AUC0-5	20	0.036	0.008	450.1	200.73, 1009.23
AUC0-10	23	0.320	0.047	687.2	423.31, 1115.69
AUC0-15	23	0.836	0.151	552.0	387.65, 785.94
AUC0-20	23	1.331	0.312	426.5	320.42, 567.68
AUC0-30	24	2.273	0.647	351.0	284.42, 433.17
AUCt	24	28.384	16.036	177.0	167.62, 186.89
AUCinf	24	30.428	17.975	169.3	161.64, 177.28
Tmax*	24	15 (5 – 60)	30 (5 – 120)		

Source: Table 11-4 from study report for NAL1005. Data is presented as geometric mean for Cmax and AUC. Units for Cmax are ng/mL; AUC are ng*h/mL, Tmax* is presented as median minutes and range in parenthesis.

In study NAL1005, PK of 1 mg IV nalmefene dose was investigated in twelve subjects. Compared to IV nalmefene injection, Zurnai Autoinjector plasma levels were lower in terms of partial AUCs (**Table 3**). Dose-normalized Cmax of Zurnai Autoinjector is lower than that noted with IV nalmefene.

Table 3: Statistical analysis comparing 1.5 mg Zurnai Autoinjector to 1 mg IV injection of nalmefene.

Parameters	N (# subjects)	Zurnai Autoinjector 1.5 mg IM	Nalmefene 1.0 mg IV Bolus	Ratio %	90% Confidence Interval
Cmax	12	7.778	6.938	112.1	79.68, 157.76
AUC0-2.5	12	0.007	0.053	14.0	4.86, 40.39
AUC0-5	12	0.042	0.279	15.0	7.92, 28.56
AUC0-10	12	0.349	0.768	45.5	28.52, 72.56
AUC0-15	12	0.925	1.161	79.7	54.97, 115.56
AUC0-20	12	1.365	1.496	91.2	66.02, 126.03
AUC0-30	12	2.333	2.066	112.9	87.48, 145.75
AUCt	12	28.673	16.253	176.4	157.75, 197.29
AUCinf	12	31.007	18.223	170.2	152.68, 189.63
Tmax*	12	15 (5 – 60)	5 (5 – 15)		

Source: Table 11-6 from study report for NAL1005. Data is presented as geometric mean for Cmax and AUC. Units for Cmax are ng/mL; AUC are ng*h/mL, Tmax* is presented as median minutes and range in parenthesis.

The applicant conducted investigational studies NAL1002 and NAL1003 with various pharmacokinetic and pharmacodynamic investigations for dose-selection and pharmacokinetic characterization of IM and intravenous nalmefene injection. Although these studies did not utilize the to-be-marketed formulation and device, they provide the rationale for dose-selection in study NAL1004. These two studies also helped with the design of study NAL1004 in terms of refining the opioid-induced respiratory depression (OIRD) model, and key methodological considerations necessary for the determination of time to onset of nalmefene in reversing opioid overdose-induced respiratory depression as described below.

Study NAL1004: 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 IM or subcutaneous doses of 1.0 mg. Agency expressed concern (advice letter dated 11/7/2019) 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 NAL1004. Pharmacokinetics and pharmacodynamics of nalmefene were evaluated in opioid-experienced but non-dependent and otherwise healthy volunteers in study NAL1004. In this study, quantifiable plasma levels of nalmefene were noted starting at 2.5 minutes which was the earliest blood sample collected after single dose Zurnai Autoinjector administration (**Table 7**). Peak nalmefene plasma levels of 8.4 ± 3.7 (mean ± SD) were noted at a median Tmax of 15 minutes (5 – 60 minutes) and AUCinf was 25.7 ± 4.6 ng*hr/mL (mean ± SD).

1) Does OCP's independent modeling & simulation support the sponsor's claim that nalmefene IM 1.5 mg IM has an onset of action appropriate for opioid reversal in a community setting?

During the development and validation of OCP's systems pharmacology model [4, 4.3.7 References], as well as the application of this model to the evaluation of a naloxone products [5, 4.3.7 References], it was found that the onset of action of an opioid antagonist can have a significant impact on two clinical endpoints: the antagonist's capability of preventing opioid-associated cardiac arrest, and its capability of shortening brain hypoxia time. OCP's independent simulation of the nalmefene IM 1.5 mg autoinjector product also focused on these two endpoints. To inform on community overdose situations, the opioids used in the simulations were fentanyl and carfentanil, using the medium overdose scenarios (1.625 mg intravenous bolus injection for fentanyl, and 0.012 mg for carfentanil) and virtual populations representing chronic opioid users (see 4.3.3 Methods below).

As shown in **Figure 3**, 1 dose of nalmefene IM 1.5 mg reduced the percentage of simulated patients experiencing fentanyl-associated cardiac arrest from 52% (median value without any antagonist administration) to below 10%. In contrast, 1 dose of naloxone IN 4 mg reduced the percentage of simulated patients with cardiac arrest from 52% to over 15%. Similarly, for the carfentanil overdose scenario, nalmefene IM 1.5 mg reduced the percentage of simulated patients with cardiac arrest to about 5%, while naloxone IN 4 mg reduced the percentage of simulated patients experiencing cardiac arrest to 20%.

As shown in **Table 4**, for fentanyl overdose without 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 IM 1.5 mg had a median brain hypoxia time of 0 min, suggesting the 50^{th} percentile of subjects did not experience any brain hypoxia. In contrast, 1 dose of naloxone IN 4 mg had a median brain hypoxia time 1.2 minutes.

For the carfentanil overdose scenario, a difference between nalmefene IM 1.5 mg and naloxone IN 4 mg was seen at the upper boundary of the inter quantile range (IQR). After 1 dose of nalmefene IM 1.5 mg, the upper IQR was 1.8 minutes, meaning 25% of the virtual subjects had a brain hypoxia time longer than 1.8 minutes. In comparison, after 1 dose of naloxone IN 4 mg, the upper IQR was 4.9 minutes, meaning 25% of the virtual subjects had a brain hypoxia time longer than 4.9 minutes.

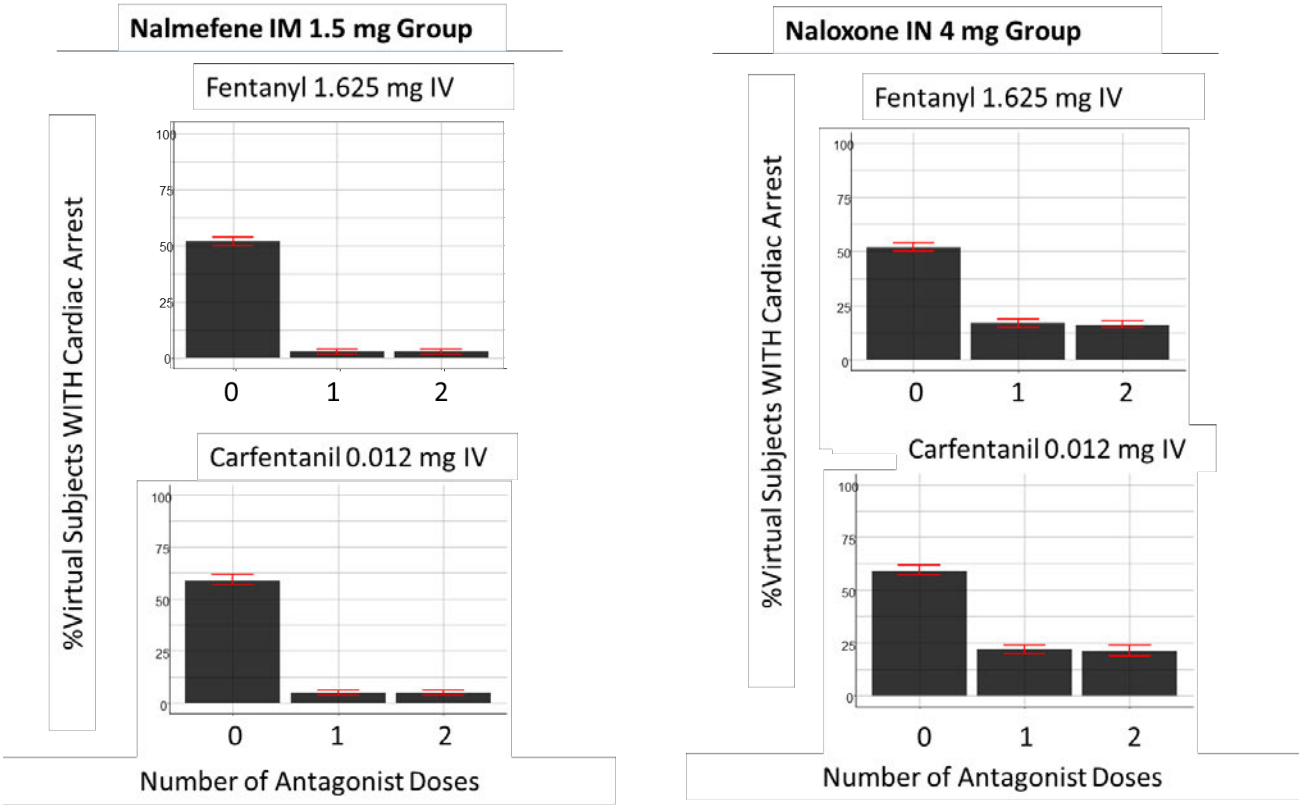


Figure 3: Percentage of virtual patients experiencing cardiac arrest for the fentanyl (top row) or carfentanil (bottom row) overdose scenarios.

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 of an antagonist, and 2 doses of an antagonist (2.5 min apart), respectively. The antagonists used in the simulations are nalmefene IM 1.5 mg (left column) and naloxone IN 4 mg (right column). 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).

Table 4: Brain hypoxia time predicted in virtual subjects for the fentanyl or carfentanil overdose scenarios.

Nalmefene IM 1.5 mg				
		Median value	Lower bound of IQR	Higher bound of IQR
Fentanyl 1.625 mg	Without Nalmefene	CA	0 min	CA
	With Nalmefene	0 min	0 min	1.6 min
	2 dose Nalmefene	0 min	0 min	1.6 min
Carfentanil 0.012 mg	Without Nalmefene	CA	0 min	CA
	With Nalmefene	0 min	0 min	1.8 min
	2 dose Nalmefene	0 min	0 min	1.8 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	1.2 min	0 min	4.0 min
	2 dose Naloxone	1.1 min	0 min	3.9 min
Carfentanil 0.012 mg	Without Naloxone	CA	0 min	CA
	With Naloxone	0 min	0 min	4.9 min
	2 dose Naloxone	0 min	0 min	4.7 min

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

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 (IQR) of brain hypoxia time are based on the total population of 2000 virtual subjects. The median and/or upper IQR of brain hypoxia time for nalmefene (left) and naloxone (right) are marked as red.

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 systems pharmacology model was used to simulate two dosing schemes of the nalmefene IM product: a single administration of nalmefene hydrochloride 1.5 mg, or two doses of 1.5 mg, with a 2.5 min delay between the doses. As shown in **Figure 3**, this 2-dose nalmefene scheme did not change the predicted cardiac arrest percentage in the virtual populations after fentanyl or carfentanil overdose, in comparison to the 1-dose nalmefene scheme. Similarly, **Table 4** shows that the 2-dose nalmefene scheme had a similar median or upper IQR brain hypoxia time as the 1-dose nalmefene scheme in the virtual populations for the fentanyl or carfentanil overdose scenarios. While it is conceivable that under other scenarios (e.g., opioids overdose through a dosing route slower than IV, the use of other interventions like rescue breathing or cardiopulmonary resuscitation, etc.) re-administration of IM nalmefene after the 1st dose may have benefits, the results in **Figure 3** and **Table 4** suggested that the proposed dose (IM 1.5 mg) does not rely on titration or re-administration to protect against opioid-associated cardiac arrest and brain hypoxia.

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 labeling "If the desired response is not obtained after 2 to 5 minutes, administer an additional dose of Zurnai (b) (4) using a new auto-injector. If there is still no response and additional doses are available, administer additional doses of Zurnai (b) (4) every 2 to 5 minutes using a new Zurnai Auto-Injector with each dose until emergency medical assistance arrives." The applicant conducted pharmacokinetic simulations to address safety of repeat dose administration in the context of previously approved REVEX injection and any available published data. The applicant submitted Kaplan J.L., et al., 1999 (doi:10.1016/s0196-0644(99)70270-2) where safety of 2 mg nalmefene IV injection doses up to four doses administered five minutes apart was evaluated. Since the publication did not evaluate pharmacokinetics, the applicant estimated pharmacokinetics of nalmefene following various scenarios of repeated doses of IM nalmefene, IV nalmefene and Zurnai Autoinjector.

Safety with respect to Peak Plasma Concentrations: 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 this regard, PK data of IV nalmefene from other investigational studies submitted to the NDA was also considered.

In the investigational study NAL1002, pharmacokinetics of IV 1.5 nalmefene were determined following bolus administration in healthy volunteers (n=7). Peak plasma levels of mean ± SD of 46.4 ± 29.1 ng/mL were noted at the median time of 2.5 minutes (range 2.5 – 5 minutes). The systemic exposure in terms of AUCinf was a mean ± SD of 23.2 ± 2.22 ng*h/mL (Source: Table 14.2.2.1.4 from study report for NAL1002). It is known from Revex label that nalmefene exhibits dose proportional pharmacokinetics following intravenous administration of 0.5 mg to 2.0 mg. Therefore, peak plasma concentration with 1 mg IV bolus nalmefene are expected to be approximately 31 ng/mL and AUCinf to be approximately around 15.4 ng*h/mL. It is possible that the IV administration in NAL1005 was a 5-minute infusion as noted by the peak plasma levels at 5 minutes and lower than usual peak plasma concentration compared to that observed in study NAL1002. Overall, peak plasma levels of Zurnai Autoinjector (1.5 mg) were lower than that noted with IV bolus injection of nalmefene (**Table 1**).

Safety with respect to AUC or Overall exposure: Observed data and simulated pharmacokinetic data, specifically AUCinf, were compared between repeated doses of Zurnai Autoinjector, IM nalmefene injection, and IV nalmefene injection. As shown in **Table 1** above, the AUC of up to two doses of Zurnai Autoinjector are expected to be lower than the AUCinf of up to two IV doses of 2 mg nalmefene hence providing safety coverage for the proposed dosing regimen in the label.

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 Zurnai Autoinjector in adolescents and adults? Is there an effect of bodyweight on PK of Zurnai Autoinjector?

Zurnai Autoinjector was not evaluated in any specific populations. As such no dosage adjustment is needed in elderly, renal impairment patients or hepatic impairment patients. No clinical adverse events were noted in the elderly following the 1 mg intravenous nalmefene dose. The basis for the recommendation is reliance on label for nalmefene injection where no dosage adjustment is recommended and since nalmefene will be administered as an acute course of therapy.

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 Zurnai Autoinjector 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.

Bodyweight: The effect of bodyweight on nalmefene PK was assessed with population pharmacokinetic analysis and simulations were conducted to assess nalmefene exposure in pediatric patients. The magnitude of the bodyweight effect on nalmefene PK does not warrant dose adjustment in adults. In pediatric patients compared to adults (median weight and height of 76 kg and 171 cm, respectively), when receiving an identical dose:

- 12-year-old subjects (median weight and height of 49 kg and 154 cm, respectively) are expected to have:
    - 27% higher Cmax and 15% higher AUC0-t for the 1.5 mg AI when compared to adults, and

- 15-year-old subjects (median weight and height of 62 kg and 166 cm, respectively) are expected to have:
    - 13% higher Cmax and 10% higher AUC0-t for the 1.5 mg AI when compared to adults, and
- 17-year-old subjects (median weight and height of 69 kg and 169 cm, respectively) are expected to have:
    - 8% higher Cmax and 4% higher AUC0-t for the 1.5 mg AI when compared to adults,

The observations from the simulations do not warrant dose-adjustment in adolescent patients requiring Zurnai Autoinjector to reverse opioid-induced respiratory depression and CNS depression.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Bioavailability study NAL1005 was conducted at Novum Pharmaceutical Research Services, Las Vegas, Nevada, and blood samples from this clinical site were analyzed (b) (4) . PK-PD study NAL1004 was conducted at Ohio Clinical Trials, Columbus, Ohio, and blood samples from this clinical site were analyzed (b) (4) . The Office of Study Integrity and Surveillance (OSIS) conducted an analytical Remote Regulatory Assessment (RRA) of studies NAL1004 and NAL1005 (NDA 218590, nalmefene) conducted (b) (4) . No objectionable conditions were observed. Based on the RRA findings, there were no identified concerns regarding reliability of the data for the audited studies for the review division consideration (OSIS review dated 6/13/2024). For the clinical site, Novum Pharmaceutical Research Services, OSIS determined that an inspection is not needed for the site as Office of Regulatory Affairs conducted an inspection of the site in September 2022 in the context of a different regulatory submission and OSIS concluded that data from the reviewed studies were reliable.

(b) (4) quantified nalmefene in human plasma over a concentration range of 0.1 to 100 ng/mL using a validated LC/MS/MS method. (b) (4) was utilized as internal standard. The standards and quality controls (QC) had an acceptable within-run and between-run precision and accuracy. Analyte and internal standard recovery, selectivity and incurred sample reproducibility were acceptable. Short-term stability, freeze/thaw stability, and long-term stability (-20°C and -80°C up to 519 days) of nalmefene were acceptable.

(b) (4) quantified naloxone in human plasma over a concentration range of 0.025 – 25 ng/mL using a validated LC/MS/MS method. Naloxone-D_5 was utilized as internal standard. The standards and quality controls (QC) had an acceptable within-run and between-run precision and accuracy. Analyte and internal standard recovery, selectivity and incurred sample reproducibility were acceptable. Short-term stability, freeze/thaw stability, and long-term stability (-20°C up to 202 days and -80°C up to 664 days) of nalmefene were acceptable.

Study NAL1004 employed a fentanyl-induced respiratory depression model. Blood samples were collected for analysis of fentanyl. (b) (4) quantified fentanyl in human plasma over a concentration range of 10.0 to 5000 pg/mL using a validated LC/MS/MS method. Fentanyl-D_5 was utilized as an internal standard. The standards and quality controls (QC) had an acceptable within-run and between-run precision and accuracy for most of the bioanalytical runs. Precision and accuracy QCs for Fentanyl from Run 16919vya44a did not meet the acceptance criteria. However, the calibration curve for this run met the acceptance criteria. Specifically, LLOQ (10 pg/mL) from Run 16919vya44a failed on account of the accuracy measured by bias being >20%. Regression, calibration curve and precision and accuracy data were reported; however, the experimental data from this run were not included in the report. Analyte and internal standard recovery, selectivity and incurred sample reproducibility were acceptable. Short-term stability, freeze/thaw stability, and long-term stability (-20°C and -80°C up to 305 days) of fentanyl were acceptable. Overall, the bioanalytical results pertinent to fentanyl from study NAL1004 are acceptable.

4.2 Clinical PK and/or PD Assessments

4.2.2 Synopsis of Study NAL1002

This was a single-center, open-label, randomized, single-dose, 2-treatment, 2-period, 2-way crossover study in 24 healthy adult male and female subjects aged 18 to 55, inclusive. A substudy was nested in the overall study design as an optional Period 3 treatment which was conducted in 12 healthy adult male and female subjects from previous treatment periods. There was at least a 7-day washout between Period 2 and treatment administration to subjects participating in the optional Period 3 substudy. Study drug was administered intramuscularly (anterolateral thigh) as 1.5 mg (0.94% $MgCl_2$) nalmefene autoinjector or 1.0 mg nalmefene hydrochloride injection. In the optional substudy Period 3, a nalmefene 1.0 mg IV bolus was administered intravenously (cubital fossa). In Periods 1 and 2 blood for pharmacokinetic analysis was collected at pre-dose (0) and at 2.5, 5, 10, 15, 20, 30 minutes and 1, 2, 4, 8, 12, 24, 36, 48 hours after dosing. In optional Period 3 substudy blood for pharmacokinetic analysis was collected at pre-dose (0) and at 1, 2.5, 5, 10, 15, 20, 30, 45 minutes and 1, 2, 4, 8, 12, and 24 hours after dosing. For each subject, the following PK parameters were calculated, whenever possible, based on the plasma concentrations of nalmefene using non-compartmental analysis of Phoenix® WinNonlin® 8.3 or higher. These plasma concentrations were used to estimate the following pharmacokinetic parameters, as appropriate: AUC0-2.5, AUC0-5, AUC0-10, AUC0-15, AUC0-20, AUC0-30, AUCt, AUCinf, Cmax, Tmax, Tlag, T½, λz (Kel), CLs, and Vdss for nalmefene. For AUC0-2.5 minutes, AUC0-5 minutes, AUC0-10 minutes, AUC0-15 minutes, AUC0-20 minutes, AUC0-30 minutes, AUCt, AUCinf and Cmax, a 90% confidence interval for the PK metrics will be constructed to compare Test (Nalmefene autoinjector) and Reference (Nalmefene HCl injection) and to compare Test (Nalmefene autoinjector) and Nalmefene 1.0 mg IV Bolus.

Identity of Investigational Products

Test: Nalmefene Autoinjector (Nalmefene Hydrochloride Injection) 1.5 mg, Nalmefene (base)/0.5 mL
Manufactured by: (b) (4) *
Lot No.: I2565
Manufacture Date: 23JUN2022
Expiration Date: AUG 2023 (Study NAL1005 was conducted between 5/24/2023 to 6/30/2023)
* (b) (4)

Reference: Nalmefene Hydrochloride Injection 2 mg/2 mL (1 mg/1 mL) (nalmefene base) for IM and IV administration
Manufactured by: (b) (4)
Distributed by: Purdue Pharma L.P.
Lot No.: 6-PPQ-0083; Bulk Lot No.: 220001
Expiration Date: MAR 2024

Bioavailability study results are discussed above in various sections of summary of clinical pharmacology. **Figure 1:** Pharmacokinetics of nalmefene (mean ± SD) following Zurnai Autoinjector administration from relative bioavailability study NAL1005 (A – Left) truncated to the first 60 minutes; (B – Right) displayed to 24 hours (1440 minutes). **Table 2:** Statistical analysis comparing 1.5 mg Zurnai Autoinjector to 1 mg

IM injection of nalmefene. **Table 3:** Statistical analysis comparing 1.5 mg Zurnai Autoinjector to 1 mg IV injection of nalmefene. Additionally, untransformed PK data is presented in **Table 5** below.

Table 5: Descriptive statistics of nalmefene pharmacokinetic parameters following single dose administration of Zurnai Autoinjector, 1 mg nalmefene IM injection and 1 mg nalmefene IV injection.

Treatment	Parameter	N	Mean	SD	Min	Median	Max
Nalmefene IM Injection 1 mg	AUC 0 to 2.5 (ng*hr/mL)	24	0	0.003	0	0	0.01
Nalmefene IM Injection 1 mg	AUC 0 to 5 (ng*hr/mL)	24	0.012	0.021	0	0.0045	0.1
Nalmefene IM Injection 1 mg	AUC 0 to 10 (ng*hr/mL)	24	0.07	0.08	0.004	0.058	0.35
Nalmefene IM Injection 1 mg	AUC 0 to 15min (ng*hr/mL)	24	0.19	0.12	0.021	0.179	0.53
Nalmefene IM Injection 1 mg	AUC 0 to 20min (ng*hr/mL)	24	0.35	0.17	0.061	0.3105	0.7
Nalmefene IM Injection 1 mg	AUC 0 to 30min (ng*hr/mL)	24	0.71	0.29	0.225	0.635	1.24
Nalmefene IM Injection 1 mg	AUC Infinity Obs (ng*hr/mL)	24	18.37	3.86	10.25	18.46	25.84
Nalmefene IM Injection 1 mg	AUCt (ng*hr/mL)	24	16.46	3.66	7.864	16.581	23.4
Nalmefene IM Injection 1 mg	T1/2 (hours)	24	7.7	1.9	4.03	7.26	13.62
Nalmefene IM Injection 1 mg	Max Conc (ng/mL)	24	2.51	0.82	1.34	2.23	4.1
Nalmefene IM Injection 1 mg	Tmax (min)	24	36.04	29.44	5	30	120
Nalmefene IM Injection 1 mg	Time to First Conc (min)	24	2.97	1.77	0	2.5	5
Zurnai Autoinjector 1.5 mg	AUC 0 to 2.5min (ng*hr/mL)	21	0.011	0.029	0	0.001	0.13
Zurnai Autoinjector 1.5 mg	AUC 0 to 5min (ng*hr/mL)	21	0.08	0.11	0	0.046	0.5
Zurnai Autoinjector 1.5 mg	AUC 0 to 10min (ng*hr/mL)	21	0.44	0.37	0.085	0.341	1.49
Zurnai Autoinjector 1.5 mg	AUC 0 to 15min (ng*hr/mL)	21	0.96	0.60	0.3	0.788	2.59
Zurnai Autoinjector 1.5 mg	AUC 0 to 20min (ng*hr/mL)	21	1.47	0.76	0.541	1.39	3.49
Zurnai Autoinjector 1.5 mg	AUC 0 to 30min (ng*hr/mL)	21	2.40	0.95	1.111	2.397	4.79
Zurnai Autoinjector 1.5 mg	AUC Infinity Obs (ng*hr/mL)	21	30.91	4.95	22.47	31.84	39.62
Zurnai Autoinjector 1.5 mg	AUCt (ng*hr/mL)	21	28.76	4.99	20.47	29.06	38.11
Zurnai Autoinjector 1.5 mg	T1/2 (hours)	21	9.07	2.41	5.24	8.95	13.50
Zurnai Autoinjector 1.5 mg	Max Conc (ng/mL)	21	8.14	3.87	3.77	7.12	16.2
Zurnai Autoinjector 1.5 mg	Tmax (min)	21	19.57	11.78	5	15	60
Zurnai Autoinjector 1.5 mg	Time to First Conc (min)	21	1.31	1.51	0	0	5
Nalmefene IV Injection 1 mg	AUC 0 to 2.5 (ng*hr/mL)	12	0.07	0.04	0.015	0.061	0.13
Nalmefene IV Injection 1 mg	AUC 0 to 5min (ng*hr/mL)	12	0.30	0.12	0.158	0.25	0.54
Nalmefene IV Injection 1 mg	AUC 0 to 10min (ng*hr/mL)	12	0.83	0.38	0.485	0.6305	1.83
Nalmefene IV Injection 1 mg	AUC 0 to 15min (ng*hr/mL)	12	1.24	0.57	0.834	1.018	2.91
Nalmefene IV Injection 1 mg	AUC 0 to 20min (ng*hr/mL)	12	1.58	0.66	1.061	1.4075	3.54
Nalmefene IV Injection 1 mg	AUC 0 to 30min (ng*hr/mL)	12	2.15	0.73	1.474	1.975	4.32
Nalmefene IV Injection 1 mg	AUC Infinity Obs (ng*hr/mL)	12	18.42	2.82	14.52	17.99	22.54
Nalmefene IV Injection 1 mg	AUCt (ng*hr/mL)	12	16.42	2.46	13.26	15.67	20.53
Nalmefene IV Injection 1 mg	T1/2 (hours)	12	9.1	1.5	6.98	9.11	12.23
Nalmefene IV Injection 1 mg	Max Conc (ng/mL)	12	7.81	4.35	4.16	5.285	18.6
Nalmefene IV Injection 1 mg	Tmax (min)	12	7.33	3.28	5	5	15

4.2.2 Synopsis of Study NAL1004

This is a study to characterize the time course of reversal of opioid (fentanyl)-induced respiratory depression following administration of nalmefene autoinjector 1.5 mg (0.94% mgcl2) IM and Narcan® 4 mg intranasal in healthy subjects. This was a 2-part study. Part 1 was a Qualification Phase conducted prior to Part 2 to identify subjects eligible for participation in the Part 2 Treatment Phase. This eligibility was based upon satisfying specified qualification criteria following completion of procedures and/or study drug administrations. Each Qualification Phase had a Screening, Treatment, End of Study (EOS) and Follow-up Phase. The Qualification Phase consisted of one period in which the pharmacodynamics (minute ventilation [MV]) of fentanyl-induced respiratory depression were evaluated. The primary criterion for qualification was a review of each subject's MV (L/min) over time profile with the goal of selecting subjects who achieved an approximate 50% average decrease in MV for approximately five minutes that was well tolerated by the subject. Subjects were monitored continuously for oxygen saturation and received supplemental oxygen by mask to enhance safety.

This study evaluated fentanyl/opioid-induced respiratory depression (OIRD or FIRD) following the administration of fentanyl and after coadministration of nalmefene or naloxone, using noninvasive respiratory volume monitoring (e.g., ExSpiron) to determine minute ventilation (the product of tidal volume × respiratory rate), and a transcutaneous CO2 monitor. The target for respiratory depression was a sustained reduction from baseline in minute ventilation (MV) of approximately 50% also called as nadir.

Part 2 was a single-center, randomized, 4-period, 2-treatment crossover replicate study to evaluate the pharmacodynamic effects (change in minute ventilation from opioid induced nadir) of nalmefene (1.5 mg) when given via an autoinjector intramuscularly (IM; into the thigh) compared to naloxone (Narcan 4 mg) when given intranasally (IN; into the nose) to reverse OIRD in healthy subjects with a history of prior non-medical opioid exposure. The Part 2 Treatment Phase included a Screening, Treatment, EOS, and Follow-up Phase. Screening was not required for subjects who were screened in the Qualification Phase within the allowed window.

OIRD model: Fentanyl infusion was administered to subjects using a calibrated programmable or manually adjustable infusion pump. In each period, a saline infusion was administered before (e.g., 30 - 45 minutes) fentanyl Infusion #1. Fentanyl was administered as a 3-step IV infusion. The OIRD model employed in this study was designed to achieve approximately 50% average decrease in minute ventilation for five minutes (nadir) during fentanyl Infusion #1. Fentanyl Infusion #2 began after OIRD (as defined above) at the end of Infusion #1 or after 2 hours, the maximum permitted duration of Infusion #1. At 10 minutes following the start of Fentanyl Infusion #2, nalmefene or naloxone was administered according to the 2-treatment, 4-period randomization sequence. Fentanyl Infusion #3 began immediately after the end of Infusion #2. The third infusion was always at a lower rate than the first and second, and the exact rate was dependent on the duration of Infusion #1. A pharmacokinetic model for fentanyl exposure as a function of IV fentanyl infusion rate and duration was developed to construct the 3-step fentanyl infusion scenarios.

For the Nalmefene Autoinjector, the dose was 1.5 mg nalmefene (0.5 mL of a (b) (4) solution containing 0.94% MgCl2). This is the final to-be-marketed formulation and product administered by the intended IM/SC route of administration. Narcan 4 mg IN was used as a comparator because it is the Standard of Care product used in the community setting for opioid overdose reversal. Identity of drug products used in the study NAL1004 and details of route of administration are provided in the ***Table 6*** below.

Table 6: Identity of drug formulations used in Part 2 of study NAL1004.

Name	**Fentanyl citrate***	**Narcan®***	**Nalmefene Autoinjector ** (Nalmefene Hydrochloride Injection)**
Dosage Form	Solution	Intranasal	Autoinjector
Dosage Regimen	Single dose	Single dose	Single dose
Route	IV infusion	Intranasal	Intramuscular
Administration Site	IV	Nose	Anterolateral thigh
Solution Supplied	50 mcg/mL	4 mg naloxone HCl per 0.1 mL solution	0.5 mL (b) (4) solution containing 0.94% (w/v) $MgCl_2$
Dose and volume administered	Up to approximately 1100 mcg	0.1 mL of 4 mg of naloxone HCl	1.5 mg (0.94% (w/v) $MgCl_2$) in 0.5 mL
Supplier	Investigative site	Investigative site	Purdue Pharma L.P.
Manufacturer	Hospira, Inc.	Distributed by Adapt Pharma, Inc.	(b) (4)
Lot/Batch No.	34019DK	220489	I2564
Expiration Date	01.OCT.2023	APR2025	Retest Date: (b) (4)

*Detailed instructions for the preparation of fentanyl and administration of Narcan were described in the pharmacy manual.
** Detailed instructions for administration of the Nalmefene Autoinjector were described in the site operations manual.

In each period of Part 2 of the study, 4 mL venous blood was collected at room temperature in K_2EDTA vacutainers at the following nominal times after dosing: 2.5, 5, 10, 15, 20, and 30 minutes and at 1, 2, 4, 8, 12, and 24 hours after nalmefene/naloxone administration. Noncompartmental pharmacokinetic analysis was performed using Phoenix WinNonlin 8.0 or higher (Certara USA, Inc) to estimate the pharmacokinetic parameters: AUC0-2.5, AUC0-5, AUC0-10, AUC0-15, AUC0-20, AUCt, AUCinf, Cmax, Tmax, Tlag and T½ for nalmefene and naloxone.

Table 7: Descriptive statistics of plasma nalmefene pharmacokinetics with Zurnai Autoinjector from study NAL1004.

	Treatment: Nalmefene Autoinjector 1.5 mg IM										
	$AUC_{0\text{-}2.5}$ (ng*hr/mL)	$AUC_{0\text{-}5}$ (ng*hr/mL)	$AUC_{0\text{-}10}$ (ng*hr/mL)	$AUC_{0\text{-}15}$ (ng*hr/mL)	$AUC_{0\text{-}20}$ (ng*hr/mL)	AUC_t (ng*hr/mL)	AUC_{inf} (ng*hr/mL)	C_{max} (ng/mL)	T_{max} (h)	T_{lag} (h)	$T_{1/2}$ (h)
Overall											
N	23	23	23	23	23	23	23	23	23	23	23
Mean	0.0440	0.2225	0.7576	1.2716	1.7479	23.1620	25.7412	8.3576	0.2208	0.0527	7.9754
SD	0.03923	0.13565	0.38147	0.52366	0.61346	3.60968	4.65028	3.71139	0.19213	0.01912	2.16550
Median	0.0427	0.1902	0.6650	1.1719	1.6267	24.0729	26.7060	6.8600	0.2083	0.0417	7.1757
Minimum	0.000	0.046	0.265	0.558	0.896	16.314	17.642	4.830	0.062	0.042	5.554
Maximum	0.136	0.504	1.660	2.468	3.099	29.332	33.239	19.300	1.017	0.117	13.003
CV%	89.07	60.97	50.35	41.18	35.10	15.58	18.07	44.41	87.00	36.27	27.15
GM	0.0163	0.1814	0.6725	1.1771	1.6521	22.8798	25.3276	7.7283	0.1788	0.0503	7.7326
GMCV%	7224.58	77.99	53.47	41.55	35.12	16.35	18.77	40.37	68.43	30.25	25.03

CV = Coefficient of Variation; GM = Geometric Mean; SD = Standard Deviation; NE = Not Estimable
AUC_{inf} was not calculated due to AUC_{extrap} percentage exceeded 20%. Parameters that rely on the terminal log-linear regression for calculation (AUC_{inf}, Lambda z, $T_{1/2}$) will be considered non-reportable if the fit of the linear regression (R^2) is less than 0.85.
Source: Table 14.2.2.1 and Listing 16.2.9.2

Pharmacokinetics of nalmefene following Zurnai Autoinjector were apparently similar to that noted in study NAL1005. Detectable plasma levels of nalmefene were noted at the first time point (2.5 minutes) of blood sample (**Table 7**). Pharmacokinetics of naloxone following Narcan nasal spray were similar to that previously noted. Detectable plasma levels of naloxone were noted at the first time point (2.5 minutes) of blood sample (**Table 8**).

Table 8: Descriptive statistics of plasma naloxone pharmacokinetics with Narcan nasal spray from study NAL1004.

	Treatment: Narcan 4 mg IN										
	$AUC_{0-2.5}$ (ng*hr/mL)	AUC_{0-5} (ng*hr/mL)	AUC_{0-10} (ng*hr/mL)	AUC_{0-15} (ng*hr/mL)	AUC_{0-20} (ng*hr/mL)	AUC_t (ng*hr/mL)	AUC_{inf} (ng*hr/mL)	C_{max} (ng/mL)	T_{max} (h)	T_{lag} (h)	$T_{1/2}$ (h)
Overall											
N	24	24	24	24	24	23	22	24	24	24	22
Mean	0.0256	0.1002	0.3311	0.6300	0.9817	13.4803	13.4938	5.6015	0.5958	0.0464	1.6353
SD	0.03663	0.11542	0.27201	0.43256	0.61050	2.78735	2.87023	2.30753	0.26388	0.01023	0.50257
Median	0.0142	0.0623	0.2359	0.5689	0.9164	12.7555	12.7754	5.2825	0.6667	0.0417	1.4948
Minimum	0.001	0.013	0.067	0.158	0.283	9.820	9.982	2.715	0.167	0.042	1.167
Maximum	0.137	0.435	1.091	1.758	2.441	19.673	19.894	12.800	1.000	0.083	3.534
CV%	143.24	115.23	82.16	68.66	62.19	20.68	21.27	41.20	44.29	22.07	30.73
GM	0.0120	0.0599	0.2433	0.5045	0.8187	13.2191	13.2183	5.2082	0.5295	0.0455	1.5830
GMCV%	203.13	137.98	96.46	77.96	68.66	20.24	20.81	39.84	57.25	18.43	24.63

CV = Coefficient of Variation; GM = Geometric Mean; SD = Standard Deviation; NE = Not Estimable
AUCt was not estimable when subject had PK samples up to 1 hr.
AUC_{inf} was not calculated due to AUCextrap percentage exceeded 20%. Parameters that rely on the terminal log-linear regression for calculation (AUC_{inf}, Lambda z, $T_{1/2}$) will be considered non-reportable if the fit of the linear regression (R^2) is less than 0.85.
Source: Table 14.2.2.2 and Listing 16.2.9.2

Several safety procedures were put in place to minimize the potential for life-threatening respiratory depression, severe bradycardia, and severe hypotension when administering fentanyl. These included continuous ACLS-certified physician monitoring of subjects during opioid dosing, supplemental oxygen (2 L/min) per mask, continuous monitoring with real-time displays of minute ventilation, respiratory rate, tidal volume, transcutaneous CO2, and SpO2 using approved medical devices, and two established IV access points for each subject. In addition, a board-certified anesthesiologist was present during the fentanyl infusions in the qualification and treatment phases of this study. Safety observations are reviewed by medical officer Dr. Zachary Dezman.

Part 2 was designed to assess the change in minute ventilation following administration of IM nalmefene and intranasal naloxone reversal from the opioid induced NADIR and to assess the time course of changes in minute ventilation of IM nalmefene and intranasal naloxone reversal from the opioid induced NADIR. The PD variables included:

• Minute Ventilation (MV) in L/min - calculated as the product of tidal volume and respiratory rate, determined in a continuous fashion by noninvasive respiratory volume monitor (**Table 9** and **Table 10**).

The study was designed to investigate the primary objective, a non-inferiority test, to assess the change in MV at 5 minutes of Zurnai Autoinjector compared to Narcan nasal spray. However, considering that this is an experimental clinical pharmacology study, the data was reviewed to understand the time to onset of pharmacodynamic effect measured as MV. Specifically, the time course of changes in MV following Zurnai Autoinjector at 2.5, 10, 15, 20 and 90 minutes from opioid induced nadir (**Figure 4**). This is to characterize the time to onset of reversal defined as 25%, 33%, 50%, 67%, 75%, 90% and 100% reversal to baseline MV. Thresholds (X%) of reversal is defined as X% of baseline reversal and calculated

as X (%) * (Baseline –NADIR) + NADIR, where X are 25, 33, 50, 67, 75, 90, and 100 (**Table 10**). Similar data from Narcan nasal spray treatment arm was used to confirm the validity of the OIRD model. Percentage change in minute ventilation from baseline, during fentanyl-induced respiratory depression, and after administration of Zurnai Autoinjector and Narcan nasal spray are described in **Figure 5**. Mean MV was similar at baseline for the two treatments, as was MV at the opioid-induced nadir, defined as median of MV between -10 minutes and -5 minutes before antagonist administration. The positive control naloxone nasal spray demonstrated reversal of fentanyl-induced respiratory depression as expected. Following Zurnai Autoinjector administration, 2.5 to 5 minutes later the onset of reversal of respiratory depression was noted.

Table 9: Mean MV ± SD at baseline, nadir, and after administration of Zurnai Autoinjector and Narcan nasal spray.

Time in relation to drug administration	Zurnai Autoinjector		Narcan Nasal Spray	
Minutes	Mean MV ± SD (L/min)	Percent MV (%)	Mean MV SD (L/min)	Percent MV (%)
-10 (Baseline)	7.27 ± 1.61	100	7.55 ± 1.28	100
0 (Nadir)	4.35 ± 1.15	60.49 ± 12.48	4.44 ± 1.07	59.01 ± 11.2
2.5	6.79 ± 1.68	94.66 ± 20.04	6.11 ± 1.47	81.43 ± 16.66
5	8.45 ± 2.23	116.22 ± 21.34	6.20 ± 1.61	82.55 ± 18.58
10	8.41 ± 1.96	116.71 ± 18.46	6.76 ± 1.84	89.50 ± 18.4
15	8.39 ± 1.72	117.93 ± 22.04	7.07 ± 1.99	93.32 ± 18.8
20	8.32 ± 1.84	117.30 ± 25.4	7.36 ± 2.22	97.38 ± 22.35
30	7.96 ± 1.61	111.93 ± 20.69	7.36 ± 1.92	97.67 ± 19.84
90	7.03 ± 1.71	96.88 ± 9.57	6.88 ± 1.54	91.51 ± 15.2

Source: Adapted from Listing 16.2.10.4 (1-minute window smooth MV data) from study report NAL1004.

In the setting of opioid overdose, onset of reversal is expected within minutes following antagonist administration (**Figure 4** below). A 30-minute window was selected to ensure the initial onset was fully captured. Regardless of which percentage (25%, 33%, 50%, 67%, 75%, 90%, or 100%) is chosen as the threshold to measure onset of reversal, Zurnai Autoinjector demonstrated full recovery within 5-15 minutes after administration(**Table 9** and **Table 10**). Narcan nasal spray, which was used as a positive control, also demonstrated reversal of opioid-induced respiratory depression within 5-15 minutes (**Table 9** and **Table 10**).

Table 10: Time to onset of reversals for MV (L/min) during 0-30 minutes after Zurnai Autoinjector or Narcan nasal spray administration.

		Nalmefene Autoinjector 1.5 mg IM			Narcan 4 mg IN		
Parameter	Statistic	Administration 1	Administration 2	Overall	Administration 1	Administration 2	Overall
Time (min) to 25% of Baseline Reversal	n	22	20	23	22	23	24
	Mean (SD)	0.279 (0.398)	0.215 (0.763)	0.245 (0.473)	1.147 (3.972)	0.363 (0.684)	0.753 (1.936)
	Median	0.06	0.05	0.06	0.05	0.05	0.05
	Min, Max	0.00, 1.17	0.00, 3.45	0.00, 2.19	0.00, 18.75	0.00, 2.50	0.00, 9.41
Time (min) to 33% of Baseline Reversal	n	22	20	23	22	23	24
	Mean (SD)	0.351 (0.469)	0.219 (0.782)	0.285 (0.535)	1.306 (4.498)	0.417 (0.762)	0.859 (2.193)
	Median	0.06	0.05	0.07	0.05	0.05	0.05
	Min, Max	0.00, 1.43	0.00, 3.53	0.00, 2.48	0.00, 21.25	0.00, 2.83	0.00, 10.66
Time (min) to 50% of Baseline Reversal	n	22	20	23	22	23	24
	Mean (SD)	0.836 (1.378)	0.436 (1.063)	0.618 (1.031)	3.118 (7.762)	1.062 (2.077)	2.000 (3.822)
	Median	0.16	0.05	0.07	0.08	0.07	0.10
	Min, Max	0.00, 4.72	0.00, 3.78	0.00, 4.11	0.00, 30.00	0.00, 7.77	0.00, 15.09
Time (min) to 67% of Baseline Reversal	n	22	20	23	22	23	24
	Mean (SD)	1.502 (2.405)	0.628 (1.197)	1.196 (2.161)	5.259 (10.522)	1.493 (2.615)	3.191 (5.453)
	Median	0.19	0.07	0.07	0.18	0.07	0.20
	Min, Max	0.00, 9.28	0.00, 4.20	0.00, 9.28	0.02, 30.00	0.00, 7.93	0.01, 16.71
Time (min) to 75% of Baseline Reversal	n	22	20	23	22	23	24
	Mean (SD)	1.623 (2.436)	0.878 (1.514)	1.363 (2.215)	5.767 (10.662)	1.617 (2.769)	3.492 (5.607)
	Median	0.22	0.07	0.08	0.35	0.07	0.38
	Min, Max	0.00, 9.28	0.00, 5.53	0.00, 9.28	0.02, 30.00	0.00, 8.02	0.01, 17.13
Time (min) to 90% of Baseline Reversal	n	22	20	23	22	23	24
	Mean (SD)	2.445 (2.654)	1.223 (1.810)	2.011 (2.294)	6.456 (10.627)	3.986 (5.978)	4.947 (6.201)
	Median	1.68	0.08	1.57	0.73	0.48	0.97
	Min, Max	0.00, 9.45	0.00, 6.03	0.00, 9.45	0.02, 30.00	0.00, 18.33	0.01, 17.25
Time (min) to 100% of Baseline Reversal	n	22	20	23	22	23	24
	Mean (SD)	2.779 (2.860)	1.615 (2.103)	2.345 (2.368)	8.042 (11.425)	6.457 (9.584)	6.859 (8.975)
	Median	2.18	0.13	2.08	1.58	0.57	1.03
	Min, Max	0.00, 9.53	0.00, 6.28	0.00, 9.53	0.02, 30.00	0.00, 30.00	0.01, 30.00

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Figure 4: MV at baseline, during fentanyl-induced respiratory depression and after treatment with Zurnai Autoinjector and Narcan nasal spray in adult healthy volunteers from study NAL1004.

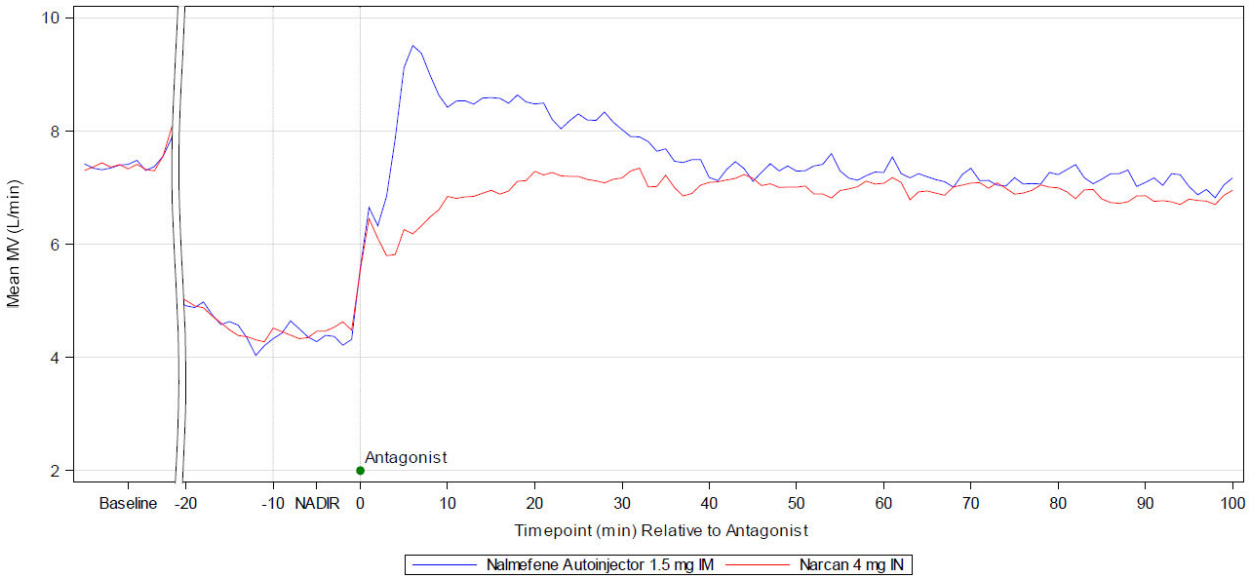
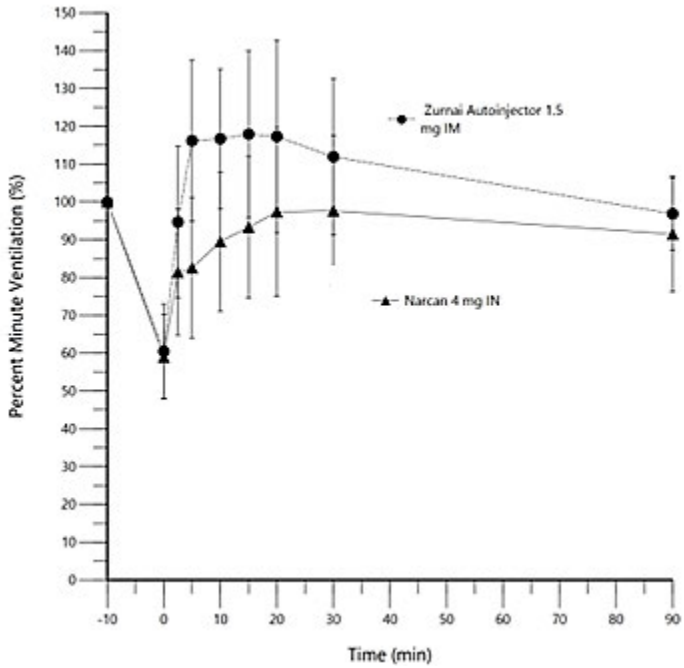


Figure 5: Percentage MV at baseline, at nadir during fentanyl-induced respiratory depression and after treatment with Zurnai Autoinjector and Narcan nasal spray in adult healthy volunteers from study NAL1004.



4.3 DARS review:

Independent Mechanistic PK-PD Modeling Analysis of

NDA218590 Nalmefene Autoinjector 1.5 mg

Division of Applied Regulatory Science, Office of Clinical Pharmacology

4.3.1 Executive Summary

The objective of this review is to perform independent modeling & simulation to translate the findings from the sponsor's healthy volunteer pharmacokinetic-pharmacodynamic (PK-PD) study using either intramuscular (IM) nalmefene or intranasal naloxone to reverse opioid-induced decreases in ventilation into labeling for community opioid overdose scenarios, focusing on two key aspects:

1) the onset of action of the nalmefene IM auto-injector 1.5 mg product in comparison to approved naloxone intranasal (IN) 4 mg product for the community setting.
2) the need for dose titration or re-administration for the nalmefene product in a community setting

OCP's independent modeling & simulation using a previously developed systems pharmacology model support the Applicant's claim that nalmefene IM 1.5 mg has an onset of action at least as fast 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 1.5 mg nalmefene IM may not 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 soon enough.

4.3.2 Background

The opioid antagonist nalmefene has been shown to reverse the respiratory depression effects of opioids. Several nalmefene products have been approved by the US Food and Drug Administration (FDA) for the indication of management of known or suspected opioid overdose, including Revex (nalmefene hydrochloride injection) [1], its generics [2], as well as Opvee (nalmefene nasal spray) [3].

Administration routes such as IM injection or IN spray have slower absorption and require more time in reaching plasma concentrations capable of reversing overdose compared to intravenous (IV) injection. Because of this, on November 7th, 2019, the FDA issued an IND advice letter to all sponsors developing nalmefene products for community use. In the letter the sponsors were advised to address three (3) potential questions in their development program: 1) whether the intended routes (usually IN or IM) provide fast enough onset of action to reverse respiratory depression in a community setting; 2) whether the intended dose is established for community use that does not 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.

To address the FDA advice letter, in Nov 2023, the sponsor Purdue Pharmaceuticals L.P. (hereafter referred to as the Applicant) proposed to use the data from a healthy volunteer PK-PD study (NAL1004) for their nalmefene 1.5 mg IM autoinjector product to address some of the questions.

OCP performed a detailed review of this study, some of which will be covered by other review documents. In this document, a previously developed systems pharmacology model [4] was used to evaluate the Applicant's nalmefene product and address first two questions from the FDA's November 7th, 2019 advice letter: 1) the onset of action in comparison to an approved naloxone IN product; 2) the potential need for dose titration or re-administration in a community setting.

4.3.3 Methods

The OCP systems pharmacology model was developed to translate the systemic exposure of different opioid agonists and antagonists into clinically interpretable outcomes such as minute ventilation, blood gas tensions, and cardiac output [4]. The goal of using the model is to evaluate the nalmefene IM product under scenarios different from those conditions in the Applicant's PK/PD study NAL1004, but closer to real-world community overdose situations (see **Table 11** for details).

To apply the OCP systems pharmacology model to the review of NDA218590, various components of the model were updated. The PK and PD components of the opioid antagonists were updated based on the data of nalmefene 1.5 mg NAI and naloxone (Narcan® Nasal Spray 4 mg) from study NAL1004 (**Figure 6** and **Figure 7**)The receptor binding component for nalmefene was updated using internal data from in vitro receptor binding kinetic experiments. For the subsequent simulation of community overdose scenarios, 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 study describing the OCP systems pharmacology model [4].

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 (1.625 mg intravenous bolus injection for fentanyl, and 0.012 mg for carfentanil). The first dose of IM nalmefene or IN naloxone was administered 1 min after the minute ventilation volume of virtual subjects dropped below 40% of the baseline. If repeat antagonists dosing was given, the second dose was assumed to be applied 2.5 min after the first antagonist dose. 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.

Table 11: Key conditions (differences and similarities) between the scenarios evaluated using OCP's systems pharmacology model and the Applicant's study NAL1004.

	Scenarios evaluated by OCP's Independent Analysis	Settings of NAL1004
Inspired air	Room air (21% O_2, 0% CO_2)	Room air with supplemental oxygen
Primary clinical outcome	Cardiac arrest; Brain hypoxia	Minute ventilation
Study participants	Chronic opioid users	Healthy subjects
Opioid dosing route	Rapid intravenous injection	Continuous infusion
Repeated dosing evaluated	Yes	No
Baseline minute ventilation (before opioids administration)	6.7 L/min	7.3 L/min
Opioids used	Fentanyl and Carfentanil	Fentanyl

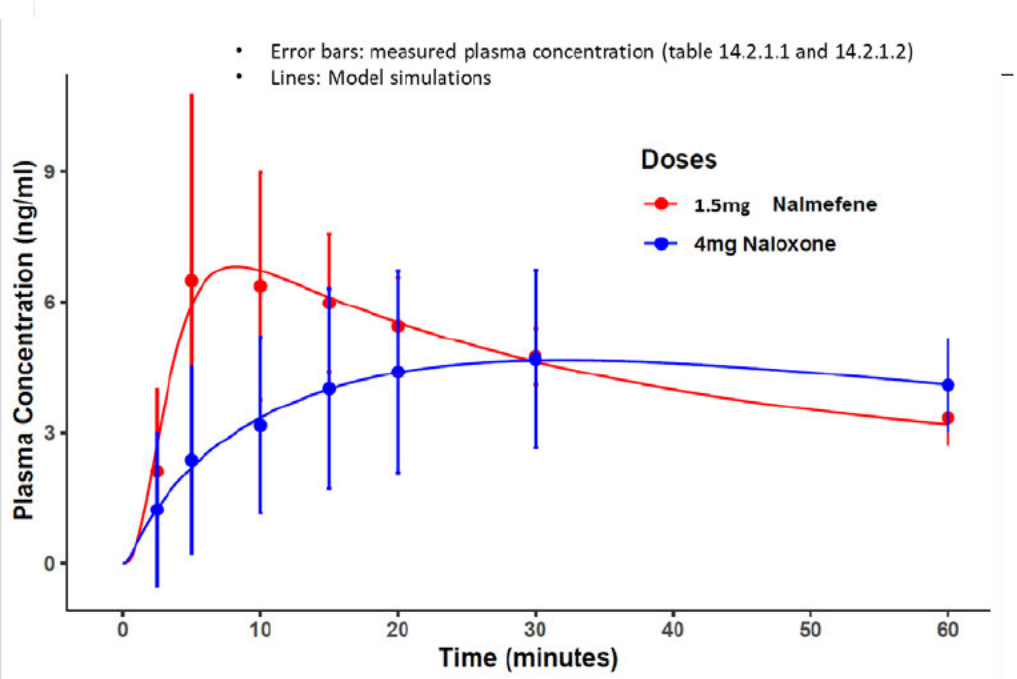


Figure 6: Comparison of the plasma profiles of nalmefene IM 1.5 mg and naloxone IN 4 mg in NAL1004.
Plasma profiles of nalmefene IM 1.5 mg (red) and naloxone IN 4 mg (blue) were obtained from the study NAL1004. The dots and error bars represent the mean and standard deviation of measured plasma concentration, respectively. The lines represent the OCP systems pharmacology model simulation of a typical subject.

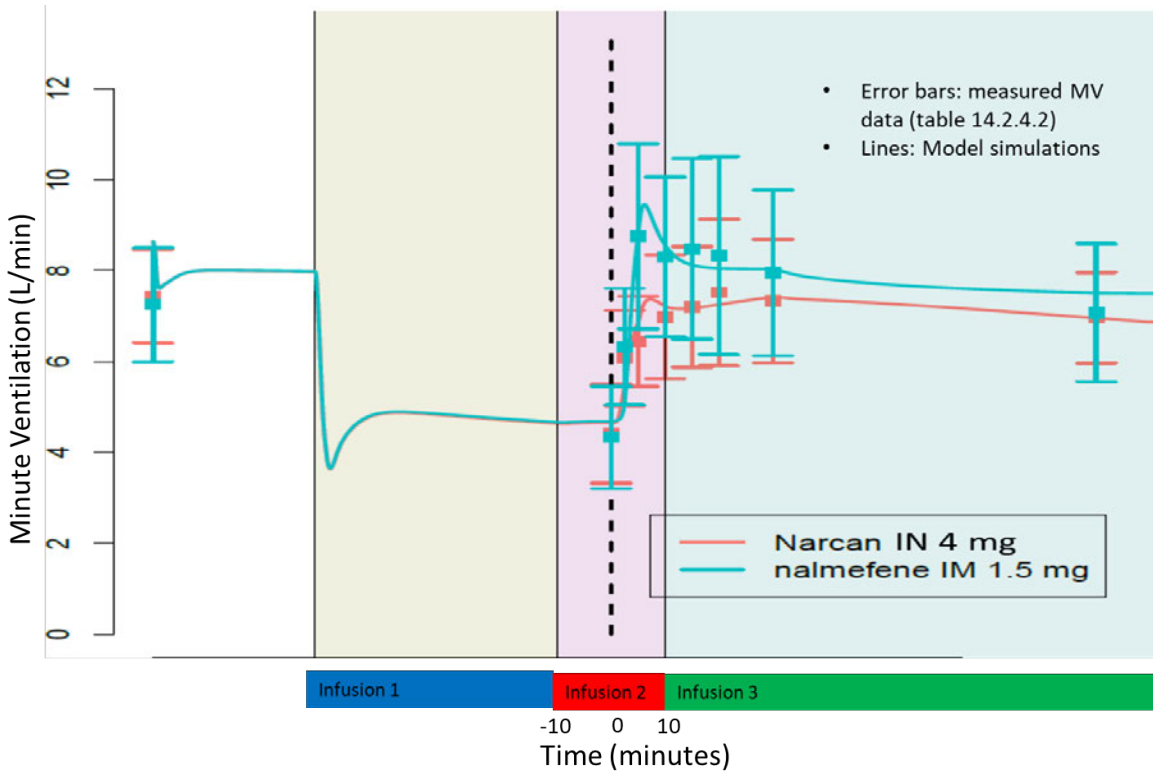


Figure 7: Comparison of the pharmacologic effects on minute ventilation (MV) from nalmefene IM 1.5 mg and naloxone IN 4 mg in NAL1004.

Error bars: mean and standard deviation of minute ventilation in the naloxone IN 4 mg group (red) and nalmefene IM 1.5 mg group (blue) from the study NAL1004. Solid lines: OCP systems pharmacology model simulation of a typical subject. During infusion 1, fentanyl IV infusion started at a rate of 5 mcg/min and stopped when there was a 50% decrease in MV. The duration of infusion 1 was adjusted for each individual subject. After infusion 1, infusion 2 started at a rate lower than infusion 1. The rate for infusion 2 was calculated according to the Applicant's prespecified table so that the predicted plasma concentration of fentanyl at the end of infusion 1 would be maintained during the course of infusion 2. During the study, subjects were breathing air with supplemental oxygen at a rate of at least 2 L/min. Ten minutes after the initiation of infusion 2, IM nalmefene 1.5 mg (blue) or IN naloxone 4 mg (red) was administered, leading to a recovery (increase) of MV. Twenty minutes after the initiation of infusion 2, infusion 2 was stopped and infusion 3 started, which had an even lower infusion rate according to the Applicant's prespecified dosing table.

4.3.4 Results (QBR)

3) Does OCP's independent modeling & simulation support the sponsor's claim that nalmefene IM 1.5 mg IM has an onset of action appropriate for opioid reversal in a community setting?

During the development and validation of OCP's systems pharmacology model [4], as well as the application of this model to the evaluation of a naloxone product [5], 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 brain hypoxia time. OCP's independent simulation of the nalmefene IM 1.5 mg autoinjector product focused on these two endpoints. To inform on community overdose situations, the opioids used in the simulations were fentanyl and carfentanil, using the medium overdose scenarios (1.625 mg intravenous bolus injection for fentanyl, and 0.012 mg for carfentanil) and virtual populations representing chronic opioid users (see Methods).

As shown in ***Figure 8***, 1 dose of nalmefene IM 1.5 mg reduced the percentage of simulated patients experiencing fentanyl-associated cardiac arrest from 52% (median value without any antagonist administration) to below 10%. In contrast, 1 dose of naloxone IN 4 mg reduced the percentage of simulated patients with cardiac arrest from 52% to over 15%. Similarly, for the carfentanil overdose scenario, nalmefene IM 1.5 mg reduced the percentage of simulated patients with cardiac arrest to about 5%, while naloxone IN 4 mg reduced the percentage of simulated patients experiencing cardiac arrest to 20%.

As shown in ***Table 12***, for fentanyl overdose without 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 IM 1.5 mg had a median brain hypoxia time of 0 min, suggesting the 50th percentile of subjects did not experience any brain hypoxia. In contrast, 1 dose of naloxone IN 4 mg had a median brain hypoxia time 1.2 minutes.

For the carfentanil overdose scenario, a difference between nalmefene IM 1.5 mg and naloxone IN 4 mg was seen at the upper boundary of the inter quantile range (IQR). After 1 dose of nalmefene IM 1.5 mg, the upper IQR was 1.8 minutes, meaning 25% of the virtual subjects had a brain hypoxia time longer than 1.8 minutes. In comparison, after 1 dose of naloxone IN 4 mg, the upper IQR was 4.9 minutes, meaning 25% of the virtual subjects had a brain hypoxia time longer than 4.9 minutes.

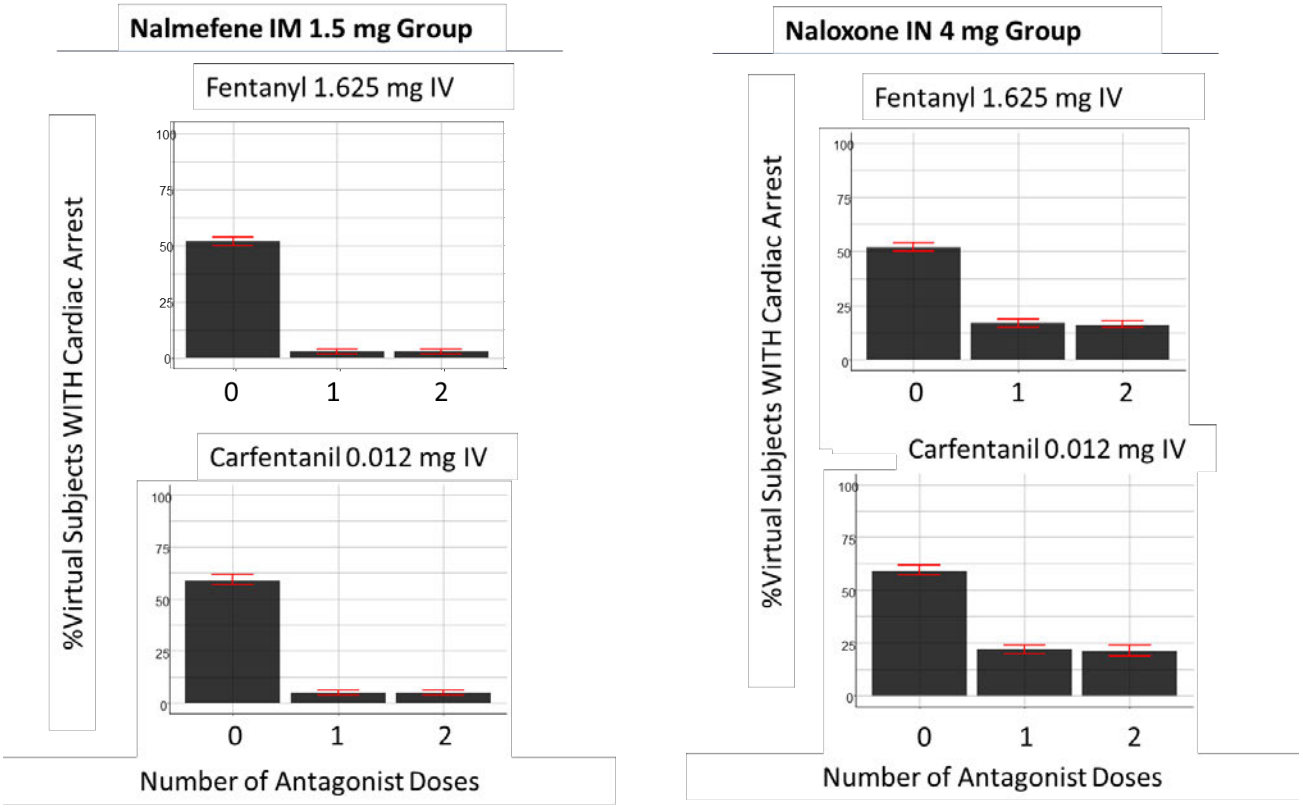


Figure 8: Percentage of virtual patients experiencing cardiac arrest for the fentanyl (top row) or carfentanil (bottom row) overdose scenarios.

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 of an antagonist, and 2 doses of an antagonist (2.5 min apart), respectively. The antagonists used in the simulations are nalmefene IM 1.5 mg (left column) and naloxone IN 4 mg (right column). 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).

Table 12: Brain hypoxia time predicted in virtual subjects for the fentanyl or carfentanil overdose scenarios.

Nalmefene IM 1.5 mg				
		Median value	Lower bound of IQR	Higher bound of IQR
Fentanyl 1.625 mg	Without Nalmefene	CA	0 min	CA
	With Nalmefene	0 min	0 min	1.6 min
	2 dose Nalmefene	0 min	0 min	1.6 min
Carfentanil 0.012 mg	Without Nalmefene	CA	0 min	CA
	With Nalmefene	0 min	0 min	1.8 min
	2 dose Nalmefene	0 min	0 min	1.8 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	1.2 min	0 min	4.0 min
	2 dose Naloxone	1.1 min	0 min	3.9 min
Carfentanil 0.012 mg	Without Naloxone	CA	0 min	CA
	With Naloxone	0 min	0 min	4.9 min
	2 dose Naloxone	0 min	0 min	4.7 min

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

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 (IQR) of brain hypoxia time are based on the total population of 2000 virtual subjects. The median and/or upper IQR of brain hypoxia time for nalmefene (left) and naloxone (right) are marked as red.

4) 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 systems pharmacology model was used to simulate two dosing schemes of the nalmefene IM product: a single administration of nalmefene hydrochloride 1.5 mg, or two doses of 1.5 mg, with a 2.5 min delay between the doses. As shown in ***Figure 8***, this 2-dose nalmefene scheme did not change the predicted cardiac arrest percentage in the virtual populations after fentanyl or carfentanil overdose, in comparison to the 1-dose nalmefene scheme. Similarly, ***Table 12*** shows that the 2-dose nalmefene scheme had a similar median or upper IQR brain hypoxia time as the 1-dose nalmefene scheme in the virtual populations for the fentanyl or carfentanil overdose scenarios.

While it is conceivable that under other scenarios (e.g., opioids overdose through a dosing route slower than IV, the use of other interventions like rescue breathing or cardiopulmonary resuscitation, etc.) re-administration of IM nalmefene after the 1st dose may have benefits, the results in ***Figure 8*** and ***Table 12*** suggested that the proposed dose (IM 1.5 mg) does not rely on titration or re-administration to protect against opioid-associated cardiac arrest and brain hypoxia.

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 [4], 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, PaO_2, $PaCO_2$, CO_2 response slope) from independent clinical studies involving different opioids (fentanyl, alfentanil, and remifentanil) [4]. 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 O_2 partial pressure PaO_2) and cardiovascular collapse/cardiac arrest is derived from animal data. The FDA 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 [4]. 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 simulation focusing on changes in baseline ventilation.

Third, there is a lack of clinical PK data for carfentanil. The FDA model assumes carfentanil PK is similar to fentanyl PK, with the plasma half-life prolonged according to limited human carfentanil PK data [4]. 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 systems pharmacology 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% (late dosing) 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 systems pharmacology model to evaluate the onset of action of nalmefene IM 1.5 mg compared to naloxone IN 4 mg. The analyses support that the onset of action for nalmefene IM 1.5 mg was at least as rapid as naloxone IN 4 mg, supporting that this nalmefene product is also appropriate for use in a community setting. OCP's evaluation also supports that the proposed dose of 1.5 mg nalmefene hydrochloride IM is unlikely to require titration or re-administration to 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 soon enough.

4.3.7 References

1. USFDA. *US FDA label for Revex (nalmefene hydrochloride injection)*. 2006; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/020459s006lbl.pdf.
2. USFDA, *FDA Label for Nalmefene Hydrochloride Injection.* 2022.
3. USFDA. *FDA Label for Opvee Nasal Spray*. 2023; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/217470Orig1s000.pdf.
4. Mann, J., et al., *Development of a Translational Model to Assess the Impact of Opioid Overdose and Naloxone Dosing on Respiratory Depression and Cardiac Arrest.* Clin Pharmacol Ther, 2022. **112**(5): p. 1020-1032.
5. USFDA. *Clinical Review for NDA215457 (Naloxone Auto-Injector 10 mg)*. 2022; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/215457Orig1s000MedR.pdf.
6. Minkowski, C.P., et al., *Differential response to IV carfentanil in chronic cocaine users and healthy controls.* Addict Biol, 2012. **17**(1): p. 149-55.

4.4 Population PK Analyses

The document purdue-nalm-report-finalv1-0-pkonly-05dec2023.pdf contains the report titled "Population Pharmacokinetic Model Development of Nalmefene using Adult Data and Simulations of Nalmefene Exposures in Pediatric Populations (12 to 17 years of age)" and was submitted to module 5335 of sequence 0001. This report describes pharmacokinetic (PK) analyses of nalmefene. The document repeat-dose-pk-report-non-parametric-simulation.pdf contains a report titled "Evaluation of repeat dose simulations for Nalmefene Auto-injector 1.5 mg IM and Nalmefene IV labeled dose regimens based on single dose concentration data from clinical study NAL1005" and was submitted to module 5354 of sequence 0001.

4.4.1 Population PK Modeling

The objectives of the population PK (PPK) analyses described in purdue-nalm-report-finalv1-0-pkonly-05dec2023.pdf are:

1) to characterize the population pharmacokinetics (PPK) of nalmefene following the IM administration of nalmefene HCl injection 1.0 mg (reference) and Nalmefene Auto-Injector (NAI) 1.5 mg (test), and
2) to simulate and compare exposure profiles of nalmefene in pediatric populations (12 to 17 years of age) vs adults.

PK data for these analyses were obtained from study NAL1005. A summary of the key information about study NAL1105 is found in ***Table 13***.

Table 13: Summary of Clinical Study NAL1005.

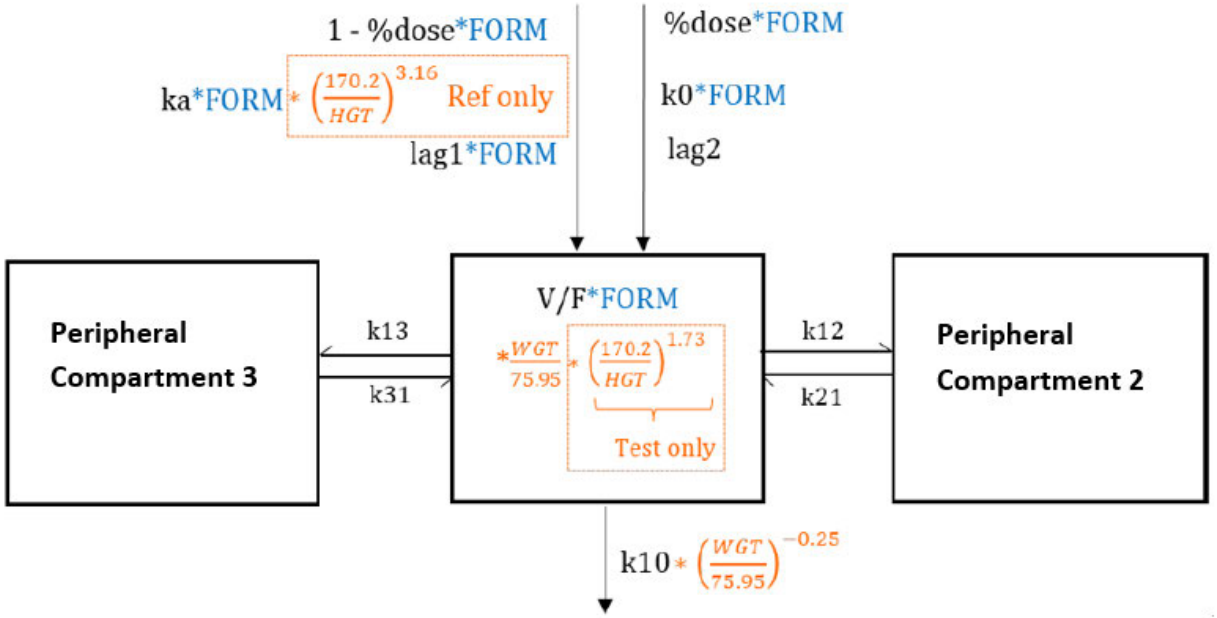
Study Design	Single-center, open-label, randomized, single-dose, 2-treatment, 2-period, 2-way crossover study in healthy adult subjects. A substudy was nested in the overall study design as an optional Period 3 treatment.
Subjects	Healthy adult males and females [n=24]
Treatments	**Nalmefene Auto-Injector (NAI), 1.5 mg** free base (test product, manufactured by Purdue Pharma, LP) / single dose IM (anterolateral thigh) **Nalmefene HCl injection, 1mg/mL** free base (comparator product manufactured by Purdue Pharma, LP comparator to REVEX® Listed Drug) / single dose IM (anterolateral thigh) Nalmefene HCl 1.0 IV administered in Period 3, but data not included in PPK analysis
Washout	7 days between each treatment period
PK Time Points	pre-dose and at 2.5, 5, 10, 15, 20, 30 minutes and at 1, 2, 4, 8, 12, 24, 36, and 48 hours after dosing

Source: Sequence 0001, module 5335, purdue-nalm-report-finalv1-0-pkonly-05dec2023.pdf, page 28.

The PK dataset includes 505 nalmefene concentration above the lower limit of quantification from a total of n=24 individuals.

Applicant utilized a non-linear mixed effects modeling approach to analyze the PK data using the NONMEM® software package version 7.5. A schematic representation of the nalmefene PK model is presented in ***Figure 9***.

Figure 9: Schematic Representation of the Structural Population PK model



Source: Sequence 0001, module 5335, purdue-nalm-report-finalv1-0-pkonly-05dec2023.pdf, page 55.
FORM refers to the formulation; reference formulation (nalmefene HCl Injection) or test formulation (NAI).

The final nalmefene PPK model includes three compartments, two parallel absorption processes (a zero-order process with lag and a first order process with lag), and linear elimination. The model is parameterized in terms of a first order absorption rate constant (ka), zero order absorption rate constant (k0), rate constant for elimination (k10), rate constant from central compartment to peripheral compartment 2 (k12), rate constant from peripheral compartment 2 to central compartment (k21), rate constant from central compartment to peripheral compartment 3 (k13), rate constant from peripheral compartment 3 to central compartment (k31), apparent volume of distribution of the central compartment (Vc/F) for IM injection, apparent volume of distribution of central compartment for AI (Vc/F), absorption lag for first order absorption (lag1), absorption lag for zero order absorption (lag2), proportion of IM injection that undergoes zero order absorption, proportion of AI administration that undergoes zero order absorption, duration of zero-order infusion for IM injection, and duration of zero-order infusion for AI administration.

[Reviewer comment: The Applicant allowed the Vc/F parameter to differ between the two formulations as each product may have distinct bioavailability. This is acceptable.]

The parameter estimates for the final nalmefene PPK model (Model 704) are presented in ***Table 14***.

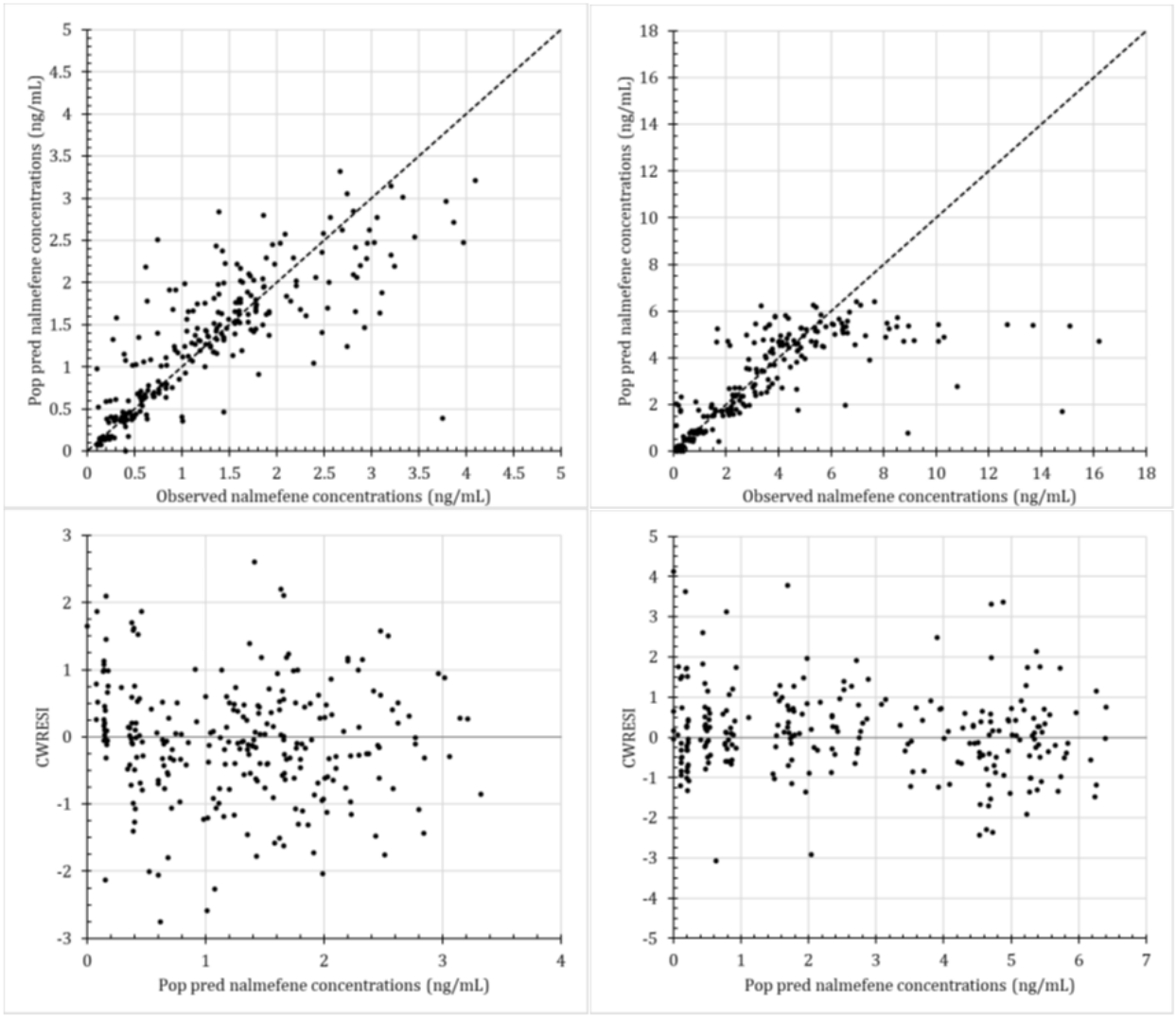
Table 14: Parameter Estimates for the Final Nalmefene PPK Model (Model 704)

PK Parameters	Population Predictions Geomean (GeoCV%) Ref	Test	Both
ABSORPTION PARAMETERS			
First-Order Absorption			
%dose	0.735 (33%)	0.658 (79%)	-
ka (h-1)	0.538 (23%)	1.68 (22%)	-
Cov on ka (Ref only): $(170.2/HGT)^{3.16}$			
t1/2 abs (h)	1.29	0.410	-
tlag1 (min)	12.2	6.9	-
Zero-Order Absorption			
%dose	0.265	0.342	-
Duration (min)	14.94 (61%)	6.42 (28%)	-
tlag2 (min)	-	-	2.526 (47%)
SYSTEMIC PARAMETERS			
Vc/F (L)	93.7 (15%)	96.9 (15%)	-
Cov on Vc/F: (WGT/75.95) for both, (170.2/HGT)1.73 for Test only			
k10 (h-1)	-	-	0.587 (16%)
Cov on k10: (WGT/75.95)-0.25			
k12 (h-1)	-	-	2.13 (19%)
k21 (h-1)	-	-	0.985 (20%)
k13 (h-1)	-	-	0.291 (21%)
k31 (h-1)	-	-	0.0787 (22%)
t1/2 distribution 1 (h)	-	-	0.18
t1/2 distribution 2 (h)	-	-	2.7
t1/2 terminal	-	-	14.7

Source: Sequence 0001, module 5335, purdue-nalm-report-finalv1-0-pkonly-05dec2023.pdf, page 61 to 62.
Abbreviations: %dose = percentage of dose associated with zero-order or first-order absorption ([% dose undergoing first-order absorption] + [% dose undergoing zero-order absorption] = 1 within each dosage form), abs = absorption, Cov = covariate, Geomean = geometric mean, GeoCV = geometric coefficient of variation, h = hour, HGT = height, k0 = zero-order rate, k10 = elimination rate, k12, k13 = rates of drug distribution from central compartment to 1st and 2nd peripheral compartments, k21, k31 = rates of drug distribution from 1st and 2nd peripheral compartments to the central compartment, ka = first-order rate constant, min = minutes, PK = pharmacokinetic, Ref = reference, nalmefene HCl injection product, Test = Nalmefene Auto-Injector product, t1/2 = half-life, tlag1, tlag2 = lag time associated with first-order (1) or zero-order (2) absorption process, Vc/F = apparent central volume of distribution, WGT = weight.

Key diagnostics plots are presented below.

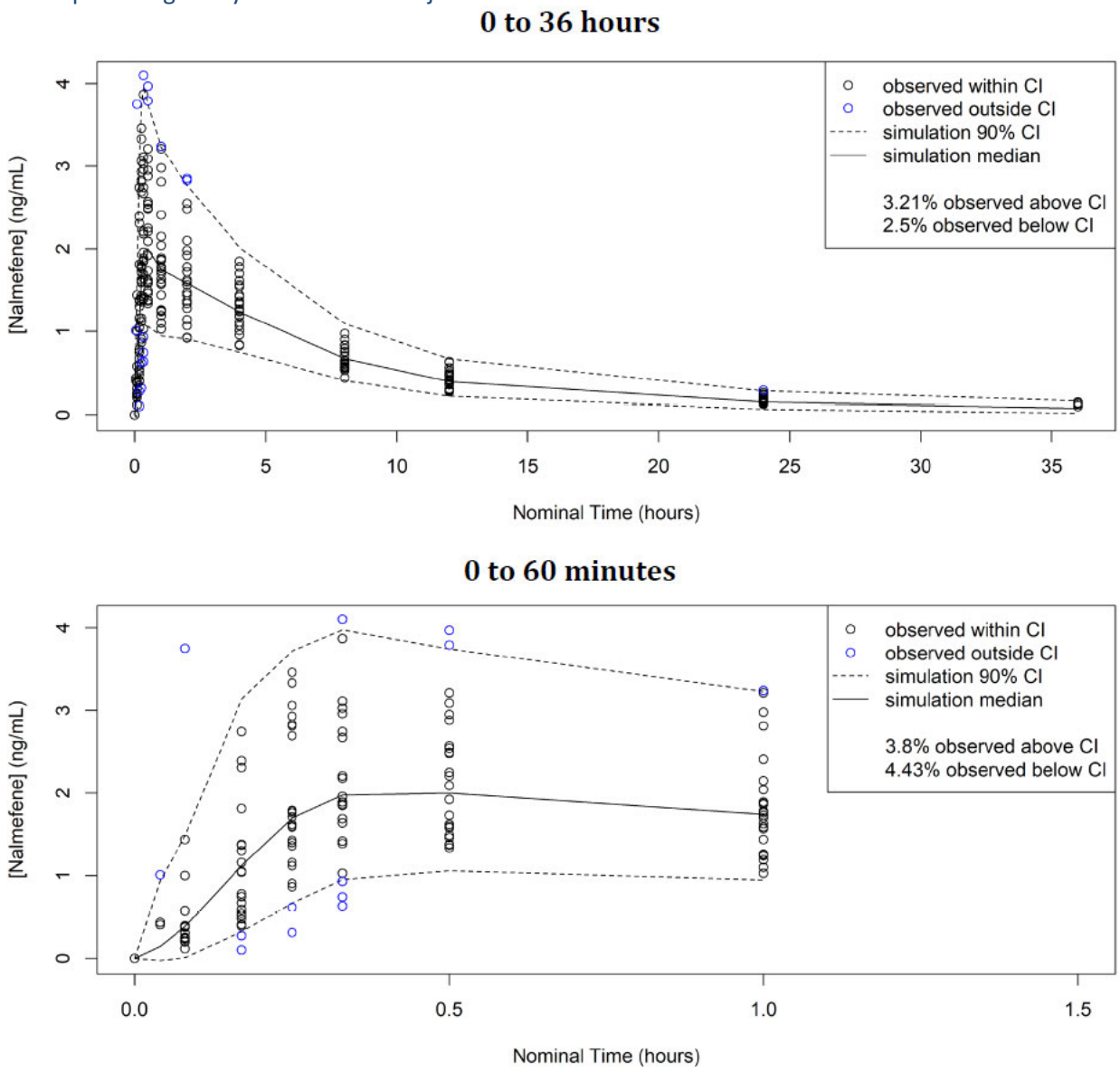
Figure 10: Goodness of fit plots for the final nalmefene PPK model.



Source: Sequence 0001, module 5335, purdue-nalm-report-finalv1-0-pkonly-05dec2023.pdf, page 59 to 60.

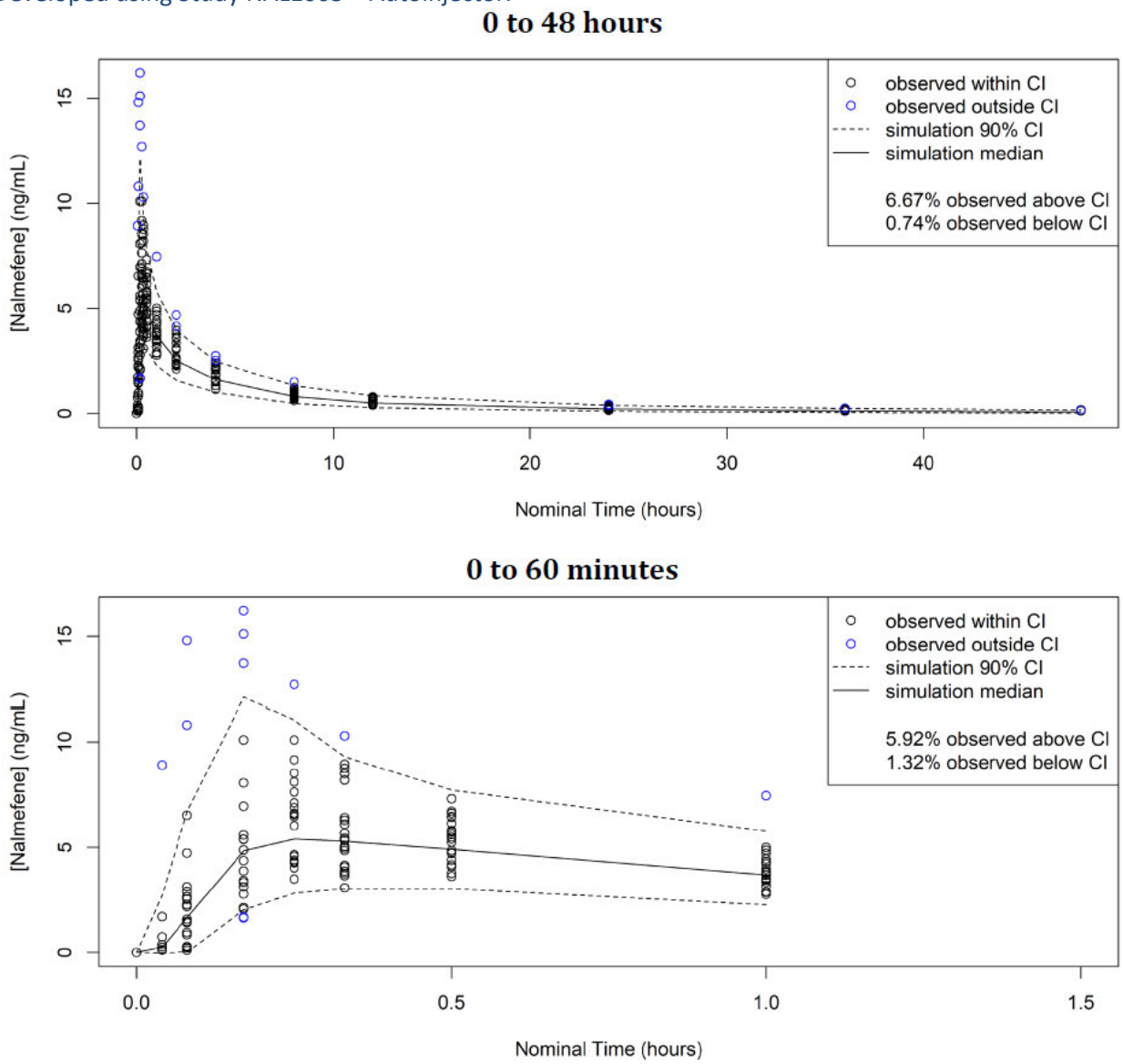
A visual predictive check (VPC) for the final nalmefene PPK model is presented in figure xxx for the IM injection and figure xx for the autoinjector.

Figure 11: Visual Predictive Checks Associated with the Final Nalmefene PPK Model (Model 704) Developed using Study NAL1005 – IM Injection.



Source: Sequence 0001, module 5335, purdue-nalm-report-finalv1-0-pkonly-05dec2023.pdf, page 63.

Figure 12: Visual Predictive Checks Associated with the Final Nalmefene PPK Model (Model 704) Developed using Study NAL1005 – Autoinjector.



Source: Sequence 0001, module 5335, purdue-nalm-report-finalv1-0-pkonly-05dec2023.pdf, page 64.

The eta shrinkage values are generally low (except for the rate constants for transfer between parent and peripheral compartments which range from 55% to 66%). Based on diagnostic plots in ***Figure 10***, there are no obvious signs of bias with respect to concentration magnitude nor time. Most of the conditional weighted residuals are within ± 2 standard deviations. The VPC (***Figure 11*** and ***Figure 12***) describes the data well for both formulations. **Overall, the PPK model is acceptable.**

4.4.2 Population PK Simulation

The Applicant conducted simulations of covariate effects in document purdue-nalm-report-finalv1-0-pkonly-05dec2023.pdf as well as simulations of repeat dosing in document repeat-dose-pk-report-non-parametric-simulation.pdf.

Simulated Covariate Effects

The Applicant conducted simulations to assess the effect of perturbations of the covariates included in the final PPK model (weight and height) on predicted nalmefene plasma PK. The Applicant used weight and height combinations published by the CDC[1] to create the virtual subjects for each of 1000 subjects at each selected age (12, 15, 17 years, and adult). ***Table 15*** shows a summary of the weight and age values of the virtual subjects in the PK simulations.

Table 15: Weight and Height used in Simulations of Nalmefene PK Profile in Adult and Pediatric Populations.

Age (years)	Weight (kg) Median* (range)*	Height (cm) Median* (range)*
12	49 (33 to 71)	154 (141 to 167)
15	62 (46 to 105)	166 (153 to 182)
17	69 (50 to 104)	169 (155 to 185)
Adults	76** (53.9 to 119.4)	171** (152.5 to 184.7)

Source: Sequence 0001, module 5335, purdue-nalm-report-finalv1-0-pkonly-05dec2023.pdf, page 65.

*Median values in children were approximated based on the average of 50th male and 50th female percentiles, as published by the CDC. The ranges in children and adults were based on the 10th and 90th percentiles of females and males for the different age categories, as published by the CDC. The value for the 10th percentile was the smallest of the female and male values. The value of the 90th percentile was the largest of the female and male values.

**Median values from data in Study NAL1005

The simulations involved a virtual single administration of 1.5 mg AI or a 1.0 mg IM injection to adult and pediatric patients. Nalmefene plasma concentrations were predicted out to 48 hours after the single administration. The simulated PK data were then analyzed using noncompartmental analyses. The geometric mean values of Cmax and AUC0-t were computed and summarized across the population as well as by weight quartile, height quartile, and age group.

[1] Fryar CD, Carroll MD, Gu Q, Afful Jo, Ogden CL, "Anthropometric reference data for children and adults: United States, 2015-2018. Series : Vital and health statistics. Series 3, Analytical and epidemiological studies ; no. 46," January 2021. [Online]. Available: https://stacks.cdc.gov/view/cdc/100478. [Accessed 2023 Oct 27].

Table 16: Effect of Weight on Simulated Nalmefene PK.

Single Dose NAI 1.5 mg		
Adult Grouping	**Geomean Cmax (ng/mL)**	**Geomean AUC0-t (ng.h/mL)**
1st quartile	8.87	28.5
4th quartile	6.39	22.2
Full dataset	7.54	25.1
% Difference (vs. full dataset)		
Adult Grouping	**Cmax**	**AUC0-t**
1st quartile	17.6	13.4
4th quartile	-15.3	-11.8

Single Dose Nalmefene HCL Injection 1.0 mg		
Adult Grouping	**Geomean Cmax (ng/mL)**	**Geomean AUC0-t (ng.h/mL)**
1st quartile	3.60	20.0
4th quartile	2.21	14.3
Full dataset	2.85	17.0
% Difference (vs. full dataset)		
Adult Grouping	**Cmax**	**AUC0-t**
1st quartile	26.4	17.7
4th quartile	-22.4	-16.0

Source: Sequence 0001, module 5335, purdue-nalm-report-finalv1-0-pkonly-05dec2023.pdf, page 66.
Abbreviations: AUC0-t = area under the curve from time 0 to the last measurable time point (t), Cmax = maximum concentrations, Geomean = geometric mean, NAI = Nalmefene Auto-Injector.

Table 17: Effect of Height on Simulated Nalmefene PK.

Single Dose NAI 1.5 mg		
Adult Grouping	**Geomean Cmax (ng/mL)**	**Geomean AUC0-t (ng.h/mL)**
1st quartile	7.95	25.7
4th quartile	7.16	24.4
Full dataset	7.54	25.1
% Difference (vs. full dataset)		
Adult Grouping	**Cmax**	**AUC0-t**
1st quartile	5.4	2.3
4th quartile	-5.1	-2.7

Single Dose Nalmefene HCL Injection 1.0 mg		
Adult Grouping	**Geomean Cmax (ng/mL)**	**Geomean AUC0-t (ng.h/mL)**
1st quartile	3.39	18.8
4th quartile	2.36	15.5
Full dataset	2.85	17.0
% Difference (vs. full dataset)		
Adult Grouping	**Cmax**	**AUC0-t**
1st quartile	19.1	10.2
4th quartile	-17.0	-8.9

Source: Sequence 0001, module 5335, purdue-nalm-report-finalv1-0-pkonly-05dec2023.pdf, page 66.
Abbreviations: AUC0-t = area under the curve from time 0 to the last measurable time point (t), Cmax = maximum concentrations, Geomean = geometric mean, NAI = Nalmefene Auto-Injector.

The applicant concludes the following regarding the effect of weight and height:

- compared to the geometric mean PK values across the full population in the PK dataset:
  - 1st quartile of weight (54.0 to 67.3 kg) is expected to have:
    - 17.6% higher Cmax and 13.4% higher AUC0-t for 1.5 mg AI
    - 26.4% higher Cmax and 18% higher AUC0-t for 1.0 mg IM
  - 4th quartile of weight (86.8 to 117.1 kg) is expected to have:
    - 15% lower Cmax and 12% lower AUC0-t for 1.5 mg AI
    - 22% lower Cmax and 16% lower AUC0-t for 1.0 mg IM
- Results for height show the same trend as seen for those of weight, but to a lesser extent.

Table 18: Simulated Nalmefene PK by Age Group.

Single Dose NAI 1.5 mg			
Age group	Geomean Cmax (ng/mL)	Median Tmax (min)	Geomean AUC0-t (ng.h/mL)
12y	9.58	17.0	28.8
15y	8.55	17.0	27.5
17y	8.13	18.0	26.1
Adults	7.54	18.0	25.1
% Difference (vs. adult)			
Age group	Cmax	Tmax	AUC0-t
12y	27.0	-5.7	14.8
15y	13.4	-5.7	9.7
17y	7.7	0.0	4.0

Single Dose Nalmefene HCL Injection 1.0 mg			
Age group	Geomean Cmax (ng/mL)	Median Tmax (min)	Geomean AUC0-t (ng.h/mL)
12y	4.67	28.0	23.3
15y	3.47	26.0	19.8
17y	3.17	25.0	18.2
Adults	2.85	25.0	17.0
% Difference (vs. adult)			
Age group	Cmax	Tmax	AUC0-t
12y	64.0	12.0	36.8
15y	21.8	3.8	16.1
17y	11.5	0.0	7.1

Source: Sequence 0001, module 5335, purdue-nalm-report-finalv1-0-pkonly-05dec2023.pdf, page 70.
Abbreviations: AUC0-t = area under the curve from time 0 to the last measurable time point (t), Cmax = maximum concentrations, Geomean = geometric mean, NAI = Nalmefene Auto-Injector.

The Applicant concludes that, compared to adults (median weight and height of 76 kg and 171 cm, respectively), when receiving an identical dose:

- 12-year-old subjects (median weight and height of 49 kg and 154 cm, respectively) are expected to have:
  - 27% higher Cmax and 15% higher AUC0-t for the 1.5 mg AI, and
  - 64% higher Cmax and 37% higher AUC0-t for the 1.0 mg IM.
- 15-year-old subjects (median weight and height of 62 kg and 166 cm, respectively) are expected to have:
  - 13% higher Cmax and 10% higher AUC0-t for the 1.5 mg AI, and
  - 22% higher Cmax and 16% higher AUC0-t for 1.0 mg IM.
- 17-year-old subjects (median weight and height of 69 kg and 169 cm, respectively) are expected to have:
  - 8% higher Cmax and 4% higher AUC0-t for the 1.5 mg AI, and
  - 12% higher Cmax and 7% higher AUC0-t for 1.0 mg IM.

[*Reviewer comment: The simulation methodology is acceptable. The reviewer agrees with the Applicant's conclusions. These simulations are used to inform label statements in section 12.3.*]

4.4.3 Simulations of Repeat Dosing

The document repeat-dose-pk-report-non-parametric-simulation.pdf describes PK simulations for repeat administration. The objectives of these analyses are:

- To evaluate repeat dose simulations for Nalmefene Auto-injector 1.5 mg IM (NAI),
- To evaluate repeat dose simulations for Nalmefene IV infusion labeled dose regimens, and
- To evaluate repeat dose simulations for Nalmefene 1.0 mg IM.

The Applicant utilized non-parametric superposition analysis based on PK data following 1.5 mg AI administration and 1.0 mg IM administration from Study NAL1005 assuming that:

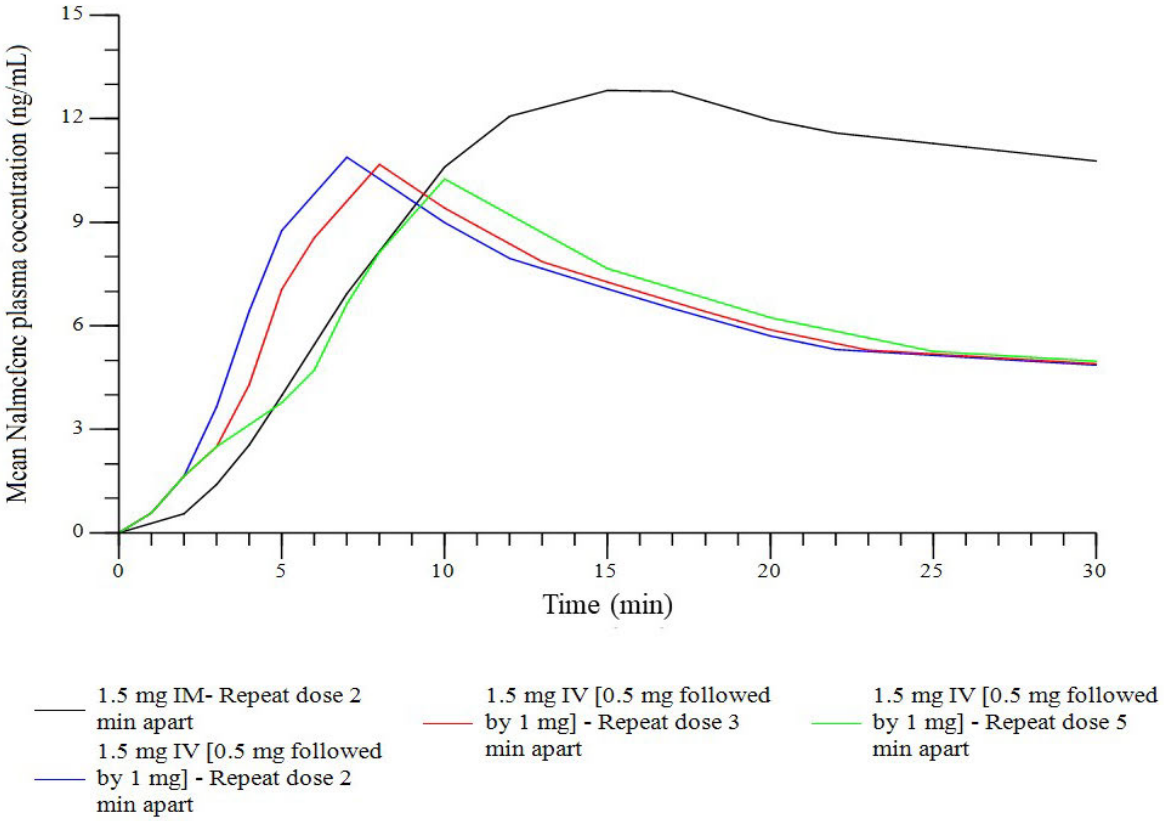
- the rate and extent of absorption and average systemic clearance are the same for each dosing interval,
- each dose of drug acts independently of every other dose, and
- linear pharmacokinetics apply

Simulations were performed using Phoenix Win-Nolin 8.3 software, non-parametric superposition module. The Applicant refers to a publication[2] of a nalmefene clinical study in which up to 4 administrations of 2 mg nalmefene IV were administered. The scenarios tested in the repeat-dose-pk-report-non-parametric-simulation.pdf report include up to 4 administrations of nalmefene AI and up to 4 administrations of nalmefene IV according.

[2] Kaplan JL, Marx JA, Calabro JJ, Gin-Shaw SL, Spiller JD, Spivey WL, Gaddis GM, Zhao N, Harchelroad FP Jr. Double-blind, randomized study of nalmefene and naloxone in emergency department patients with suspected narcotic overdose. Ann Emerg Med. 1999 Jul;34(1):42-50. doi: 10.1016/s0196-0644(99)70270-2. PMID: 10381993.

depicts PK following two administrations of 1.5 mg AI administered 2 minutes apart compared with two nalmefene IV infusions (0.5 mg followed by 1.0 mg) administered 2, 3, and 5 minutes apart.

Figure 13: Simulated PK Profile for Two Administrations of 1.5 mg Nalmefene AI (2 minutes apart) Compared to Two IV Infusion Nalmefene Administrations (0.5 mg followed by 1.0 mg) administrated 2, 3 and 5 Minutes Apart.



Source: Sequence 0001, module 5354, repeat-dose-pk-report-non-parametric-simulation.pdf, page 38.

The corresponding PK parameters for this scenario are presented in ***Table 19***.

Table 19: Mean ± SD Systemic Exposure for Two Administrations of 1.5 mg Nalmefene AI (2 minutes apart) Compared to Two IV Infusion Nalmefene Administrations (0.5 mg followed by 1.0 mg) administrated 2, 3 and 5 Minutes Apart.

Parameter	Nalmefene Auto-injector 1.5 mg	Nalmefene IV		
	Mean ± SD			
	2 Repeat Doses	Repeat Dose (0.5 mg followed by 1.0 mg)		
	2 minute interval	2 minute interval	3 minute interval	5 minute interval
C_{max} (ng/mL)	15.49 ± 6.91	11.27 ± 6.30	11.02 ± 6.18	10.51 ± 5.96
AUCt * (ng.hr/mL)	60.14 ± 9.42	24.64 ± 3.77	24.64 ± 3.77	24.63 ± 3.77
$AUC_{0-\infty}$ (ng.hr/mL)	61.95 ± 10.31	26.71 ± 4.12	26.72 ± 4.13	26.72 ± 4.13

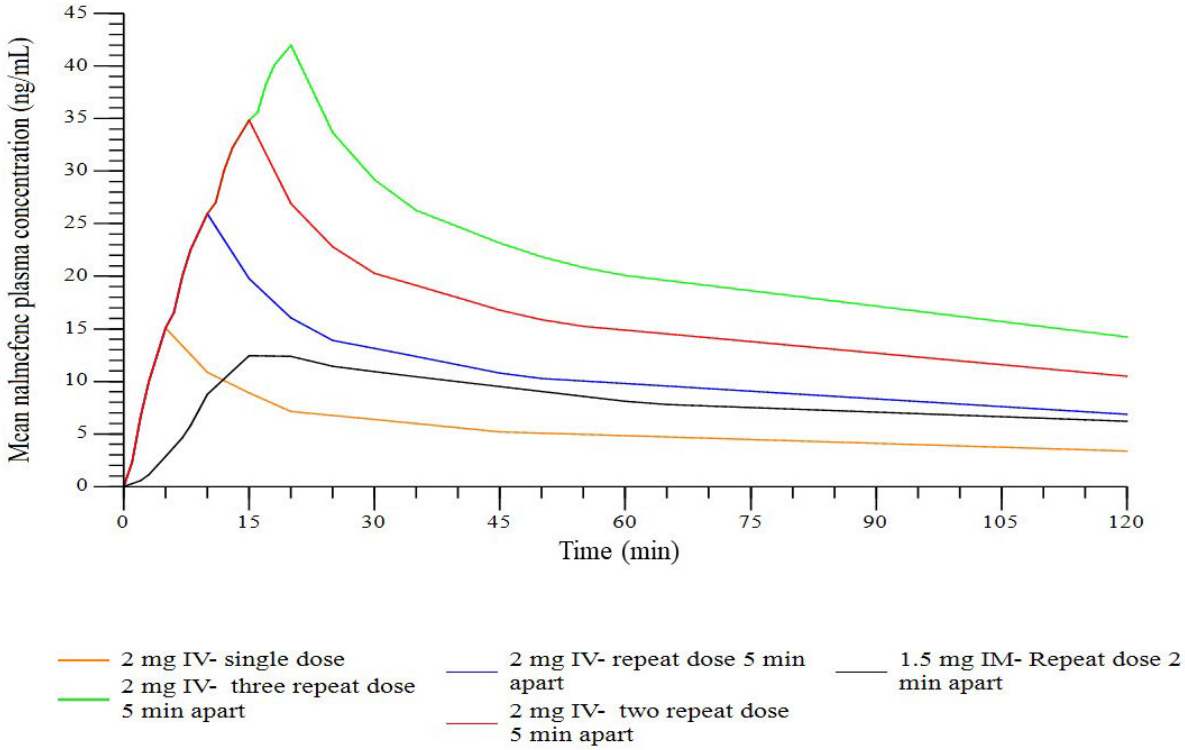
Source: Sequence 0001, module 5354, repeat-dose-pk-report-non-parametric-simulation.pdf, page 39.

*AUCt: 0-48 hours for Nalmefene Auto-injector; 0-24 hours for Nalmefene IV infusion.

Multiple AI Administrations vs Multiple IV Administrations

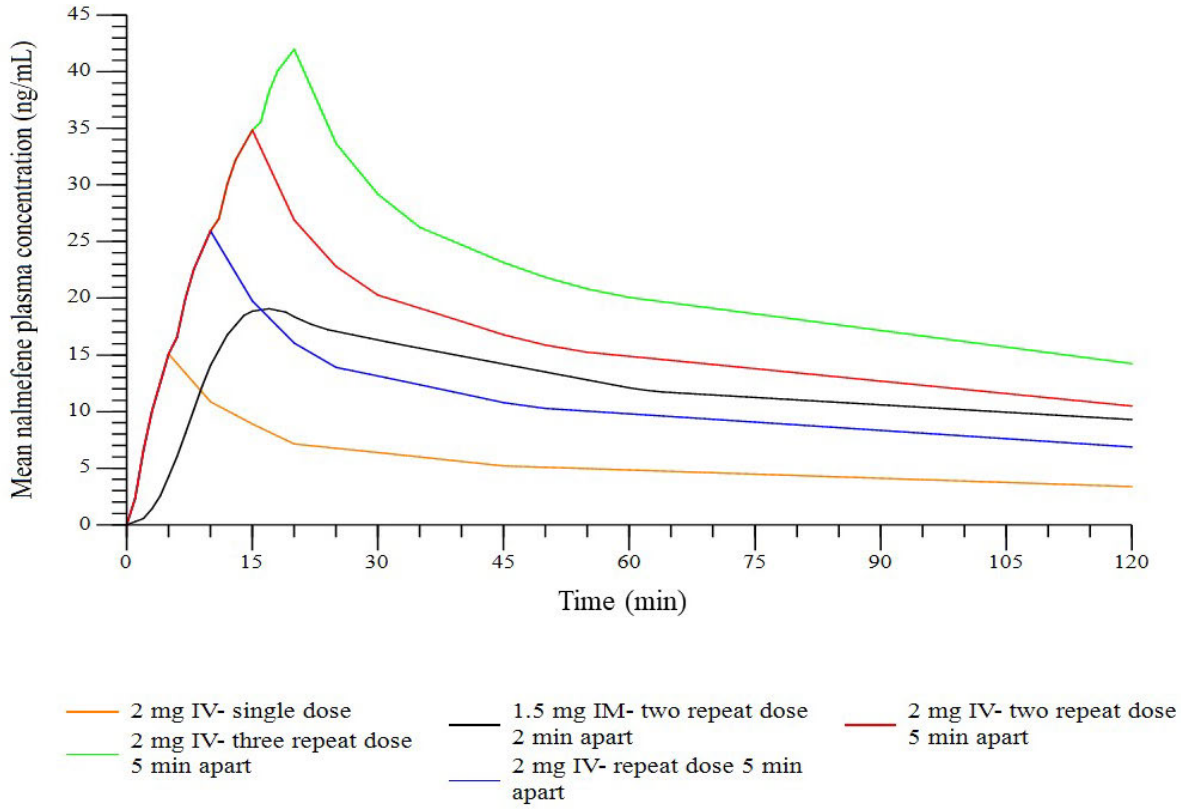
The Applicant assessed the PK of two, three, and four administrations of 1.5 mg nalmefene AI to one, two, three, and four administrations of IV nalmefene infusions. The results of these simulations are depicted in ***Figure 14***, ***Figure 15***, ***Figure 16***.

Figure 14: Simulated PK Profile for Two Administrations of 1.5 mg Nalmefene AI (2 minutes apart) Compared With One To Four IV Infusion Nalmefene Administrations (0.5 mg followed by 1.0 mg) administrated 5 Minutes Apart.



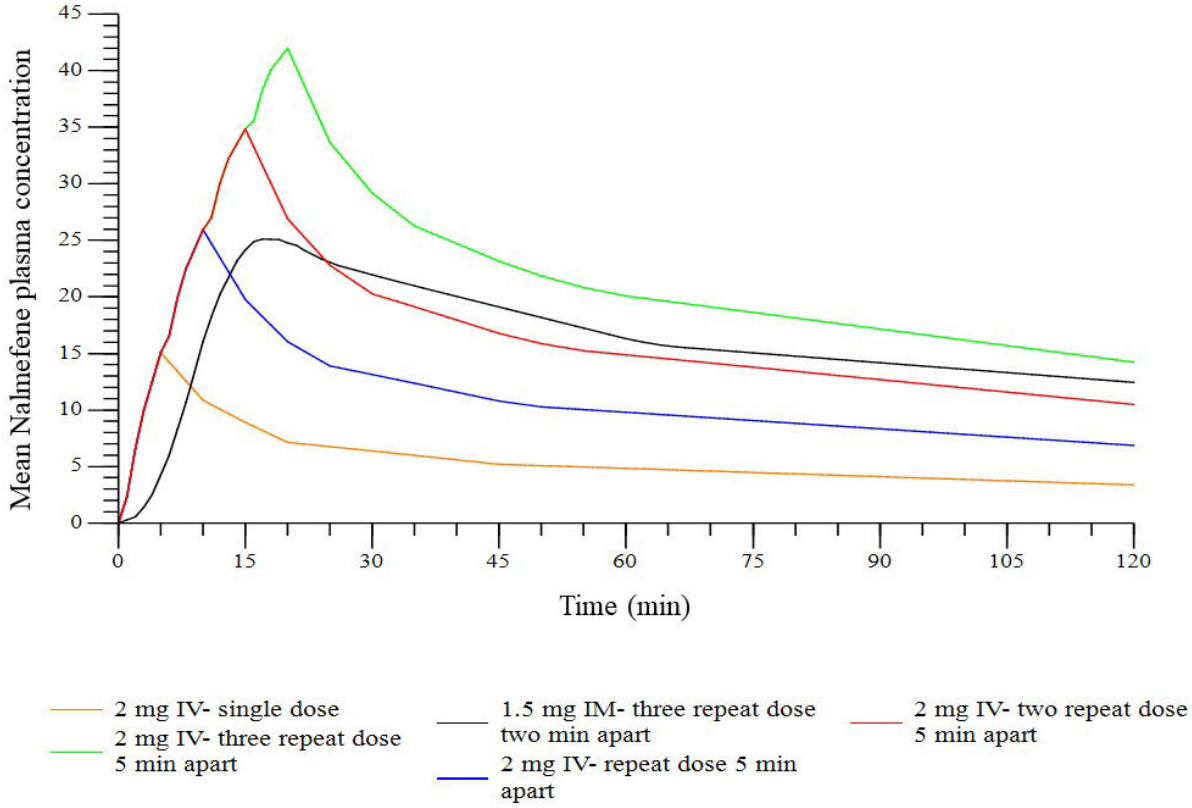
Source: Sequence 0001, module 5354, repeat-dose-pk-report-non-parametric-simulation.pdf, page 38.

Figure 15: Simulated PK Profile for Three Administrations of 1.5 mg Nalmefene AI (2 minutes apart) Compared With One To Four IV Infusion Nalmefene Administrations (0.5 mg followed by 1.0 mg) administrated 5 Minutes Apart.



Source: Sequence 0001, module 5354, repeat-dose-pk-report-non-parametric-simulation.pdf, page 41.

Figure 16: Simulated PK Profile for Four Administrations of 1.5 mg Nalmefene AI (2 minutes apart) Compared With One To Four IV Infusion Nalmefene Administrations (0.5 mg followed by 1.0 mg) administrated 5 Minutes Apart.



Source: Sequence 0001, module 5354, repeat-dose-pk-report-non-parametric-simulation.pdf, page 42.

The corresponding PK parameters for these scenarios are summarized presented in ***Table 20***.

Table 20: Mean ± SD Systemic Exposure for Two to Four Administrations of 1.5 mg Nalmefene AI (2 minutes apart) Compared With Two To Four IV Infusion Nalmefene Administrations (0.5 mg followed by 1.0 mg) administrated 5 Minutes Apart.

Parameter	Nalmefene Auto-injector 1.5 mg			Nalmefene 2mg IV (Kaplan 1999)		
	Mean ± SD			Mean ± SD		
	Repeat doses			Repeat doses		
	2 doses	3 doses	4 doses	2 doses	3 doses	4 doses
	2 minute interval			5 minute interval		
C_{max} (ng/mL)	15.49 ± 6.91	22.27 ± 9.34	28.62 ± 11.52	26.53 ± 15.33	35.58 ± 18.06	42.59 ± 19.09
AUCt * (ng.hr/mL)	60.14 ± 9.42	90.20 ± 14.13	120.27 ± 18.84	65.69 ± 10.06	98.50 ± 15.08	131.29 ± 20.10
$AUC_{0-\infty}$ (ng.hr/mL)	61.95 ± 10.31	92.93 ± 15.46	123.91 ± 20.61	71.25 ± 11.0	106.92 ± 16.51	142.61 ±22.01

Source: Sequence 0001, module 5354, repeat-dose-pk-report-non-parametric-simulation.pdf, page 43. *AUCt: 0-48 hours for Nalmefene Auto-injector; 0-24 hours for Nalmefene IV. Note: Nalmefene Auto-injector 1.5 mg administration 2 minutes apart represents the highest systemic exposure which can be compared to Nalmefene IV infusion administration 5 minutes apart, which results in the lowest predicted Cmax of the IV infusion regimens evaluated.

The Applicant concludes Nalmefene Auto-injector 1.5 mg IM repeat dose (up to 4 repeat doses 2 min apart) PK exposure is bracketed by up to 4 repeat doses of Revex IV described in Revex LD label and Kaplan 1999 article.

[Reviewer comment: The repeat dose simulation methodology is reasonable. ***Figure 13*** suggest that two administrations of 1.5 mg AI two minutes apart are expected to produce higher plasma PK than two IV infusions of nalmefene (0.5 mg followed by 1.0 mg). According to ***Table 19***, the two 1.5 mg AI administrations two minutes apart produce a mean Cmax of 15.49 ng/mL whereas the two IV infusions of 0.5 mg followed by 1.0 mg two minutes later produce mean Cmax of 11.27 ng/mL.

The Kaplan 1999 article describes a study where 2 mg nalmefene (Revex) is administered via infusion up to 4 times. ***Table 20*** shows a comparison of two to four administrations of 1.5 mg AI with two to four administrations of 2 mg nalmefene via IV infusion. Overall, repeat administrations of 1.5 mg nalmefene AI generate lower Cmax and AUC compared to the same number of repeat administrations of 2 mg nalmefene IV infusion. For example, according to ***Table 20***, the mean Cmax and mean AUC0-t for two

administrations of 1.5 mg nalmefene AI are 15.49 ng/mL and 60.14 ng*h/mL (respectively) and for two infusions of 2 mg IV infusion are 26.53 ng/mL and 65.69 ng*hr/mL (respectively).

The current Revex label recommends an initial dose of 0.5 mg/70 kg followed by a 1 mg/70 kg 2 to 5 minutes later. As the mean weight in Study NAL1005 is 76.5 mg, then the 2 mg IV infusion in these simulations is likely to exceed the nalmefene plasma concentrations when dosed according to the current Revex label recommendations.]

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/s/

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