# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 215457Orig1s000

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

# Office of Clinical Pharmacology Review

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| **NDA or BLA Number** | 215457 |
| **Link to EDR** | \\CDSESUB1\evsprod\NDA215457\0001 |
| **Submission Date** | 8/31/2021; PDUFA date: 2/31/2022 |
| **Submission Type** | Priority; 505(b)(2) to Narcan (naloxone hydrochloride) injection (NDA 016636) |
| **Brand Name** | Naloxone Auto-Injector 10 mg |
| **Generic Name** | - |
| **Dosage Form and Strength** | Solution for Injection; 10 mg |
| **Route of Administration** | Intramuscular or subcutaneous injection |
| **Proposed Indication** | (b) (4) |
| **Dosage Regimen** | • Naloxone Auto-injector 10 mg is for intramuscular or subcutaneous use only.<br>• Seek emergency medical care immediately after use.<br>• Administer Naloxone Auto-injector 10 mg to patients 12 years of age and older into the anterolateral aspect of the thigh, through clothing if necessary.<br>• If the patient relapses into respiratory or central nervous system depression after the first dose of Naloxone Auto-injector 10 mg, additional naloxone HCl may be administered.<br>• Additional supportive and/or resuscitative measures may be helpful. |
| **Applicant** | Kaleo, Inc |
| **Associated IND** | IND 112292 |
| **OCP Reviewer** | Wei Qiu, Ph.D. |
| **OCP Team leader** | Yun Xu, Ph.D. |
| **DPM Reviewer** | Vishnu Sharma, Ph.D. |
| **DPM Team leader** | Atul Bhattaram, Ph.D. |
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| **DARS Team leader** | Jeffry Florian, Ph.D. |

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# 1. EXECUTIVE SUMMARY

## 1.1 Recommendations

The Office of Clinical Pharmacology/Division of Neuropsychiatric Pharmacology (OCP/DNP), OCP/Division of Pharmacometrics (DPM) and OCP/Division of Applied Regulatory Science (DARS) has reviewed the information submitted in the current application, NDA 215457, for Naloxone Auto-injector 10 mg, submitted on 8/31/2021. From a clinical pharmacology perspective, the information submitted in the NDA submission is acceptable.

| **Review Issue** | **Recommendations and Comments** |
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| **Pivotal or supportive evidence of effectiveness** | In the dose proportionality study (KA-900DV-002), a single dose of the proposed naloxone auto-injector 10 mg (NAI 10 mg) exhibited greater naloxone concentrations in the early absorption phase (e.g., 2.5, 5 min post-dose) through the entire 12-hour sampling period, 6-fold greater Cmax, and 5.5-fold greater AUC0-t and AUC0-inf values than a single dose of naloxone auto-injector 2 mg (NAI 2 mg approved under NDA 209862). Naloxone AUC0-t and AUC0-inf values were dose proportional while naloxone Cmax values were slightly greater than dose proportional for the comparison of NAI 10 mg and NAI 2 mg.<br><br>The FDA's independent modeling & simulation supports the sponsor's claim that administration of NAI 10 mg resulted in a higher percentage of subjects recovering from respiratory depression for middle and high opioid doses compared to NAI 2 mg. However, for middle and high overdose of carfentanil, the NAI 10 mg product needs to be administered as early as possible (e.g., immediately with suspected opioid exposure, or with early signs of respiratory depression) to achieve a higher rescue percentage than NAI 2 mg. In addition, the FDA's independent modeling & simulation supported the sponsor's second claim that administration of NAI 10 mg prior to fentanyl or carfentanil exposure can prevent rapid and profound opioid-induced respiratory depression. |
| **Tentative Revised Indications by the Review Team** | (b) (4) NALOXONE HYDROCHLORIDE injection is indicated in patients 12 years of age and older for<br>• emergency treatment of known or suspected opioid overdose in military and civilian first responders or victims, 12 years of age and older, in mass casualty situations with known or suspected airborne exposures to high potency opioids such as fentanyl analogues.<br>• the prophylaxis of respiratory and/or central nervous system depression in military or civilian first responders entering an area believed to contain aerosolized high potency opioids.<br>(b) (4) |

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| | (b) (4) |
| **General dosing instructions** | • Administer Naloxone Auto-injector 10 mg as quickly as possible because prolonged respiratory depression may result in damage to the central nervous system or death.<br>• Since the suspected opioid exposure may occur outside of supervised medical settings: Seek immediate emergency medical assistance after administration of the first dose of Naloxone Auto-injector 10 mg, keep the patient under continued surveillance until medical care is available, if the patient does not show some improvement after administering the dose of Naloxone Auto-injector 10 mg, consider if the respiratory depression is due to a non-opioid etiology, if the patient exhibits renarcotization after the first dose of Naloxone Auto-injector 10 mg, administer additional naloxone HCl, as necessary, until emergency medical assistance becomes available<br>• Do not attempt to reuse Naloxone Auto-injector 10 mg.<br>• Periodically visually inspect Naloxone Auto-injector 10 mg through the viewing window for particulate matter. Request a replacement if the solution is cloudy or contains particles, or if the glass container is damaged. If a replacement is not readily available, the benefit of naloxone treatment in known or suspected exposure of opioids may outweigh the risks.<br>• Once the red safety guard is removed, Naloxone Auto-injector 10 mg must be used immediately or disposed of properly. Do not attempt to replace the red safety guard once it is removed.<br>• Naloxone Auto-injector 10 mg must be administered according to the printed instructions on the device label.<br>• Upon actuation, Naloxone Auto-injector 10 mg automatically inserts the needle intramuscularly or subcutaneously, delivers the naloxone HCl injection, and retracts the needle into the device.<br>• Post-injection, the black base locks in place and a red indicator appears in the drug viewing window.<br><br>Edits are made on the general dosing instructions by the review team. See Section 2.4 of this review for more details. |
| **Dosing in patient subgroups (intrinsic and extrinsic factors)** | Same as Narcan (naloxone hydrochloride) injection (NDA 016636) |

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| **Labeling** | Edits are made on presentation of pharmacodynamics in Section 12.2 of the proposed label. See section 2.4 of this review for more details. |
| **Bridge between the to-be-marketed and clinical trial formulations** | The final to-be-marketed formulation was used in the dose proportionality study KA-900DV-002. |
| **Other (specify)** | Not applicable. |

## 2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

(1) In the dose proportionality study (KA-900DV-002), a single dose of the proposed naloxone auto-injector 10 mg (NAI 10 mg) exhibited greater naloxone concentrations in the early absorption phase (e.g., 2.5, 5 min post-dose) through the entire 12-hour sampling period, 6-fold greater Cmax, and 5.5-fold greater AUC0-t and AUC0-inf values than a single dose of naloxone auto-injector 2 mg (NAI 2 mg approved under NDA 209862). Naloxone AUC0-t and AUC0-inf values were dose proportional while naloxone Cmax values were slightly greater than dose proportional for the comparison of NAI 10 mg and NAI 2 mg.

(2) The FDA's independent modeling & simulation supports the sponsor's claim that administration of NAI 10 mg resulted in a higher percentage of subjects recovering from respiratory depression for middle and high opioid doses compared to NAI 2 mg. However, for middle and high overdose of carfentanil, the NAI 10 mg product needs to be administered as early as possible (e.g., immediately with suspected opioid exposure, or with early signs of respiratory depression) to achieve a higher rescue percentage than NAI 2 mg. In addition, the FDA's independent modeling & simulation supported the sponsor's second claim that administration of NAI 10 mg prior to fentanyl or carfentanil exposure can prevent rapid and profound opioid-induced respiratory depression.

- **Regulatory History**

In Naloxone Auto-Injector 10 mg (naloxone HCl injection USP) (NAI 10 mg), a new dosage strength for the NAI products, was developed in collaboration with the Department of Defense (DoD) to serve as a medical countermeasure against opioids, including synthetic ultra-potent opioids. At the Pre-NDA meeting held on February 24, 2020, the Applicant proposed a dose proportionality study of NAI 10 mg using the approved NAI 2 mg as the reference product. The Applicant was recommended to characterize the early exposure because onset of action is critical for reversal of opioid overdose. In addition, NAI 10 mg was expected to have higher systemic exposure than the reference product, therefore, justification may be required to demonstrate the higher systemic exposure would not pose a safety concern. In the Advice/Information Request letter dated December 29, 2020, the Applicant was recommended that "To support use of your product for reversal of highly potent opioids, conduct mechanistic pharmacokinetic and pharmacodynamic modeling that demonstrates whether a timely reversal of opioid effects is possible with your product across a range of different opioids and doses…". Advice on the Applicant's mechanistic PK-PD modeling Data Analysis Plan was provided to the Applicant on April 28, 2021 and July 12, 2021.

The Applicant submitted a 505(b)(2) NDA 215457 for NAI 10 mg and proposed to rely on the FDA's previous finding of safety and efficacy for Narcan (naloxone hydrochloride) injection (NDA 016636). The Applicant conducted a comparative bioavailability study (Study IJ-900DV-03O) to establish a scientific bridge between NAI 0.4 mg (NDA 205787) and Narcan (NDA 016636), which was used to support approval of NDA 205787 for the indication of emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. Because the original NDA 016636 for Narcan injectable was withdrawn not for reasons of safety or efficacy, a generic product (ANDA 072076) to the original NDA was used as the comparator in the comparative bioavailability study to establish the scientific bridge. The Applicant then conducted a dose proportionality study (Study KA-900DV-05A) between the approved NAI 0.4 mg (NDA 205787) and NAI 2 mg (NDA 209862), which was used to support approval of NDA 209862. For the current submission NDA 215457, a dose proportionality study (Study KA900DV-002) was conducted between the proposed new strength NAI 10 mg and the approved NAI 2 mg (NDA 209862) to characterize the PK of NAI 10 mg and evaluate dose proportionality of NAI 10 mg and NAI 2 mg. Refer to the clinical review regarding the systemic safety associated with the higher naloxone exposure for the proposed NAI 10 mg.

The clinical pharmacology program consists a dose proportionality study (Study KA900DV-002) comparing the proposed NAI 10 mg to the approved NAI 2 mg (NDA 209862) and a mechanistic PK-PD modeling simulation to predict reversal or delay of ventilatory depression in lethal doses of a variety of opioids, including morphine, buprenorphine, fentanyl and carfentanil (KA-910DV-002).

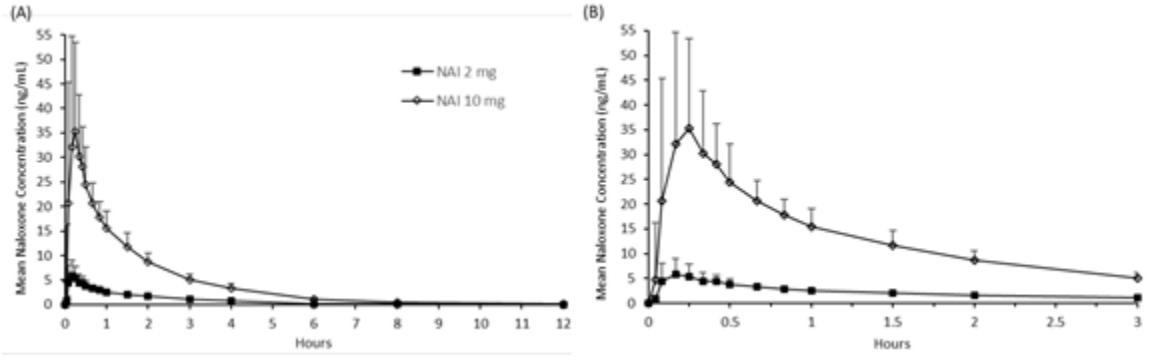
- **Summary of Pharmacokinetic Results**

Dose Proportionality of NAI 10 mg and NAI 2 mg (Results from Study KA-900DV-002)

Study KA-900DV-002 was a randomized, open-label, single-dose, two-sequence, two-period crossover study in adult male and female subjects to evaluate the dose proportionality of NAI 10 mg and NAI 2 mg. Twenty-four (24) fasted subjects received a single dose of NAI 2 mg (reference product) and NAI 10 mg (test product) in a randomized manner with at least 47-hour washout period between doses. All doses were injected into the anterolateral aspect of the thigh, so injections were either IM or SC depending on the tissue layer thickness of the subjects. Blood samples for determination of free naloxone concentrations in plasma was collected prior to dosing and at 2.5, 5, 10, 15, 20, 25, 30, 40, and 50 minutes, and 1, 1.5, 2, 3, 4, 6, 8, and 12 hours post-dose for each treatment.

The mean (± SD) naloxone plasma concentration-time profiles are shown in **Figure 1**. The PK results and statistical analysis results for dose proportionality assessment of naloxone PK parameters including Cmax, AUC0-t, and AUC0-inf are presented in **Table 1**. Naloxone Partial AUCs during the Early Absorption Phase are presented in **Table 2**. Naloxone was rapidly absorbed following IM/SC injection of NAI 2 mg and NAI 10 mg to healthy subjects. The median Tmax (min, max) was 0.17 h (0.08 to 0.67 h) and 0.26 h (0.09 to 0.67 h) for NAI 2 mg and NAI 10 mg, respectively. Naloxone was clearly from plasma rapidly with a mean half-life of approximately 1.5 hours for both doses. A single dose of NAI 10 mg exhibited greater naloxone concentrations in the early absorption phase (e.g., 2.5, 5 min post-dose) through the entire 12-hour sampling

period, 6-fold greater Cmax, and 5.5-fold greater AUC0-t and AUC0-inf values than a single dose of NAI 2 mg. Naloxone AUC0-t and AUC0-inf values were dose proportional for the comparison of NAI 10 mg and NAI 2 mg as the geometric mean ratios (90% CI) for dose-normalized naloxone AUC0-t and AUC0-inf fell within the 0.80 to 1.25 bioequivalence limits. Naloxone Cmax values were slightly greater than dose proportional as the upper 90% CI bound exceeded the upper limit of 1.25 (**Table 1**). Dose proportionality assessed by the power model showed slope point estimates close to 1.0 for naloxone Cmax, AUC0-t, and AUC0-inf.




Source: KA-900DV-002 Figure 14.2.1.1

**Figure 1** Mean (± SD) Free Naloxone Plasma Concentration-Time Profiles (A) 12-hour and (B) 3-hour for NAI 10 mg and NAI 2 mg (Study KA-900DV-002)

**Table 1** Summary of Naloxone Pharmacokinetic Parameters and Dose Proportionality Results for NAI 10 mg and NAI 2 mg (Study KA-900DV-002, N = 24)

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| Treatment | Statistic | $C_{max}$ (ng/mL) | $T_{max}$ (h) | $T_{1/2}$ (h) | $AUC_{0-t}$ (ng.h/mL) | $AUC_{0-inf}$ (ng.h/mL) |
|---|---|---|---|---|---|---|
| **Pharmacokinetic Parameters** | | | | | | |
| Reference IMP (NAI 2 mg) | Mean (SD) | 6.95 (3.11) | | 1.46 (0.16) | 9.22 (1.35) | 9.25 (1.35) |
| | %CV | 44.8 | | 11.1 | 14.6 | 14.6 |
| | Median (Min-Max) | 6.79 (2.66-12.5) | 0.17 (0.08-0.67) | 1.43 (1.16-1.77) | 9.37 (6.75-11.4) | 9.39 (6.76-11.4) |
| Test IMP (NAI 10 mg) | Mean (SD) | 42.0 (21.0) | | 1.46 (0.21) | 51.1 (9.12) | 51.3 (9.15) |
| | %CV | 49.9 | | 14.1 | 17.9 | 17.8 |
| | Median (Min-Max) | 35.0 (17.2-92.7) | 0.26 (0.09-0.67) | 1.50 (1.08-1.96) | 51.5 (36.9-73.4) | 51.6 (37.0-73.5) |
| **Statistical Assessments of Dose Proportionality** | | | | | | |
| Dose normalized 10 mg / 2 mg | GMR | 1.21 | | | 1.10 | 1.10 |
| | 90% CI for ratio | 1.07, 1.37 | | | 1.06, 1.15 | 1.06, 1.15 |
| Power Model | Slope | 1.12 | | | 1.06 | 1.06 |
| | 95% CI | 0.95, 1.29 | | | 1.00, 1.12 | 1.00, 1.12 |

Data source: KA-900DV-002 (Tables 14.2.2.1, 14.2.3.2, and 14.2.3.3)
Abbreviations: CI = confidence interval; %CV = percent coefficient of variation; GMR = geometric mean ratio; Min = minimum; Max = maximum; NAI = naloxone auto-injector; SD = standard deviation

**Table 2** Summary of Naloxone Partial AUCs during the Early Absorption Phase (KA-900DV-002, N = 24)

| Treatment | Statistic | $AUC_{0-2.5min}$ (ng.h/mL) | $AUC_{0-5min}$ (ng.h/mL) | $AUC_{0-10min}$ (ng.h/mL) | $AUC_{0-15min}$ (ng.h/mL) |
|---|---|---|---|---|---|
| Reference IMP (NAI 2 mg) | Mean (SD) | 0.016 (0.016) | 0.114 (0.101) | 0.520 (0.358) | 0.980 (0.555) |
| | %CV | 101.4 | 89.2 | 68.9 | 56.6 |
| | Median (Min-Max) | 0.012 (0.001-0.060) | 0.0769 (0.009-0.367) | 0.432 (0.061-1.290) | 0.916 (0.167-2.090) |
| Test IMP (NAI 10 mg) | Mean (SD) | 0.099 (0.247) | 0.618 (0.921) | 2.770 (2.760) | 5.550 (4.290) |
| | %CV | 248.4 | 148.9 | 99.8 | 77.3 |
| | Median (Min-Max) | 0.029 (0.003-1.210) | 0.224 (0.027-4.260) | 1.570 (0.210-10.80) | 4.100 (0.715-16.10) |

Data source: KA-900DV-002 (Table 14.2.2.1)
Abbreviations: %CV = percent coefficient of variation; IMP = investigational medicinal product; Min = minimum; Max = maximum; NAI = naloxone auto-injector; SD = standard deviation

- **Summary of PK-PD Modeling Results**

FDA conducted independent modeling and simulation to evaluate conclusions in the Applicant's mechanistic PK-PD analysis regarding the following two questions:

- The efficacy of the intramuscular (IM) naloxone auto-injector (NAI) 10 mg product in reversing opioid-induced respiratory depression in comparison to that of NAI 2 mg.
- The utility of prophylactic administration of NAI 10 mg to prevent opioid-induced respiratory depression.

The FDA model is comprised of multiple components (sub-models). The naloxone PK component of the FDA's model is the same as the Applicant's (both based on study KA-900DV-002). The aim of this independent modeling approach was to further increase the credibility of using the modeling approach to evaluate naloxone dosing schemes. The key differences between the FDA's and Applicant's modeling approaches are reported in **Table 3**.

**Table 3** Key differences between the FDA model and the model used by the Applicant

| | **FDA Model** | **Sponsor Model** |
|---|---|---|
| **Simulated Physiological Conditions** | Poikilocapnic (breathing room air)<br>Isocapnic (end-tidal CO2 fixed) | Isocapnic (end-tidal CO2 fixed) |
| **Definition of Rescue** | Cardiac arrest prevented | Minute ventilation above certain percentage of baseline |
| **Timing of the 1st naloxone dose after opioid exposure** | 1 min after minute ventilation below 40% - 90% of baseline | Immediately after minute ventilation below 40% of baseline |
| **Carfentanil IV PK model** | Fentanyl PK model adjusted based on Minkowski et al. 2011 | Rabbit and rat PK model extrapolated to human |
| **Opioid inhalation route considered?** | Yes | No |
| **Model validation** | Clinical data not seen during model calibration were used for model validation | No strict separation between model calibration and validation |

The FDA's independent evaluation supports the Applicant's claim that administration of NAI 10 mg resulted in a higher percentage of subjects recovering from respiratory depression for middle and high opioid doses compared to NAI 2 mg (**Figure 2**). However, for the middle and high overdose of carfentanil (0.154 and 0.294 mg, respectively), early naloxone dosing (e.g., 1 min after minute ventilation dropped to 90% of baseline, or even earlier dosing) might be needed for the NAI 10 mg product to achieve a significantly higher rescue percentage than NAI 2 mg (**Figures 3** and **4**). These results emphasize that reversal is dependent on the specific opioid, the amount of opioid exposure, the amount of naloxone initially administered, and the timing of the naloxone administration relative to opioid exposure.

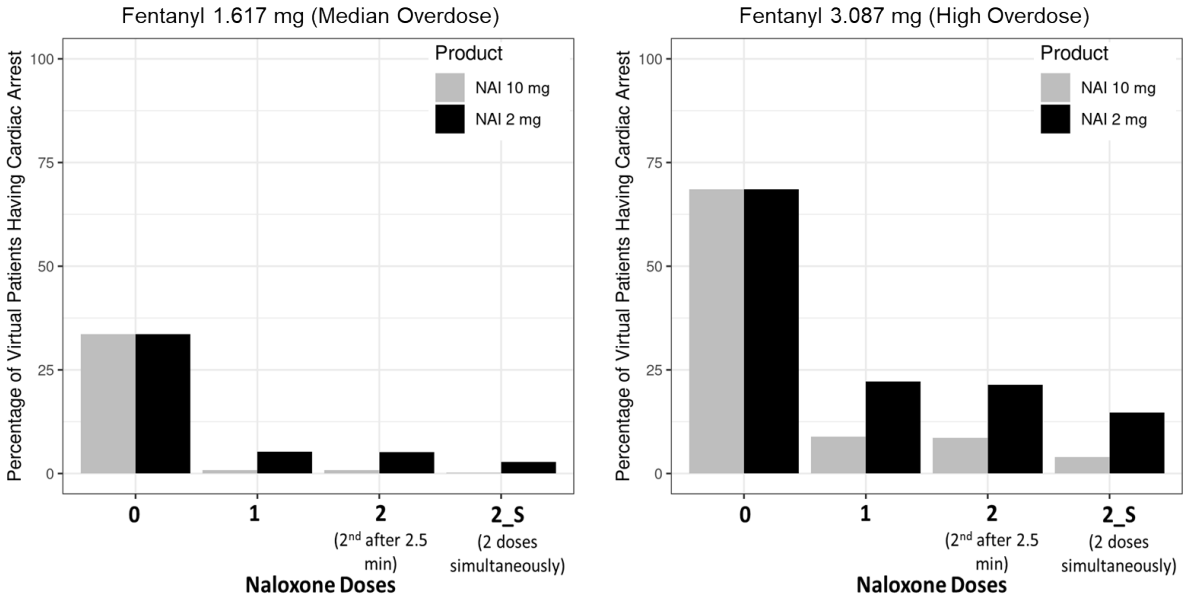


**Figure 2** Percentage of patients experiencing cardiac arrest after inhalation fentanyl exposure and followed by IM naloxone administration 1-min after ventilation is 40% of baseline. The fentanyl dose is based on Applicant-provided median (left) and high (right) dose values assuming a 70 kg body weight. Naloxone doses 0, 1, 2, 2_S represent no naloxone administration, 1 dose of naloxone, 2 doses administered 2.5 min apart, and 2 doses administered simultaneously, respectively. The simulation was based on a population of 2000 virtual patients and includes variability on opioids and naloxone pharmacokinetic parameters, as well as uncertainty in the binding kinetic parameters between the mu receptor and its agonists (opioids) and antagonists (naloxone).

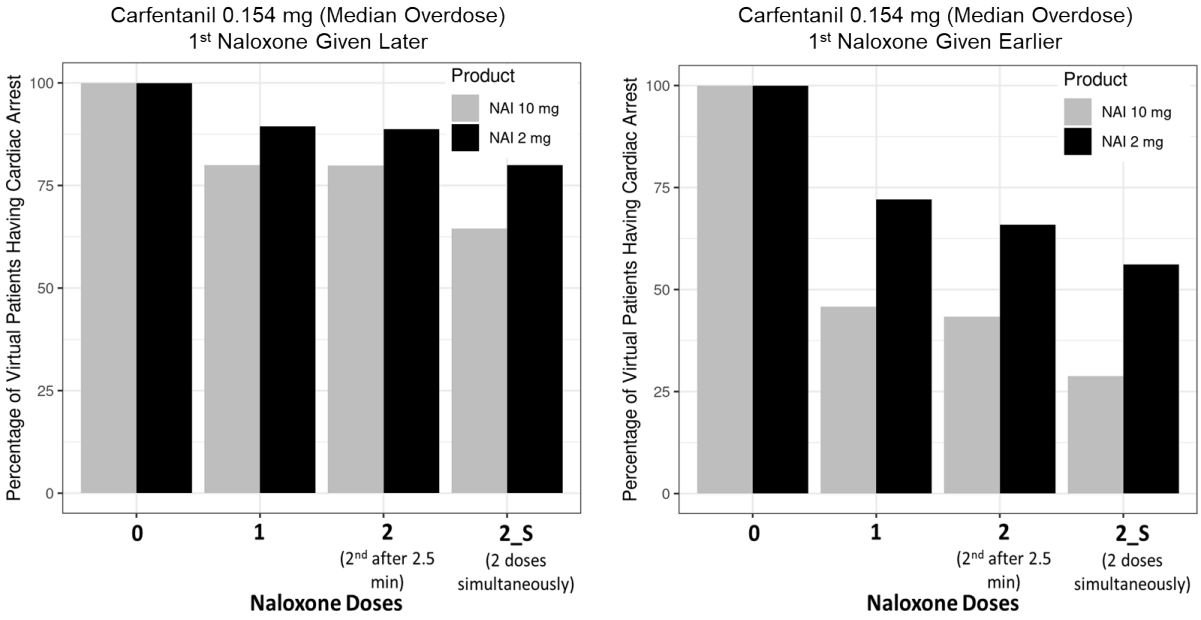


**Figure 3** Percentage of patients experiencing cardiac arrest after inhalation carfentanil median overdose exposure followed by IM naloxone administration. The 1st naloxone was administered

1 min after minute ventilation dropped to 40% (left) and 90% (right) of baseline. Naloxone doses 0, 1, 2, 2_S represent no naloxone administration, 1 dose of naloxone, 2 doses administered 2.5 min apart, and 2 doses administered simultaneously, respectively. Simulations are as described in Figure 2.

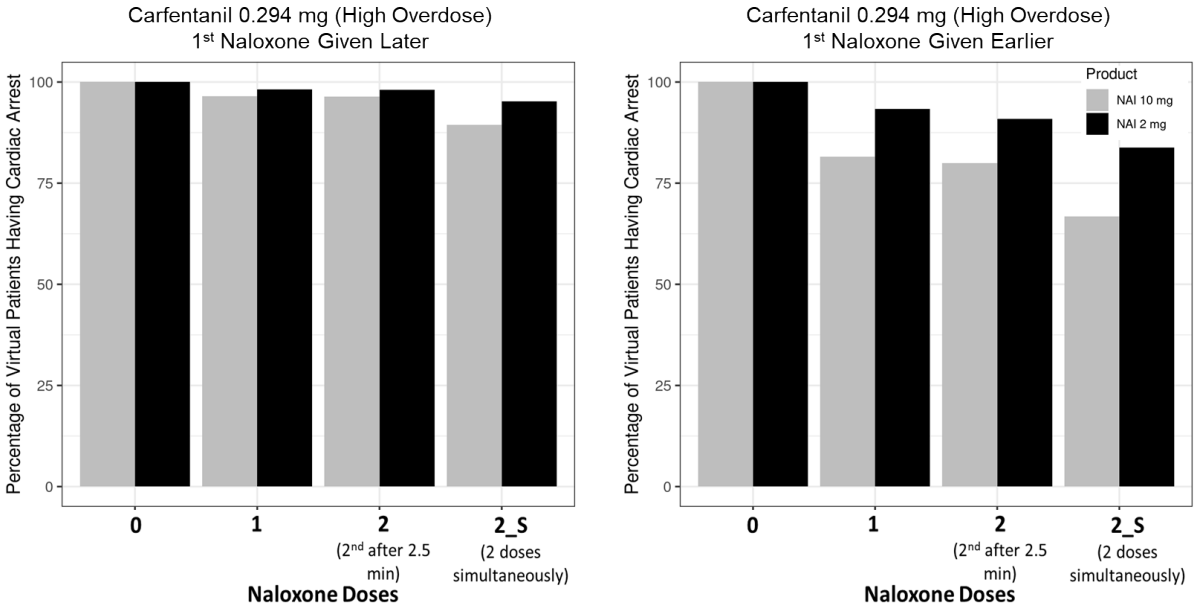


**Figure 4** Percentage of patients experiencing cardiac arrest after inhalation carfentanil high overdose exposure followed by naloxone administration. The 1st naloxone was administered 1 min after minute ventilation dropped to 40% (left) and 90% (right) of baseline. Carfentanil exposure is through inhalation while naloxone administration is intramuscular (IM). Naloxone doses 0, 1, 2, 2_S represent no naloxone administration, 1 dose of naloxone, 2 doses administered 2.5 min apart, and 2 doses administered simultaneously, respectively. Simulations are as described in Figure 2.

The FDA model was used to simulate prophylactic administration of the NAI 10 mg naloxone product, where naloxone was administered 5 min or 30 min prior to opioid exposure. Only high dose fentanyl (3.087 mg) and high dose carfentanil (0.294 mg) were used in this set of simulations due to the expectation that prophylactic administration should be able to counteract higher doses of opioid exposure. The simulations show that even 1 dose of NAI 10 mg can prevent > 90% patients from experiencing opioid-associated cardiac arrest if administered 5 min prior to exposure to high dose of fentanyl (**Figure 5**) and carfentanil (**Figure 6**). If administered 30 min prior to exposure, virtually no patients are predicted to experience cardiac arrest.

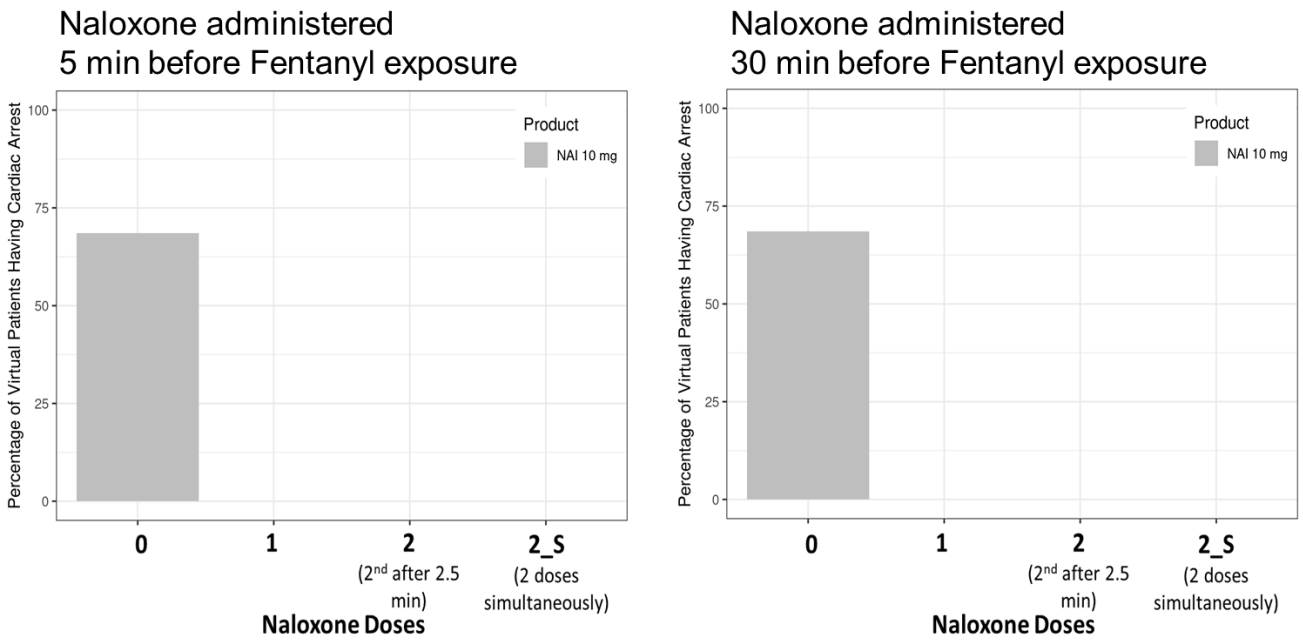


**Figure 5**. Percentage of patients experiencing cardiac arrest after inhalation fentanyl high overdose (3.087 mg) exposure with NAI 10 mg administered 5 min prior to fentanyl exposure (left) or 30 min prior to fentanyl exposure (right). Naloxone doses 0, 1, 2, 2_S represent no naloxone administration, 1 dose of naloxone, 2 doses administered 2.5 min apart, and 2 doses administered simultaneously, respectively. Simulations are as described in Figure 2.

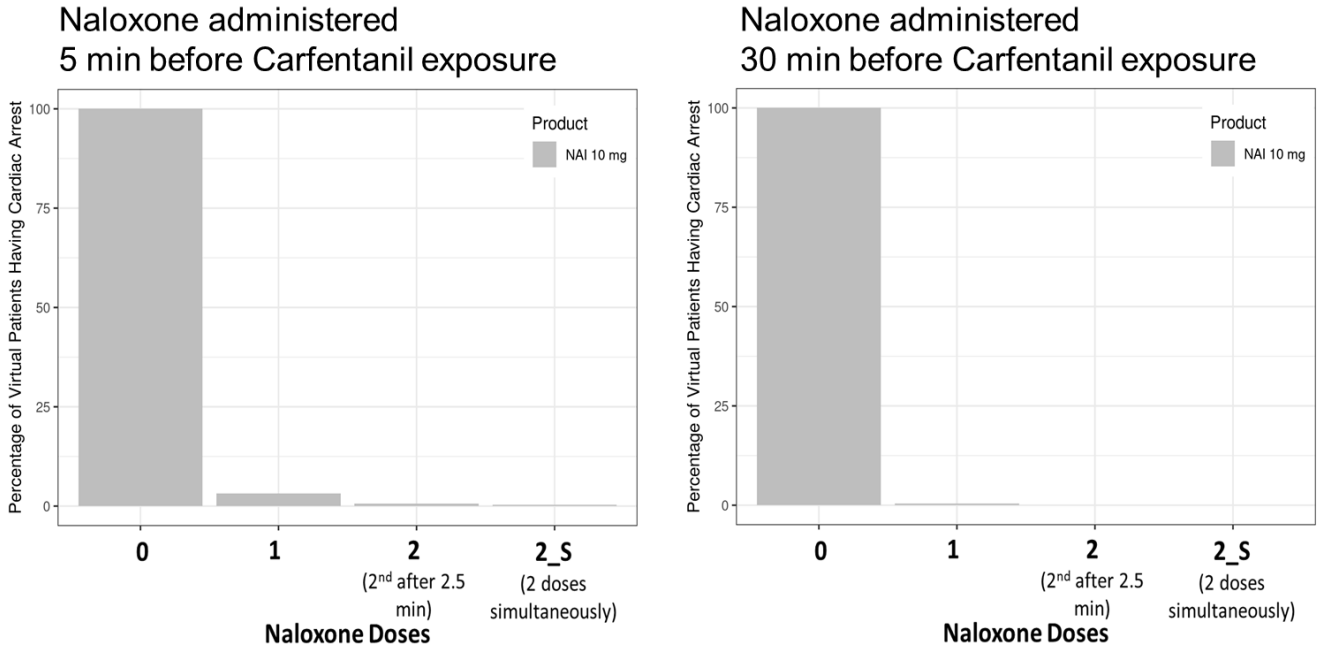


**Figure 6**. Percentage of patients experiencing cardiac arrest after inhalation carfentanil high overdose (0.294 mg) exposure with NAI 10 mg administered 5 min prior to carfentnail exposure (left) or 30 min prior to carfentanil exposure (right). Naloxone doses 0, 1, 2, 2_S represent no naloxone administration, 1 dose of naloxone, 2 doses administered 2.5 min apart, and 2 doses administered simultaneously, respectively. Simulations are as described in Figure 2.

## 2.1 Pharmacology and Clinical Pharmacokinetics

### *2.1.1. What is the proposed indication?*

(b) (4)

## 2.2 Dosing and Therapeutic Individualization

### *2.2.1 General dosing*

Naloxone Auto-injector 10 mg is for intramuscular or subcutaneous use only.
Seek emergency medical care immediately after use.
Administer Naloxone Auto-injector 10 mg to patients 12 years of age and older into the anterolateral aspect of the thigh, through clothing if necessary.
If the patient relapses into respiratory or central nervous system depression after the first dose of Naloxone Auto-injector 10 mg, additional naloxone HCl may be administered.
Additional supportive and/or resuscitative measures may be helpful.

## 2.3 Outstanding Issues

There are no outstanding issues.

## 2.4 Summary of Labeling Recommendations

As of today (1/31/2022), labeling negotiation is still ongoing. Tentative labeling recommendations are shown below: recommended deletions are shown as ~~red strikethrough~~ and additions are shown as blue underlined text:

Under Section **1 INDICATIONS AND USAGE**

(b) (4) NALOXONE HYDROCHLORIDE injection is indicated in patients 12 years of age and older for

- emergency treatment of known or suspected opioid overdose in military and civilian first responders or victims, 12 years of age and older, in mass casualty situations with known or suspected airborne exposures to high potency opioids such as fentanyl analogues.
- the prophylaxis of respiratory and/or central nervous system depression in military or civilian first responders entering an area believed to contain aerosolized high potency opioids.

***Comment***: *Recommendations are based on review team discussion.*

Under Section **2.1 Important Administration Instructions**

• NALOXONE ALOXONE HYDROCHLORIDE injection contains 10 mg/0.4 mL in a single- dose, pre-filled autoinjector for ~~is for~~ intramuscular or subcutaneous use only.

• Each pre-filled autoinjector contains a single dose of naloxone hydrochloride (HCl).

Read the Instructions for Use at the time of receiving NALOXONE HYDROCHLORIDE injection.

• Do not attempt to reuse the NALOXONE HYDROCHLORIDE injection autoinjector.

• Periodically visually inspect NALOXONE HYDROCHLORIDE injection through the viewing window for particulate matter. Request a replacement if the solution is cloudy or contains particles, or if the glass container is damaged.

• Once the red safety guard is removed, NALOXONE HYDROCHLORIDE injection must be used immediately or disposed of properly. Do not attempt to replace the red safety guard once it is removed.

• Administer NALOXONE HYDROCHLORIDE injection as soon as possible after known or suspected opioid exposure or just before anticipated opioid exposure because prolonged respiratory depression may result in damage to the central nervous system or death.

2.2 Dosing in Adults and Pediatric Patients at Least 12 Years Old

• Administer NALOXONE HYDROCHLORIDE injection as soon as opioid exposure is suspected.

• NALOXONE HYDROCHLORIDE injection must be administered intramuscularly or subcutaneously into the anterolateral aspect of the thigh according to the Instructions for Use and the printed instructions on the device label.

• In summary,

- Ensure that the injection site is free of other materials, except for clothing.
- Pull the autoinjector from the outer case.
- When ready to use, firmly pull off the red safety guard. Do not touch the black base of the autoinjector, which is where the needle comes out.

- Place the black end of the autoinjector against the anterolateral aspect of the thigh, through clothing, if needed.
- Press firmly until you hear a click and a hiss sound and then hold inplace for 5 seconds.

• Upon actuation, the autoinjector automatically inserts the needle intramuscularly or subcutaneously, delivers the naloxone HCl injection, and retracts the needle into the device.
• Post-injection, the black base locks in place and a red indicator appears in the drug viewing window.

For suspected opioid exposure occurring outside (b) (4) (b) (4) of supervised medical settings:

o Seek immediate emergency medical assistance after administration of the first dose of (b) (4) NALOXONE HYDROCHLORIDE injection
o Keep the patient under continued surveillance until medical care is available
o If the patient does not show some improvement after administering the dose of (b) (4) NALOXONE HYDROCHLORIDE injection, consider if the respiratory depression is due to a non-opioid etiology
o If the patient exhibits renarcotization after the first dose of (b) (4) (b) (4) NALOXONE HYDROCHLORIDE injection, administer additional naloxone HCl, as necessary, until emergency medical assistance becomes available

For prophylactic use of NALOXONE HYDROCHLORIDE injection: Administer immediately prior to entering an area believed to contain aerosolized high potency opioids.

(b) (4)

***Comment**: Recommendations are based on review team discussion.*

Under Section **12.2 Pharmacodynamics**

When naloxone HCl is administered intravenously, the onset of action is generally apparent within two minutes. The time to onset of action is shorter for intravenous compared to subcutaneous or intramuscular routes of administration.

The duration of action is dependent upon the dose and route of administration of naloxone HCl.

(b) (4) Simulations based on data from healthy volunteer studies demonstrated that a single 10 mg naloxone dose could partially reverse decreases in ventilation (b) (4) induced by doses of morphine or buprenorphine (b) (4) . The ability to reverse decreased (b) (4) ventilation rate after naloxone treatment was dependent on the administered opioid (b) (4) , amount of opioid, amount of naloxone, and timing of naloxone administration relative to opioid exposure (b) (4)

***Comment***: *The general statement on pharmacodynamics based on PK-PD modeling and simulation is recommended based on team discussion.*

Under Section **12.3 Pharmacokinetics** Elimination
The mean plasma half-life of naloxone in healthy adults was 1.46 hours (14.1 %CV) following a single administration of NALOXONE AUTO-INJECTOR 10 mg. (b) (4)

***Comment***: *The sentence of neonatal half-life included in Evzio label is deleted because this product is not approved in this patient population.*

# 3. APPENDICES

## 3.1 Summary of Bioanalytical Method Validation and Performance

The bioanalytical LC/MS/MS method for the determination of free, unconjugated naloxone concentrations in human plasma in Study KA-900DV-002 were adequately validated. This bioanalytical method was also used in Studies IJ-900DV-03O supporting NAI 0.4 mg (NDA 205787) and KA-900DV-05A supporting NAI 2 mg (NDA 209862) for the determination of free naloxone concentration. The lower limit of quantitation is 2 pg/mL. In Study KA-900DV-002, the assay precision (%CV) was 4 to 11.9% and accuracy (% difference from theoretical) was -1.26 to 4.42%, respectively.

## 3.2 DARS Review

# Independent Mechanistic PK-PD Modeling Analysis of

# NDA215457 Naloxone Auto-injector 10 mg

# Division of Applied Regulatory Science, Office of Clinical Pharmacology

## Executive Summary

The objective of this review is to perform independent modeling & simulation to evaluate two key conclusions from the sponsor's mechanistic PK-PD analysis

1) the efficacy of the intramuscular (IM) naloxone auto-injector (NAI) 10 mg product in reversing opioid-induced respiratory depression in comparison to that of NAI 2 mg
2) the utility of prophylactic administration of NAI 10 mg to prevent opioid-induced respiratory depression

The FDA's independent modeling & simulation supports the sponsor's claim that administration of NAI 10 mg resulted in a higher percentage of subjects recovering from respiratory depression for middle and high opioid doses compared to NAI 2 mg. However, for middle and high overdose of carfentanil, the NAI 10 mg product needs to be administered as early as possible (e.g., immediately with suspected opioid exposure, or with early signs of respiratory depression) to achieve a higher rescue percentage than NAI 2 mg. In addition, the FDA's independent modeling & simulation supported the sponsor's second claim that administration of NAI 10 mg prior to fentanyl or carfentanil exposure can prevent rapid and profound opioid-induced respiratory depression.

## Background

The opioid antagonist naloxone can reverse the respiratory depression effects of opioids and is being increasingly used in the prehospital setting, including by Emergency Medical Service (EMS) personnel, community members, or subjects experiencing opioid overdose. Several naloxone products have been approved by the US Food and Drug Administration (FDA) for pre-hospital or community use, including intranasal (IN) spray up to 8 mg [1] and IM NAI up to 5 mg [2].

On December 13, 2018, the DoD (Department of Defense) held a pre-IND meeting with the FDA regarding development of a high dose of naloxone hydrochloride (HCl) in an auto-injector as a medical countermeasure to treat the effects of exposure to ultra-potent opioids. On February 24, 2020, Kaleo, Inc (referred to as the Applicant)., the DoD, and the FDA held a pre-NDA meeting to discuss the development program of a 10 mg naloxone auto-injector (NAI 10 mg), where the Applicant agreed to conduct clinical PK studies to evaluate the bioavailability and safety of NAI 10 mg compared to the currently approved product EVZIO® (NAI 2 mg) [3]. On December 29, 2020, the FDA sent the Applicant an advice letter recommending a pharmacokinetic (PK)-pharmacodynamic (PD) modeling approach to support a claim for reversal of opioid effects with NAI 10 mg. On March 1, 2021, the Applicant sent the

FDA a PK-PD data analysis plan (DAP). On April 28, 2021, the FDA provided the Applicant an advice letter with comments and recommendations. The Applicant sent a clarification letter to FDA on June 14, 2021

regarding comments received. On July 12, 2021 the FDA provided further advice to the Applicant regarding the DAP.

The NDA was submitted on August 31, 2021, which included a report executing the PK-PD DAP. In the report, the Applicant developed a PK-PD model, which consists of a PK component for naloxone based on its clinical PK study KA-900DV-002 using the NAI 10 mg product, a PK component for various opioids based on literate data, and a PD component linking effect compartment concentrations of opioids and naloxone (or estimated fraction of mu receptor occupied by opioids) to the clinical endpoint of minute ventilation volume. A detailed review of the PK-PD model used by the Applicant, as well as the simulation results, will be covered by another document. In this document, a new PK-PD model developed by the FDA was used to repeat some of the simulations and evaluate two of the key conclusions from the Applicant's modeling analysis: 1) administration of NAI 10 mg resulted in a higher percentage of subjects recovering from respiratory depression for middle and high opioid doses compared to NAI 2 mg; 2) administration of NAI 10 mg prior to fentanyl or carfentanil exposure can prevent rapid and profound opioid-induced respiratory depression.

## Methods

The FDA model is comprised of multiple components (sub-models) (Figure 1). The naloxone PK component of the FDA's model is the same as the Applicant's (both based on study KA-900DV-002). However, all other components are different from the Applicant's model. The goal of developing the new model for independent evaluation is to address two comments raised by the FDA when discussing the PK-PD DAP with the Applicant:

1) PD component (equation to link drug concentration or receptor occupancy to ventilation) was developed from clinical studies where the end-tidal CO2 partial pressure was fixed (isocapnic condition). This is different from the real-world poikilocapnic condition, where the end-tidal CO2 and O2 levels will change and trigger physiological responses after the initial respiratory depression
2) There is a lack of scientific data supporting the determination of a relative minute ventilation volume (percentage of the baseline) as the threshold of "rescue"

The new FDA model addressed these two comments, along with other considerations, to increase the credibility of using the modeling approach to evaluate naloxone dosing schemes. The key considerations are reported in Table 1 and summarized below.

Simulated physiological conditions: As pointed out by the FDA's response to the Applicant on July 12, 2021 regarding the DAP, the PD equations in the DAP, as well as the PD equation in the FDA Github repository, all predict a clinical endpoint where end-tidal CO2 tensions were fixed (isocapnic condition). In the same document, the FDA notified the Applicant that a new model was being developed by FDA that would simulate a condition where a patient is breathing room air (poikilocapnic condition), and

encouraged the Applicant to explore this possibility too. Subsequently the FDA has developed a new model, based on previous work from Magosso and Ursino [4-6]. This new model has mechanistic details of various physiology processes including CO2 and O2 metabolism and transfer, human ventilation control, and blood flow regulation (Figure 1). It can be used to simulate conditions when the end-tidal CO2 is fixed (isocapnic ventilation), and when breathing room air (poikilocapnic ventilation).

Definition of rescue: As pointed out by the FDA's response to the Applicant on July 12, 2021 regarding the DAP, when calculating rescue time based on minute ventilation, it may be necessary to explore different definitions of "rescue" as minute ventilation recovering to different levels of baseline. One reason is that if the model's PD equation is based on clinical studies of isohypercapnic ventilation, for example Yassen et al. with a baseline ventilation of ~20 L/min, then even recovering to 20% of this baseline is 4 L/min already. While the new model developed by the FDA is capable of simulating breathing room air (baseline minute ventilation ~6-8 L/min), it is still unclear what threshold can be considered as a rescue threshold. Extensive literature review only identified one paper suggesting 40% of baseline minute ventilation as a threshold of unsafe (inadequate) ventilation, but this threshold was based on criteria for weaning patients off mechanical ventilation [7]. Due to the lack of quantitative data supporting a minute ventilation level as a rescue threshold, the FDA's new model explores another endpoint: cardiac arrest. Opioid-associated out-of-hospital cardiac arrest (OA-OHCA) is one of the leading causes of death associated with opioid overdose, and among all OHCA cases treated by emergency EMS, 8.9% are caused by opioid overdose [8]. By defining rescue as preventing a patient from opioid-associated cardiac arrest due to respiratory depression, the FDA new model has an easy-to-interpret endpoint for evaluating naloxone dosing regimen.

Timing of the first naloxone dose: Both the Applicant's and FDA model use minute ventilation below 40% baseline as the sign of significant respiratory depression after opioid exposure. The Applicant's model assumes the NAI10 mg product can be administered immediately when minute ventilation drops to 40% of baseline. The FDA model assumes there is an additional 1 minute delay before the naloxone product can be delivered. This is consistent with the Applicant's claim that "Human Factors studies with NAI have demonstrated that users can complete the injection in under one minute". In addition, the FDA model also explored an earlier dosing scenario where the 1$^{st}$ dose of naloxone was given 1 minute after the minute ventilation dropped to 90% of baseline.

Carfentanil IV PK model: The Applicant's model used animal carfentanil PK model extrapolated to humans to simulate IV bolus injection of carfentanil. FDA model utilized Minkowski et al. 2021, a study that investigated carfentanil IV injection in humans [9]. While Minkowski et al. did not report the plasma concentrations of carfentanil after IV injection, they reported that the initial half-life of plasma carfentanil profiles were ~45 minutes, significantly longer than reported fentanyl values [10]. The FDA model adjusted fentanyl IV PK parameters to capture this reported half-life difference between fentanyl and carfentanil (Figure 2).

Relative bioavailability difference between IV and inhalation: Both the FDA and Applicant's model contain PK models for opioids after IV administration. As it is expected that the context of use of this NAI10 mg product is in an environment with high concentrations of aerosolized opioids, the most

probable exposure route is through inhalation. It was reported that, compared to IV exposure, inhalation exposure of fentanyl had reduced bioavailability initially [11]. As this amount of opioid entering the system may significantly impact the difficulty of reversal of respiratory depression, the FDA model adjusted the IV fentanyl PK model to reflect the initial reduction of relative bioavailability through inhalation (Figure 3).

Model validation: Model development usually has two sequential steps: calibration and validation. In the calibration step, some observed data were used to guide the adjustment of model structure (equations) and parameters, and in the validation step, model prediction is compared to observed data to evaluate its credibility. In the Applicant's model validation, there is an overlap between calibration and validation data. For example, the model's PD equation for fentanyl (Eq 15 in Applicant's model report) is primarily based on a clinical study investigating fentanyl effect on ventilation [12]. This same dataset, after being used for model calibration (to derive parameters in Eq 15), was used for model validation (comparing model prediction to observed data) (Figure 17 in

Applicant's model report). While this is a widely used strategy in the modeling community, a more stringent approach is to use validation data that were not utilized during calibration step, a strategy recommended by established principles for complex model reliability assessment [13] and guidelines for biomarker qualification [14]. The FDA new model followed such a stringent validation approach. Some sets of data were used to calibrate the model to describe physiology and pharmacodynamics, and totally different sets of data were used to validate the model prediction (Figures 4-6). Despite the complexity of the model (simultaneously simulating multiple physiological variables) and the stringent validation plan (model development was not informed at all by any of the validation data), the uncertainty bands or error bars from model prediction overlap with those from observed data for vast majority of data points for all tested physiological variables (minute ventilation, PaO2, PaCO2, CO2 response slope) in the validation study (Figure 6).

The FDA model was used to simulate fentanyl and carfentanil overdose scenarios using the top two doses provided by the Applicant: 23.1 and 44.1 µg/kg for fentanyl, and 2.2 and 4.2 µg/kg for carfentanil, respectively. Consistent with the Applicant's DAP, we assumed a body weight of 70 kg, and calculated a middle (also referred to as median) and high overdose scenario for each opioid. For fentanyl the doses are 1.617 (median) and 3.087 (high) mg. And for carfentanil the doses are 0.154 (median) and 0.294 (high) mg. For naloxone we simulated different dosing schemes: 1 dose of NAI 10 mg, 2 doses of NAI 10 mg with the 2$^{nd}$ dose given 2.5 min after the 1$^{st}$, and 2 doses of NAI 10 mg given simultaneously (equivalent to 20 mg naloxone). For the reversal of opioid-induced respiratory depression, we assumed the 1$^{st}$ dose naloxone was given 1 min after minute ventilation dropped to 40% or 90% of baseline. For the prophylactic administration, we simulated situations where NAI 10 mg was given 5 min or 30 min prior to opioid exposure. Each of these simulations were performed on a population of 2000 virtual patients that represent the PK variability of opioids and naloxone, as well as uncertainty in estimating the binding kinetics between the mu receptor and its agonists (opioids) and antagonists (naloxone). All simulations were conducted up to 90 min after the opioid exposure. The percentage of patients experiencing cardiac arrest (not rescued) was reported for each simulation.

Table 1. Key differences between the FDA model and the model used by the Applicant

| | FDA Model | Sponsor Model |
|---|---|---|
| Simulated Physiological Conditions | Poikilocapnic (breathing room air)<br>Isocapnic (end-tidal CO2 fixed) | Isocapnic (end-tidal CO2 fixed) |
| Definition of Rescue | Cardiac arrest prevented | Minute ventilation above certain percentage of baseline |
| Timing of the 1st naloxone dose after opioid exposure | 1 min after minute ventilation below 40% - 90% of baseline | Immediately after minute ventilation below 40% of baseline |
| Carfentanil IV PK model | Fentanyl PK model adjusted based on Minkowski et al. 2011 | Rabbit and rat PK model extrapolated to human |
| Opioid inhalation route considered? | Yes | No |
| Model validation | Clinical data not seen during model calibration were used for model validation | No strict separation between model calibration and validation |

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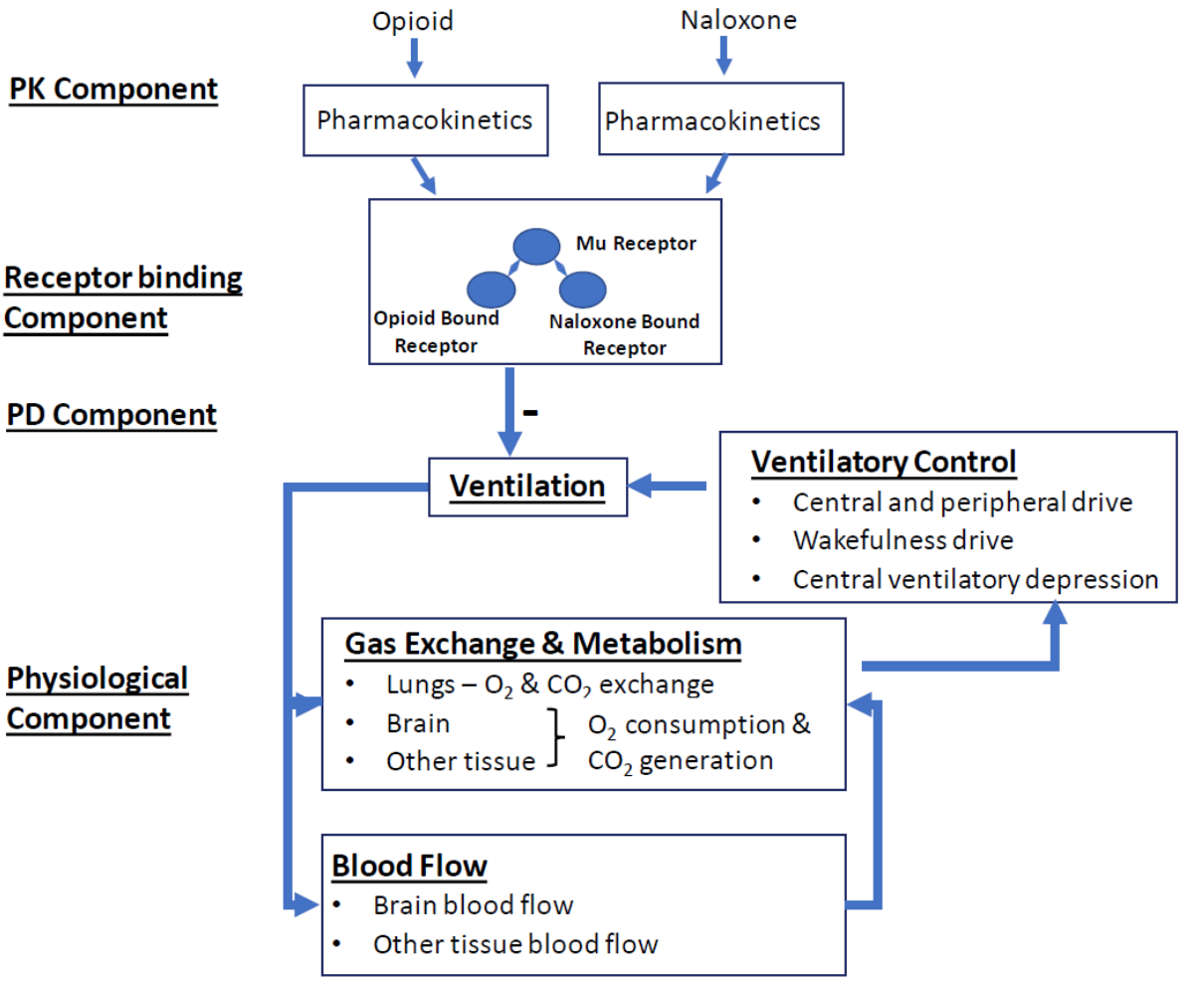


Figure 1. The FDA model has 4 components (sub-models). In the pharmacokinetic (PK) component, compartment PK models convert the doses of opioid and naloxone through different dosing routes to their free concentrations in the effective compartment. In the receptor binding component, opioid and naloxone compete to bind to the mu receptor. In the pharmacodynamic (PD) component, the opioid-bound receptors, but not the naloxone-bound-receptors, lead to respiratory depression, through reducing all three ventilatory drives (the peripheral chemoreflex, central chemoreflex, and wakefulness drive). The physiological component describes the gas ($O_2$ and $CO_2$) exchange and metabolism, ventilatory control, and blood flow control.

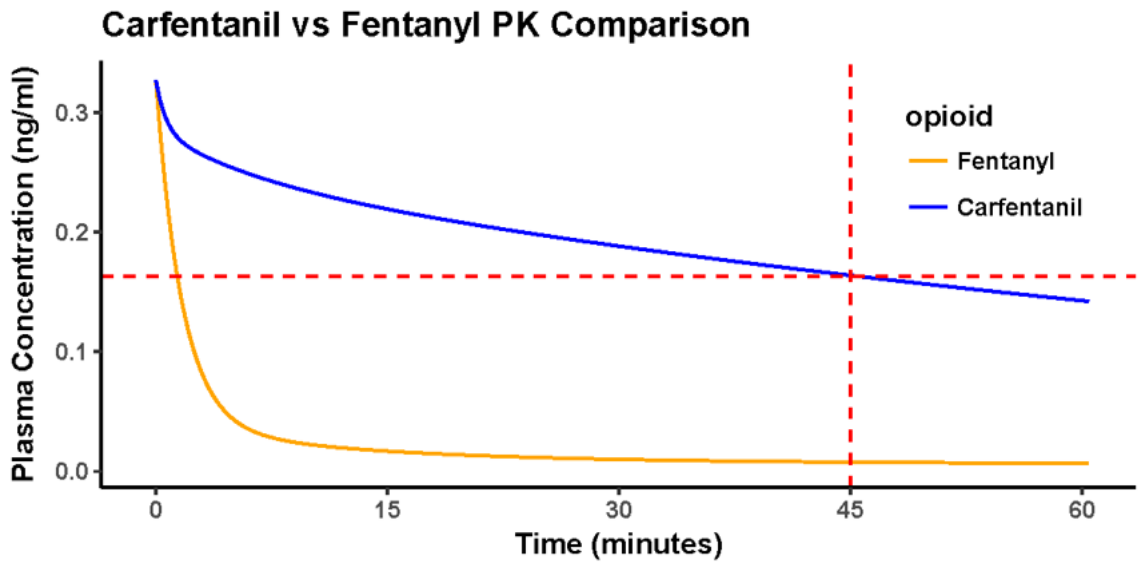


Figure 2. Fentanyl PK parameters were taken from Algera et al. [3] to create the plasma profile (orange). A micro-dosing study by Minkowski et al. indicated that carfentanil has an initial half-life of 45 minutes [6]. Carfentanil PK parameters were modified to achieve a plasma profile (blue) that matched this behavior, reaching 50% of the initial microdose concentration in 45 minutes

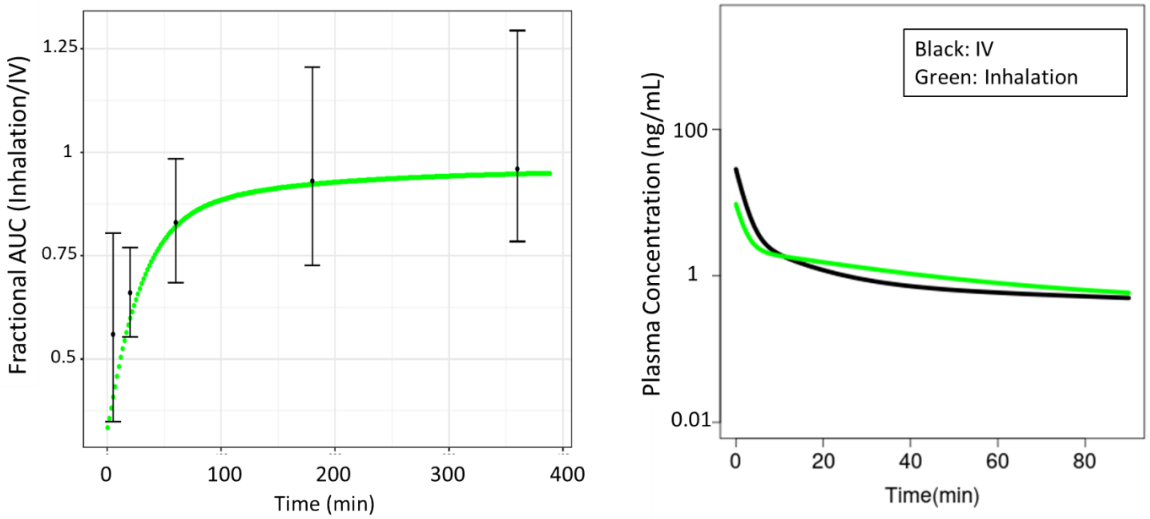


Figure 3. Comparison between IV and inhalation exposure. Left: Simulated (green dots) and observed (black error bars) relative bioavailability (inhalation vs IV) of fentanyl exposure. X axis: time (minutes) after fentanyl exposure. Y axis: Area Under the Curve (AUC) of plasma profiles of fentanyl through inhalation divided by that of fentanyl through IV bolus injection. Data are from [11] using 100 – 300 µg of fentanyl. Right: simulated plasma profiles after IV (black) and inhalation (green) exposure to 300 µg of fentanyl. Note that the plasma profile of inhalation was initially lower than that of IV, but subsequently surpassed IV plasma profile at later time points, resulting in a "crossover" of the two plasma profiles. The Y axis (plasma concentration) is log-transformed to highlight the crossover. Similar crossover pattern between IV and inhalation plasma profiles was observed clinically [11].

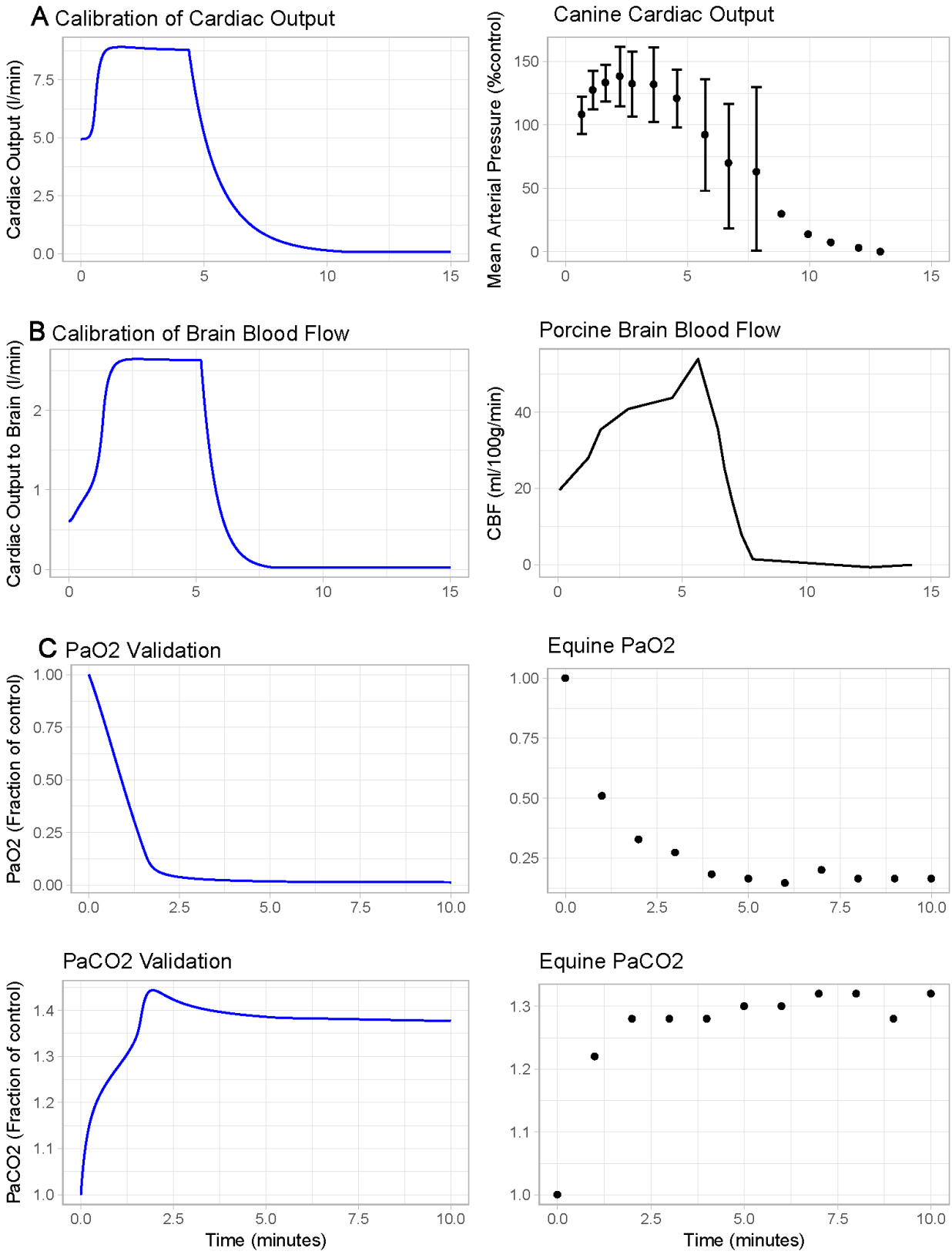

Figure 4. Calibration and validation of the cardiac arrest mechanism in the physiological component. A and B compare model simulations (left) to animal data (right) used to calibrate the model, while C compares model simulations (left) to animal data (right) as model validation. Despite the anticipated species (model simulation is for human while calibration/validation data from animals of a variety of species) and endpoint (model simulation is for blood flow while animal data may use blood pressure as a surrogate for cardiac output) differences, model simulations are consistent with observed data. A) Right: dog studies [15] with 0.5%-1% inspirational O2 levels showing the initial cardiac compensation (blood pressure increasing) and subsequent collapse (blood pressure decreasing). Left: model simulation of cardiac output (total blood flow) of a human with 0.5% inspirational O2 level. B) Right: pig data [16] showing the rise and fall of cerebral blood flow due to asphyxia. Left: model simulation of human after asphyxia. Of note the collapse rate in B is faster than in A, presumably due to the fact that animals in B suffered from hypoxia plus hypercapnia while those in A only suffered from hypoxia. C) Right: horse data [17] showing the change of arterial partial pressures of O2 (upper panel) and CO2 (bottom panel) during the development of cardiac arrest induced by asphyxia. The model simulations (left) of a typical human suffering from asphyxia showed similar changes of arterial O2 and CO2 pressures. These are considered model validation because model equations and parameters were not adjusted based on the horse data.

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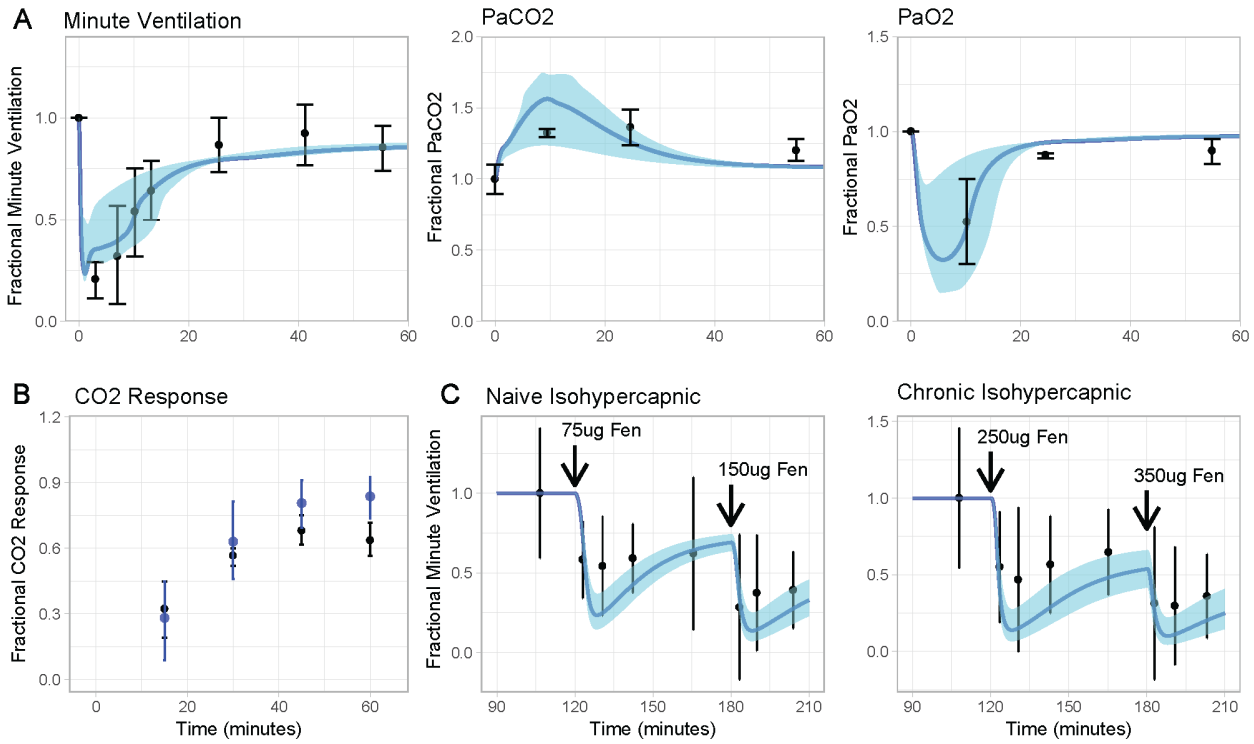


Figure 5. Calibration of the pharmacodynamic (PD) component of the model. The PD component describes the drug effects on the ventilatory drives, and subsequently on plasma gas ($O_2$ and $CO_2$) tensions. A) the minute ventilation volume, arterial $CO_2$ (fraction of baseline) and $O_2$ (fraction of baseline) partial pressures ($PaCO_2$ and $PaO_2$) after 0.5 mg fentanyl bolus injection while subjects were breathing room air [18]. Solid lines and bands are typical patient (the virtual patient with typical parameters) and population simulations, respectively. Black dots and error bars are mean and standard deviation (SD) of the clinical data, respectively. B) The same subjects had their CO2 response slopes measured in the same study. The blue error bars are model simulations. Black dots and error bars are mean and SD of clinical observations, respectively. C) minute ventilation volume (fraction of baseline) changes after bolus fentanyl injection for healthy volunteers (left) and chronic opioid users (right) when their end-tidal CO2 was fixed at ~50 mm Hg (isohypercapnic condition) [10]. The solid lines and bands are typical patient and population simulations, respectively. Black dots and error bars are mean and 95% confidence interval (CI) of clinical data, respectively. At the 120$^{th}$ minute (X axis), healthy and chronic user subjects received a bolus injection of 75 and 250 ug fentanyl/70 kg body weight, respectively. At the 180$^{th}$ minute (X axis), healthy and chronic user subjects received a bolus fentanyl IV injection of 150 and 350 ug/70 kg body weight, respectively. Of note the original study delivered more than two doses of fentanyl. However, subsequent higher doses excluded some patients due to adverse events or fentanyl tolerance. We only used the first two doses' data for model calibration to represent the general population as much as possible.

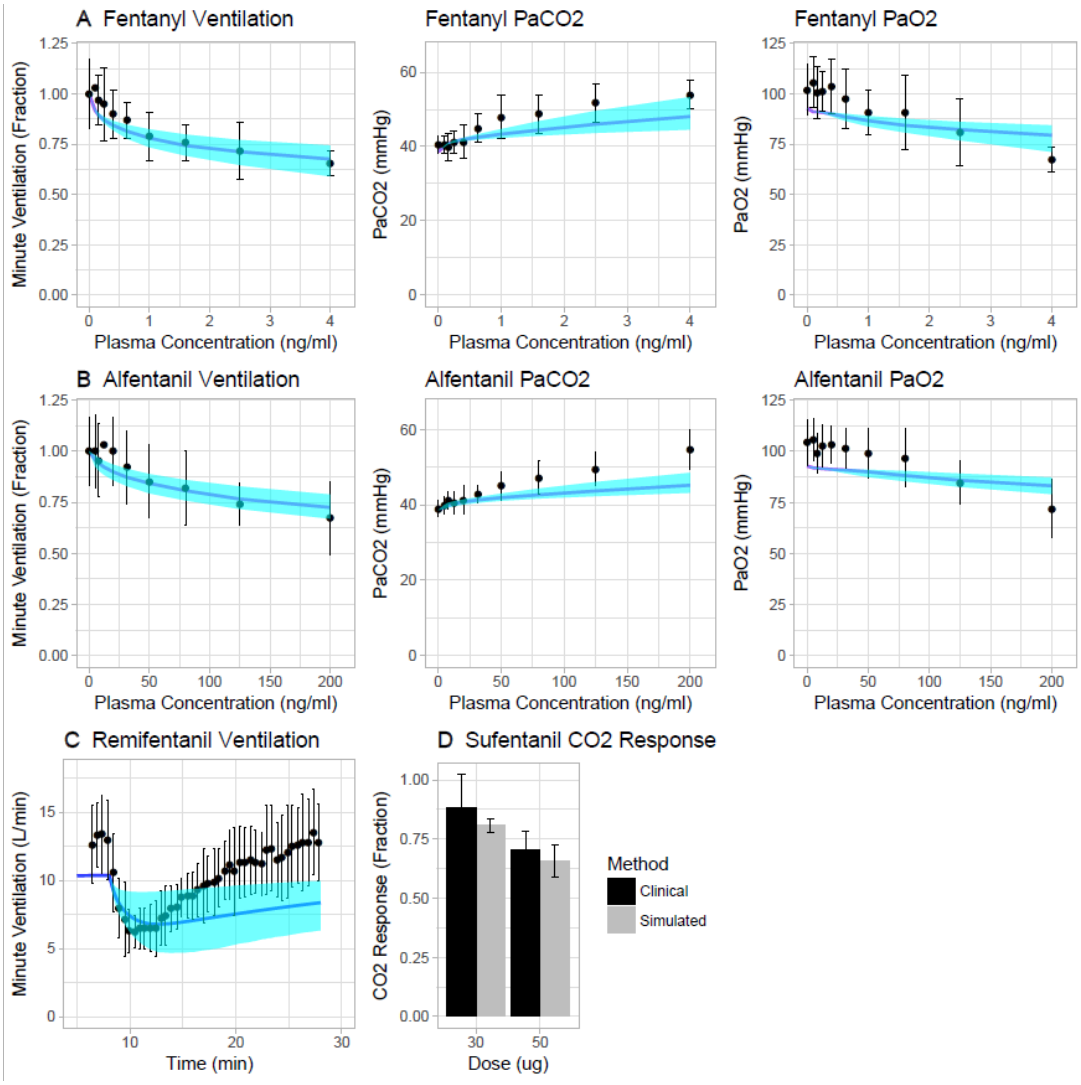


Figure 6. Validation of the PD component of the model. The model was "frozen" without any changes and used to predict clinical outcome of studies not used for model calibration. A) minute ventilation volume, arterial $O_2$ ($PaO_2$) and $CO_2$ ($PaCO_2$) partial pressures after computer-driven continuous fentanyl infusion to achieve various pseudo steady state plasma concentrations while subjects breathed room air [19]. X axis: plasma concentration of fentanyl. Black points and error bars are clinical data and simulated results are the dark blue line (typical) and light blue band (95% CI). B) the same study with various pseudo steady state plasma concentrations of alfentanil. C) a study reporting minute ventilation volume after 35 ug/70 kg body weight bolus injection of remifentanil when subjects' end-tidal $CO_2$ partial pressure was fixed at 50 mm Hg [20]. Black points are clinical error bars and simulated results indicated by dark blue line (optimal) and light blue band (95% CI) D) A study [21] reporting $CO_2$ response slopes (fraction of baseline) through rebreathing 15 min after epidural administration of 30 (left) and 50 (right) ug of sufentnail. The model prediction (grey) is consistent with clinical data (black). Of note the study measured another two time points: 45 min and 120 min after epidural administration. However, the observed $CO_2$ response slope changes at these two later time points were inconsistent with measured plasma concentrations of sufentanil and hence were not included in the model validation.

## Results (QBR)

1) Does FDA's independent modeling & simulation support the sponsor's claim that administration of NAI 10 mg resulted in a higher percentage of subjects recovering from respiratory depression for middle and high opioid doses compared to NAI 2 mg?

The FDA's independent simulation focused on fentanyl and carfentanil, using the middle and high opioid doses provided by the sponsor and assuming a 70 kg body weight. As shown in Figure 7, NAI 10 mg reduced the percentage of patients experiencing fentanyl-associated cardiac arrest in comparison to NAI 2 mg. Even at high fentanyl overdose (3.087 mg), 1 dose of NAI 10 mg resulted in less than 10% patients (rescue rate > 90%) experiencing cardiac arrest. This is because the high dose of NAI 10 mg delivered relatively high amount of naloxone into the systemic circulation and subsequently effect site of the patients. Naloxone was able to drive fentanyl off of the mu receptors, resulting in a partially relieved respiratory depression and an increase in arterial oxygen partial pressure (PaO2) from hypoxia. With a relatively high amount of naloxone delivered within a short period of time, PaO2 would be able to increase fast enough to avoid cardiovascular collapse and cardiac arrest (demonstrated in Figure 4).

As shown in Figure 8, NAI 10 mg also reduced the percentage of patients experiencing cardiac arrest after median overdose carfentanil exposure (0.154 mg) compared to NAI 2 mg. However, due to the slow unbinding kinetics of carfentanil, nearly 80% patients still experienced cardiac arrest even with NAI 10 mg, and the difference between NAI 10 mg and 2 mg is small (Figure 8, left). As the simulation assumes the 1$^{st}$ dose of naloxone was given 1 min after significant respiratory depression (minute ventilation 40% of baseline), we explored another scenario where the 1$^{st}$ dose of naloxone was given 1 min after early signs of respiratory depression (minute ventilation 90% of baseline). Such early dosing is plausible given that the context of use of the NAI 10 mg product includes military personnel under chemical attack, or first responders entering a mass casualty environment. As shown in Figure 8 (right), early dosing of NAI 10 mg is predicted to result in less than 50% patients experiencing cardiac arrest, and the benefit of using NAI 10 mg vs NAI 2 mg became more apparent.

Similarly, for a carfentanil high overdose (0.294 mg), both the absolute percentage of patients rescued from cardiac arrest by NAI 10 mg and the difference in rescued patients percentage between NAI 10 and NAI 2 mg are low (most patients experiencing cardiac arrest) if the 1$^{st}$ dose of naloxone was given 1 min after minute ventilation dropped to 40% of baseline (Figure 9, left). If naloxone was dosed earlier (1 min after minute ventilation dropped to 90% of baseline), then NAI 10 mg rescued more patients, and the difference between NAI 10 mg and NAI 2 mg became larger (Figure 9, right). Of note under this scenario there was still only ~20% patients predicted to be rescued from overdose with NAI 10 mg (compared to ~10% rescued with NAI 2 mg). Earlier naloxone dosing (e.g., immediately after suspected opioid exposure) was predicted to further increase the percentage of rescued patients. In all cases, administration of NAI 10 mg was predicted to result in more patients recovering from overdose compared to NAI 2 mg. There was limited value in repeated dosing of the same amount of naloxone 2.5 minutes after the first dose (percentage recovery was similar to one dose alone), but there were further gains by doubling the initial amount of naloxone administered (2_S scenario compared to 1 scenario).

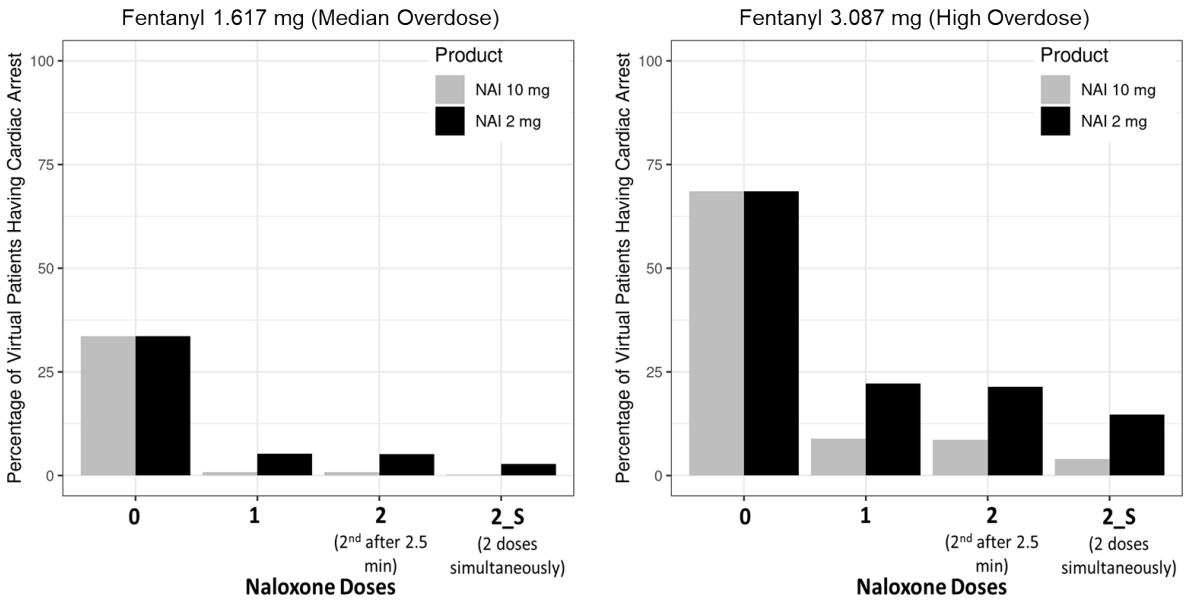


Figure 7. Percentage of patients experiencing cardiac arrest after inhalation fentanyl exposure and followed by IM naloxone administration 1-min after ventilation is 40% of baseline. The fentanyl dose is based on sponsor-provided median (left) and high (right) dose values assuming a 70 kg body weight. Naloxone doses 0, 1, 2, 2_S represent no naloxone administration, 1 dose of naloxone, 2 doses administered 2.5 min apart, and 2 doses administered simultaneously, respectively. The simulation was based on a population of 2000 virtual patients that represent the PK variability of opioids and naloxone, as well as uncertainty in estimating the binding kinetics between the mu receptor and its agonists (opioids) and antagonists (naloxone).

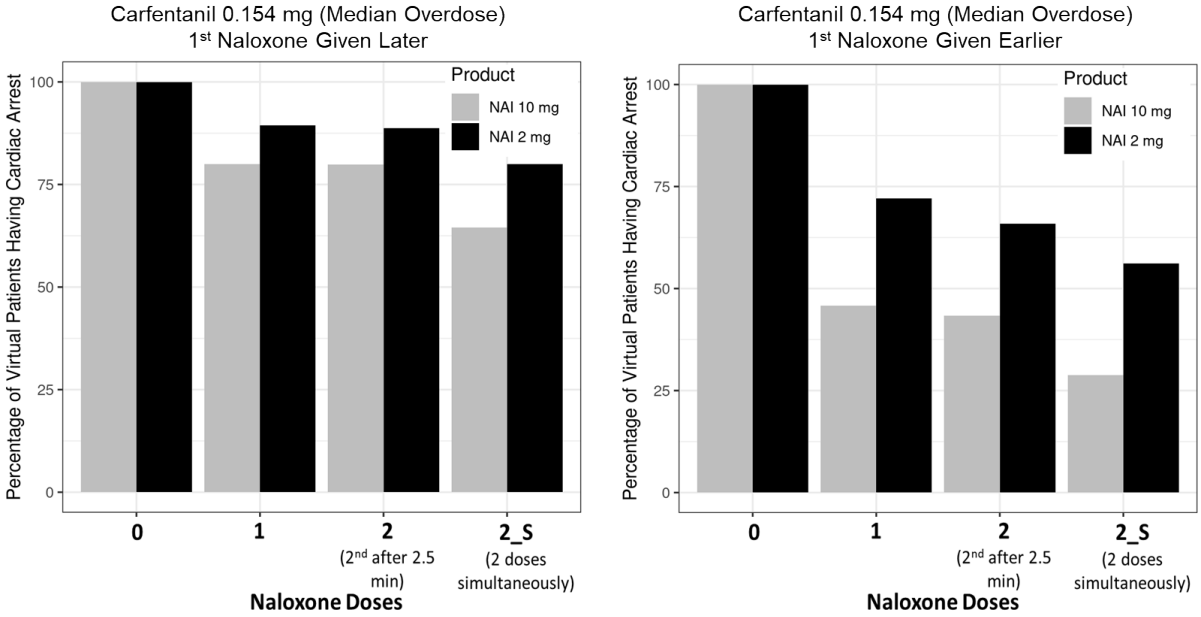


Figure 8. Percentage of patients experiencing cardiac arrest after inhalation carfentanil median overdose exposure followed by IM naloxone administration. The 1st naloxone was administered 1 min after minute ventilation dropped to 40% (left) and 90% (right) of baseline. Naloxone doses 0, 1, 2, 2_S

represent no naloxone administration, 1 dose of naloxone, 2 doses administered 2.5 min apart, and 2 doses administered simultaneously, respectively. Simulations are as described in Figure 7.

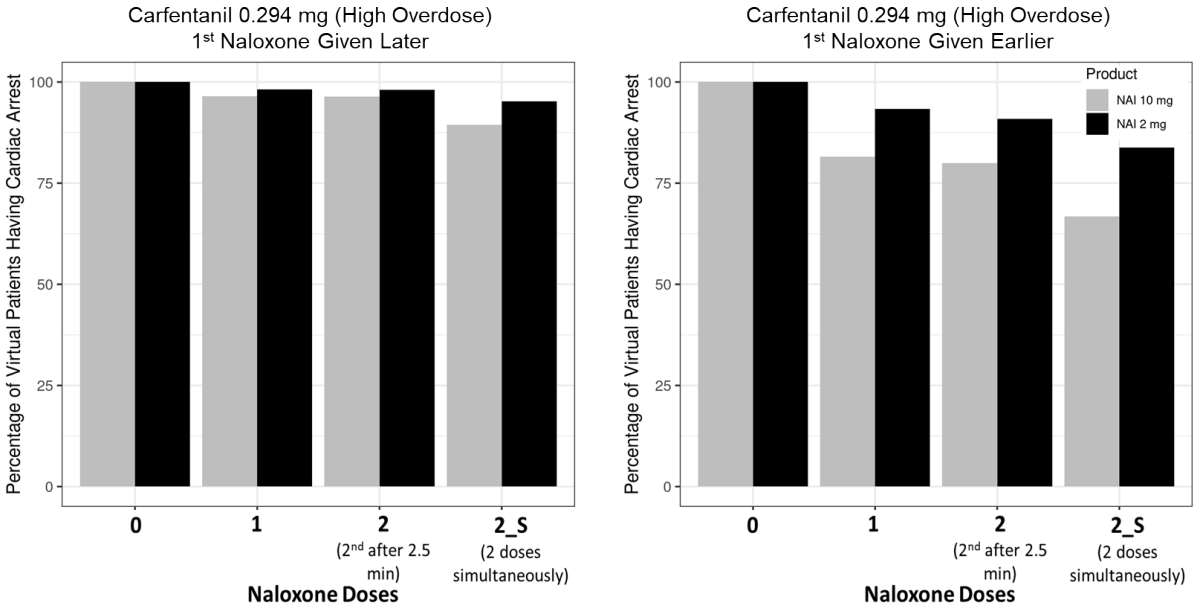


Figure 9. Percentage of patients experiencing cardiac arrest after inhalation carfentanil high overdose exposure followed by naloxone administration. The 1st naloxone was administered 1 min after minute ventilation dropped to 40% (left) and 90% (right) of baseline. Carfentanil exposure is through inhalation while naloxone administration is intramuscular (IM). Naloxone doses 0, 1, 2, 2_S represent no naloxone administration, 1 dose of naloxone, 2 doses administered 2.5 min apart, and 2 doses administered simultaneously, respectively. Simulations are as described in Figure 7.

2) Does FDA's independent modeling & simulation support the sponsor's claim that administration of NAI 10 mg prior to fentanyl or carfentanil exposure can prevent rapid and profound opioid-induced respiratory depression?

The FDA model was used to simulate prophylactic administration of the NAI 10 mg naloxone product, where naloxone was administered 5 min or 30 min prior to opioid exposure. As stated for the previous assessment, such early dosing is plausible given that the context of use for the NAI 10 mg product includes military personnel under chemical attack, or first responders entering a mass casualty environment. Only high dose fentanyl (3.087 mg) and high dose carfentanil (0.294 mg) were used in this set of simulations due to the expectation that prophylactic administration should be able to counteract higher doses of opioid exposure. The simulations show that even 1 dose of NAI 10 mg can prevent > 90% patients from experiencing opioid-associated cardiac arrest if administered 5 min prior to exposure to high dose of fentanyl (Figure 10) and carfentanil (Figure 11). If administered 30 min prior to exposure, virtually no patients are predicted to experience cardiac arrest.

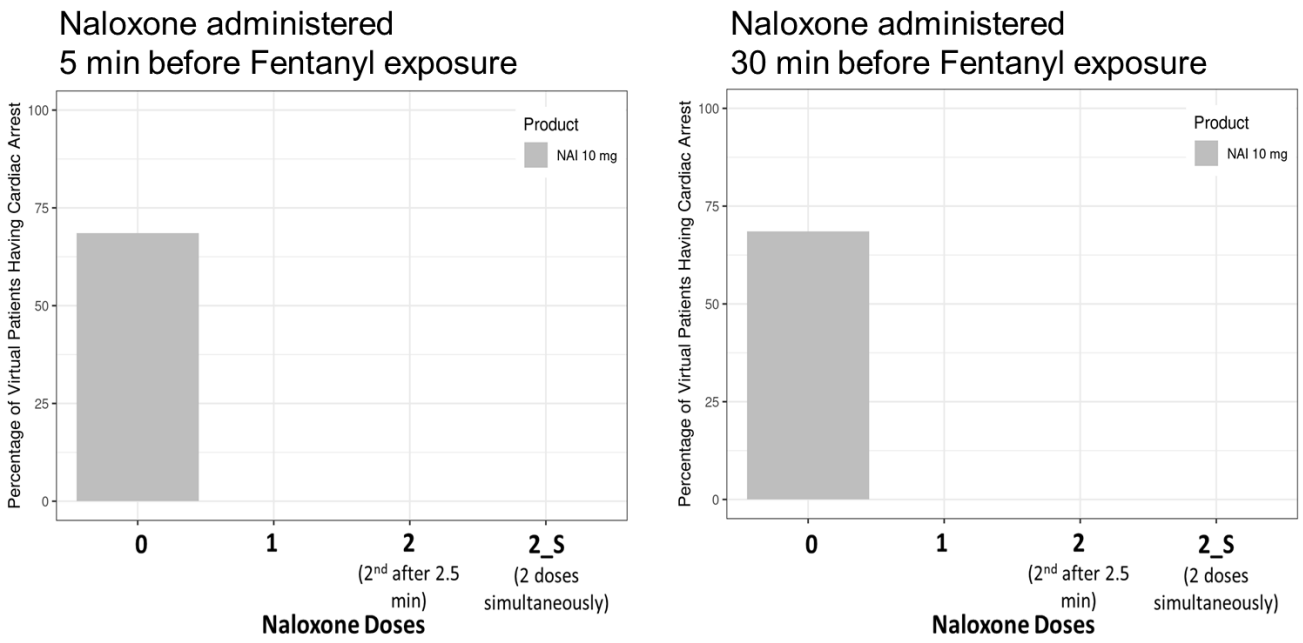


Figure 10. Percentage of patients experiencing cardiac arrest after inhalation fentanyl high overdose (3.087 mg) exposure with NAI 10 mg administered 5 min prior to fentanyl exposure (left) or 30 min prior to fentanyl exposure (right). Naloxone doses 0, 1, 2, 2_S represent no naloxone administration, 1 dose of naloxone, 2 doses administered 2.5 min apart, and 2 doses administered simultaneously, respectively. Simulations are as described in Figure 7.

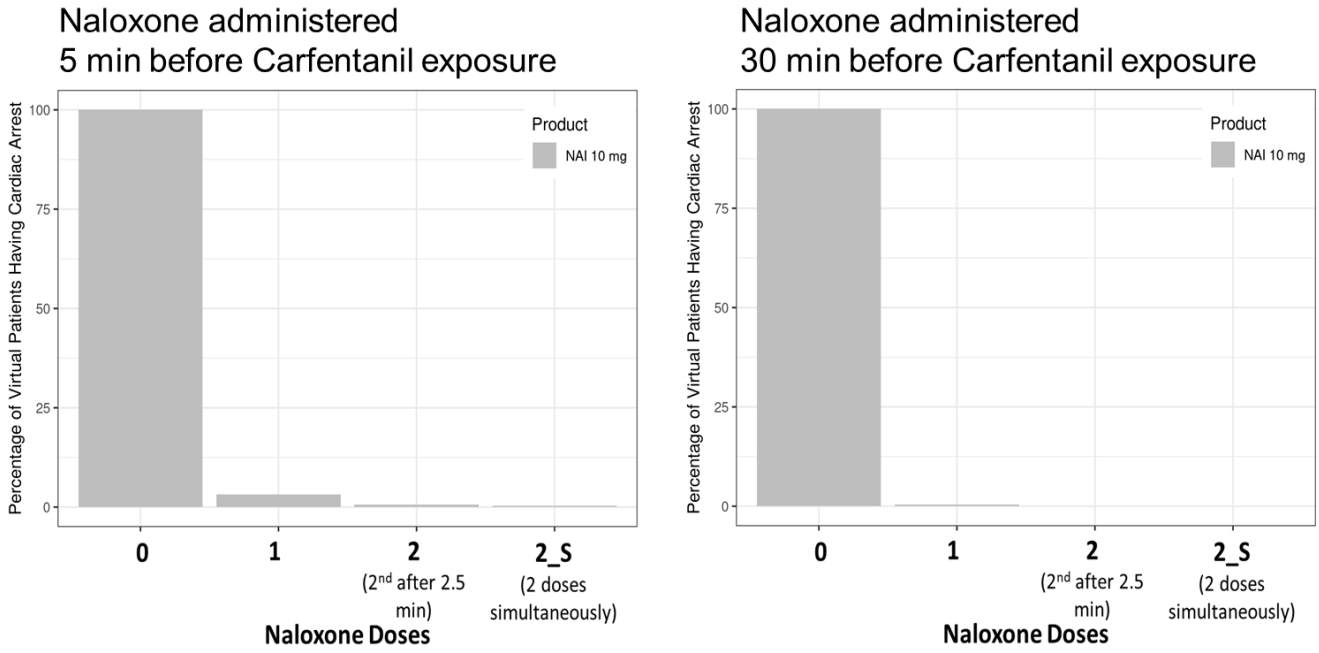


Figure 11. Percentage of patients experiencing cardiac arrest after inhalation carfentanil high overdose (0.294 mg) exposure with NAI 10 mg administered 5 min prior to carfentnail exposure (left) or 30 min prior to carfentanil exposure (right). Naloxone doses 0, 1, 2, 2_S represent no naloxone administration, 1 dose of naloxone, 2 doses administered 2.5 min apart, and 2 doses administered simultaneously, respectively. Simulations are as described in Figure 7.

## Limitations

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

First of all, the relationship between mu receptor occupancy and human ventilatory suppression (PD equations) are derived from various clinical studies investigating fentanyl effects on respiration (Figure 5). It was assumed that the same relationship can be approximately applied to other fentanyl derivatives, like carfentanil. This assumption is necessary because many opioids, such as carfentanil, do not have clinical data where the opioid dose was high enough to induce respiratory depression, which are the necessary data to derive PD equations for each opioid. This assumption is partially supported by the validation study, where the PD equations derived from fentanyl, together with other parts of the model developed during calibration, were used to predict various physiological variables (minute ventilation, PaO2, PaCO2, CO2 response slope) from independent clinical studies involving different opioids (fentanyl, alfentanil, remifentanil, and sufentanil). The overlap between predictions and the vast majority of observed data points suggests this PD relationship is similar (although not identical) among different fentanyl derivatives. Consequently, applying the fentanyl-derived PD relationship to structurally similar analogues like carfentanil may be an acceptable approximation.

Along the same line as above, the relationship between respiratory depression (more specifically the decrease of arterial O2 partial pressure PaO2) and cardiovascular collapse/cardiac arrest is derived from animal data. The 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 a relationship. Multiple species (dogs, pigs, horses) were used to calibrate and validate this relationship in the model (Figure 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 also 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.

Second, there is a lack of clinical PK data for carfentanil. This has led to two different strategies for developing a carfentnail PK model for IV administration. The Applicant relied on animal data, and the FDA model assumes carfentanil PK is very similar to fentanyl PK, with the plasma half-life prolonged according to limited human carfentnail PK data (Figure 2). It is unclear which strategy is a better reflection of real carfentanil PK. The advantage of the FDA model's strategy is that it can reproduce the observed pattern (long half-life) from human carfentnail IV study. Consistent with the Applicant's model, the FDA model assumes carfentanil has the same biophase equilibration rate (the rate to pass the blood-brain-barrier to reach the effect site) as fentanyl.

Third, it is hard to estimate the expected opioid exposure under scenarios the NAI 10 mg product is intended to be used for (chemical weapon, mass casualty situation, etc.). The sponsor assumed ~3 and

~0.3 mg as the "high overdose" scenarios for fentanyl and carfentanil, respectively, for a body weight of 70 kg. As a reference, it was estimated that the lethal dose for fentanyl is 2 mg, and carfentanil is 100 times more potent (https://www.justice.gov/usao-edky/file/898991/download). The high overdose scenarios estimated by the Applicant for fentanyl and carfentanil are well above the estimated lethal dose. Further, the FDA model assumes the opioid exposure route is bolus inhalation, with all the inhaled dose entering the lung at once.

Fourth, the FDA model assumes the 1st dose of naloxone would be given 1 min after some signs of respiratory depression, defined as minute ventilation reducing to 40% (late dosing) or 90% (early dosing) of baseline. It is difficult to estimate how soon naloxone can be given after opioid exposure. If the administration of naloxone is further delayed, more patients will be predicted to experience opioid-associated cardiac arrest. On the other hand, the context of use of the NAI 10 mg product suggests it could be possible that the product is given even earlier (e.g., immediately with suspected opioid exposure). Under that dosing scenario then more patients will be rescued, even with high dose carfentanil.

Finally, the FDA model suggests prophylactic administration of NAI 10 mg can rescue many patients even if they are subsequently exposed to a high dose of carfentanil (Figure 11). However, it is important to note that, due to the computational complexity of the FDA model, the simulation was only conducted up to 90 minutes post opioid exposure. While during this period no significant renarcotization was observed, it is possible that beyond this time frame the prophylactically administered naloxone might leave the system and renarcotization would occur.

## Conclusions

The FDA's independent modeling & simulation supports the Applicant's claim that administration of NAI 10 mg resulted in a higher percentage of subjects recovering from respiratory depression for middle and high opioid doses compared to NAI 2 mg. However, for middle and high overdose of carfentanil (0.154 and 0.294 mg, respectively), early naloxone dosing (e.g., 1 min after minute ventilation dropped to 90% of baseline, or even earlier dosing) might be needed for the NAI 10 mg product to achieve a significantly higher rescue percentage than NAI 2 mg. All simulations predicted more patients would recover with NAI 10 mg compared to NAI 2 mg. The simulations also suggest that more patients would recover by doubling the initial dose, but that little additional recovery occurs by administering a second dose 2.5 minutes after the first dose. These results emphasize that reversal is dependent on the specific opioid, the amount of opioid exposure, the amount of naloxone initially administered, and the timing of the naloxone administration relative to opioid exposure.

Emphasizing the last point, FDA's independent modeling & simulation support the Applicant's second claim that administration of NAI 10 mg prior to fentanyl or carfentanil exposure can prevent rapid and profound opioid-induced respiratory depression.

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## 3.3 DPM Review

**Pharmacometric Review**

### EXECUTIVE SUMMARY

This document is a review of the sponsor's mechanistic pharmacokinetic (PK)-pharmacodynamic (PD) modeling and simulation of reversal of opioid-induced respiratory depression (OIRD) by naloxone auto-injector (NAI) 10 mg across a range of different opioids and doses.

### SPONSOR'S ANALYSIS

**Objectives:**

- To perform population PK analysis of naloxone that describe PK of naloxone following intramuscular/subcutaneous administration using NAI in healthy subjects
- To construct mechanistic PK-PD models of OIRD for different opioids (morphine, buprenorphine, fentanyl, and carfentanil) in combination with population PK model of NAI
- To conduct model-based simulations to determine the effectiveness of NAI 10 mg for different opioids and doses, to evaluate the effect of a second dose of NAI 10 mg on OIRD, and to examine how the timing of NAI 10 mg administration prior to fentanyl and carfentanil exposure affects OIRD

**Data:** The PK data of 48 subjects from Studies KA-900DV-002 and KA-900DV-05A were used to develop population PK models for naloxone. The covariate characteristics of the data is provided in **Table 1**. The data for the population PK-PD models of OIRD were obtained from publications and the FDA source (Table 2).

**Table 1:** Summary statistics of the *48* subjects included in the PK dataset

| Covariates* | |
|---|---|
| **Demographics** | |
| *Age (years)* | 39.5 (23, 54) |
| *Body weight (kg)* | 77.8 (57.2, 100.2) |
| *BMI (kg/m2)* | 26.6 (18.8, 31.6) |
| *Male -* | 25 (52) |
| *Race -* | |
| *White* | 10 (21) |
| *Black* | 36 (75) |
| *Others* | 2 (4) |

* Mean (Min, Max) is provided for continuous variables; total number of subjects and its percentage is shown for categorial variables.
**Source:** Reviewer's analysis

**Method:** Nonlinear mixed effect PK modeling was conducted using NONMEM v7.3. The base structural model was first developed to describe naloxone PK profiles. Covariate modeling was done using stepwise forward ($p=0.05$) and backward ($p<0.001$) approach. Continuous and categorical covariates were included into the model. The final PK model of naloxone was evaluated using goodness-of-fit plots and visual predictive checks.

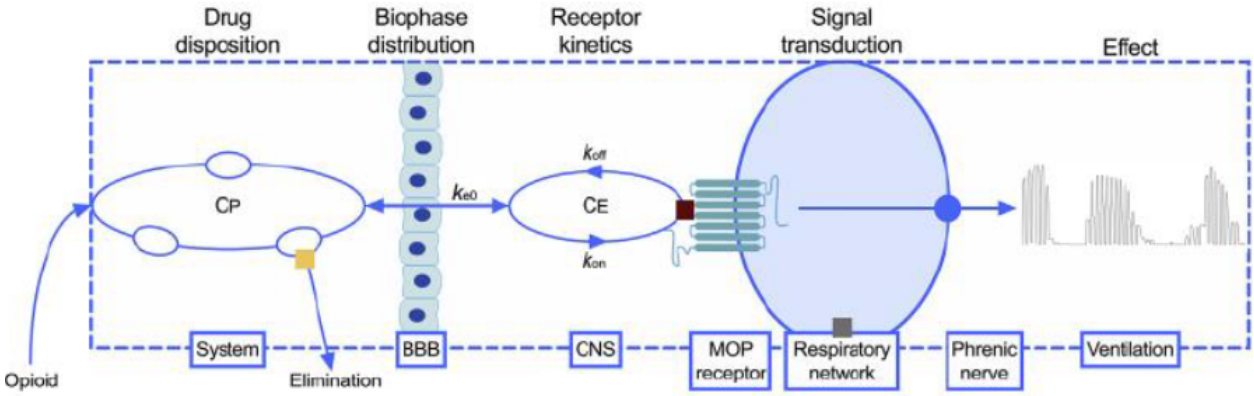
The mechanistic PK-PD models of OIRD (**Table 2**) and the reversal effect by naloxone was constructed using the combined biophase equilibration-receptor association/dissociation model (**Figure 1)**. Briefly, the opioid will pass across the blood-brain barrier (biophase distribution) after entering body and then interact with the MOP receptor expressed on neurons within the respiratory network according to association and dissociation kinetics. The decreased neuronal activity is transduced via the phrenic nerve to the lungs and cause various effects including depressed breathing. In case of naloxone administration to counter opioid effects, both the opioid and naloxone competitively bind to the MOP receptor at the site of action, which results in reversal effects of opioids.

**Table 2:** Summary of the mechanistic PK-PD models of opioids

| Opioid | Mechanistic PK-PD model | Reference |
|---|---|---|
| Morphine | • Three compartmental PK model for morphine<br>• Combined effect-compartment and receptor kinetics model with sigmoidal transduction function | Olofsen et al, 2010 |
| Buprenorphine | • Three compartmental PK model for buprenorphine<br>• Combined effect-compartment and receptor kinetics model with linear transduction function | Yassen et al, 2007 |
| Fentanyl | • Two compartmental PK model for fentanyl<br>• Combined effect-compartment and a fractional Emax PD model | Yassen et al, 2007 |
| Carfentanil | • PK exposure in human extrapolated using animal data from rabbit and mice<br>• Combined effect-compartment and receptor binding kinetics model with linear relationship between ventilation and carbon dioxide at steady state | Feasel et al, 2017; Smith et al, 2019; Olofsen et al, 2010; Github FDA, 2021 |

**Source:** Applicant's PK/PD modeling report: Page 22, Table 2.

**Figure 2:** Schematic representation of PK-PD of an opioid in the human body




BBB=blood brain barrier; CE=effect-site concentration; CNS=central nervous system; CP=plasma concentration; MOP=mu-opioid
**Source:** Applicant's PK/PD modeling report: Page 30, Figure 2.

The PK-PD simulations (200 trials of 100 subjects per each scenario) were then conducted to determine the effectiveness of NAI 10 mg for different opioids and doses, to evaluate the effect of a second dose of NAI 10 mg on OIRD, and to examine how the time of NAI 10 mg administration prior to fentanyl and carfentanil exposure affects OIRD, using the mechanistic PK-PD models of OIRD.

- **Impact of NAI on OIRD:** The effect of NAI 10 mg on reversal of OIRD was evaluated in simulation scenarios of different IV doses of opioids i.e., buprenorphine (0.9 µg/kg, 9.9 µg/kg, 18.9 µg/kg), morphine (0.2 mg/kg, 2.2 mg/kg, 4.2 mg/kg), fentanyl (2.1 µg/kg, 23.1 µg/kg, 44.1 µg/kg), and carfentanil (0.2 µg/kg, 2.2 µg/kg, 4.2 µg/kg). For all opioids, the maximum dose was 21 times the starting dose (i.e., the dose evaluated in the literature (except for carfentanil) or based on the EC50 of carfentanil). The time to give the first dose of naloxone was at a 60% reduction from ventilation baseline (i.e., 40% ventilation) for morphine, fentanyl and carfentanil. For buprenorphine, the first dose was given at 70% ventilation as it is a partial agonist characterized by a slow onset of the respiratory depressant effect. The simulations did not include a delay of time for administering the NAI as it did not require preparation time and can be injected in <1 min based on the Human Factors studies.

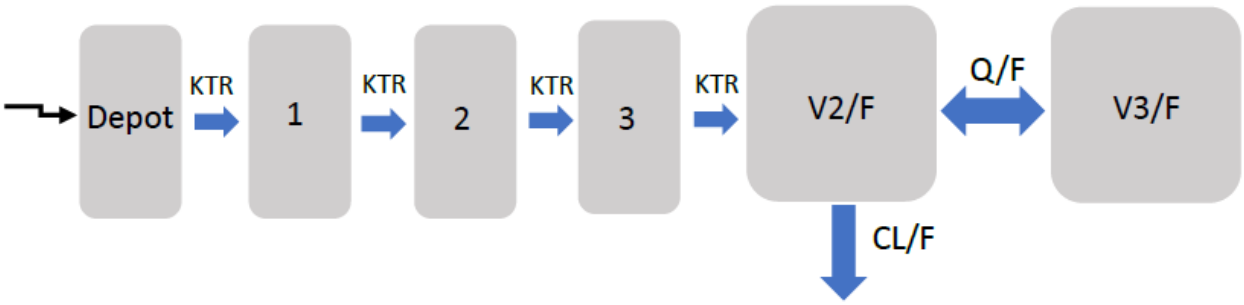
- **Impact of second NAI dose:** The subjects who received the first naloxone dose at the pre-defined threshold levels received the second dose of NAI 10 mg at 60 minutes after the opioid exposures. Only the highest dose for all 4 opioids was examined (i.e., 18.9 µg/kg buprenorphine, 4.2 mg/kg morphine, 44.1 µg/kg fentanyl and 4.2 µg/kg carfentanil) to simulate the effect of NAI 10 mg on the reversal of OIRD.

- **Impact of prior NAI exposure:** NAI 10 mg was administered at -60 min, -30 min, -15 min and -5 min before exposure to fentanyl (44.1 µg/kg fentanyl) or carfentanil (4.2 µg/kg carfentanil).

The median and 90th percentiles of medians from the simulations on ventilation versus time profiles were obtained and presented graphically to evaluate the reversal of OIRD by NAI 10 mg. Various metrics were derived from the results including % subjects recovered to threshold (40%, 70%, or 85% baseline ventilation), rescue time and renarcotization time, etc. The rescue time was defined as the difference between the timepoint when naloxone was first administered and when minute ventilation volume first recovered back above the threshold (40% or 70% of baseline ventilation). The renarcotization time was defined as the difference between the timepoint when naloxone was first administered and when ventilation first recovered back above 85% of baseline but then returned below 85% of baseline.

**Results:** The PK of naloxone was described by a two compartments model with 3 transit absorption compartments and linear first order elimination from the central compartment (**Figure 2**). Body weight was added on clearance using allometric exponents. The parameter estimates of the final pop PK model for naloxone are shown in **Table 3**. The population PK model for naloxone was assessed with diagnostics plots including goodness-of-fit and visual predictive checks (**Figure 3**). In general, the median, 5th and 95th percentiles of the observed data are contained within the 95% confidence intervals of the corresponding simulations, confirming the predictive performance of the model.

**Figure 2**: Schematic representation of the PK model for naloxone




KTR: transit rate constant; CL/F: apparent clearance of naloxone; V2/F: apparent volume of central compartment; V3/F: apparent volume of peripheral compartment; Q/F: apparent intercompartmental clearance of naloxone
**Source:** Applicant's PK/PD modeling report: Page 50, Figure 5.

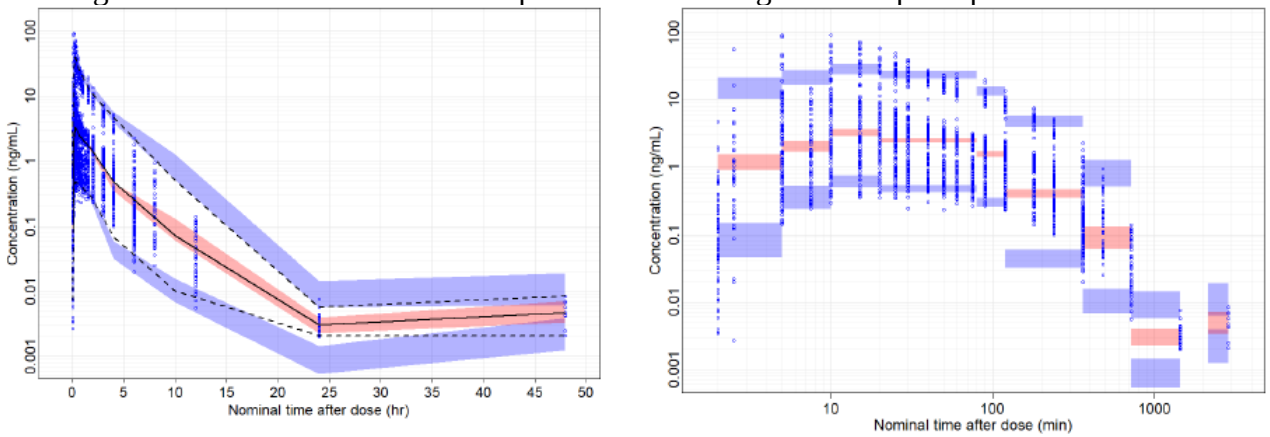
**Table 3**: Parameter estimates of sponsor's final population PK model for naloxone using NAI

| Parameters (Unit) | Estimate | RSE (%) | Shrinkage (%) |
|---|---|---|---|
| **Primary parameters** | | | |
| CL/F (L/min) | 3.26 | 2.5 | n/a |
| V2/F (L) | 404 | 4.2 | n/a |
| Q/F (L/min) | 0.0847 | 7.7 | n/a |
| V3/F (L) | 81.8 | 10.5 | n/a |
| KTR (1/min) | 0.696 | 6.0 | n/a |
| Body weight on CL/F | 0.538 | 14.4 | n/a |
| **Random effect** | | | |
| BSV CL/F (CV%) | 0.0129 (11.4) | 22.6 | 12 |
| BSV V2/F (CV%) | 0.0658 (25.7) | 19.5 | 4.2 |
| BSV KTR (CV%) | 0.111 (33.3) | 40.2 | 20.5 |
| BOV KTR (CV%) | 0.127 (35.6) | 21.1 | 13.9/27.9/45.2 |
| **Residual variability** | | | |
| Proportional residual error (CV%) | 0.157 (39.6) | 10.3 | n/a |

Minimum value of the objective function = -1232.879
Condition number was = 25.69 (indicating no over-parametrization is observed in the model)
CV % of proportional residual error is calculate as 100 * sqrt(SIGMA); CV % of exponential ETAs are calculated as 100 * sqrt(exp(OMEGA)).
RSE: Relative Standard Error; n/a: not applicable; KTR: transit rate constant, CL/F: apparent clearance, Q/F: apparent intercompartmental CL; V2/F: apparent central volume of distribution: V3/F: apparent peripheral volume of distributions; BSV: Between Subject Variability; BOV: Between Occasional Variability.
Source: run45.lst

**Source:** Applicant's PK/PD modeling report: Page 61, Table 13.

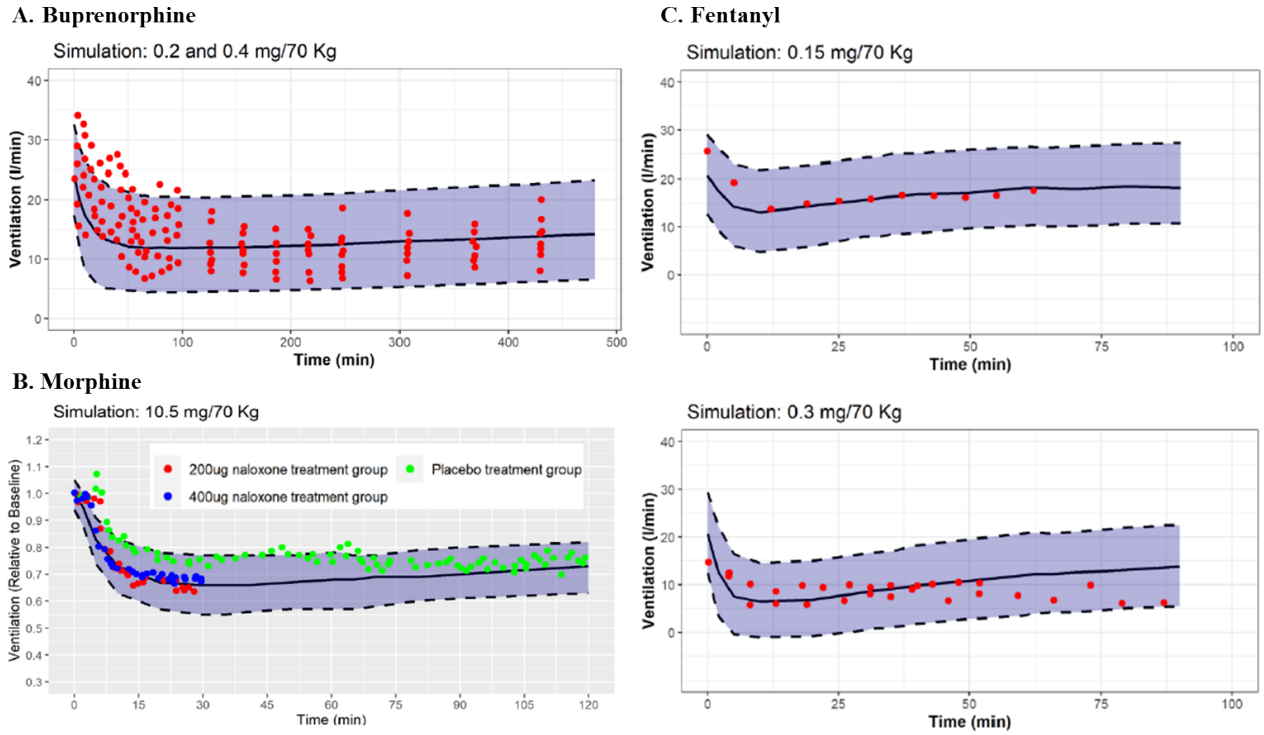
**Figure 3**: Visual predictive check of naloxone final population pk model; Right panel is presented with log scale on x-axis to check model performance during the absorption phase.




**Source:** Applicant's PK/PD modeling report: Page 62, Figure 12.

The PK-PD models of opioids, as described in **Table 2**, were validated with external clinical observation from the literature on the time course of OIRD (**Figure 4**) except for carfentanil due to a lack of PK and PD carfentanil data in humans. As per sponsor, most of the observed clinical data were contained within the 90% prediction interval of the corresponding simulations, confirming the predictive performance of the model for buprenorphine, morphine, and fentanyl (**Figure 4**).

**Figure 4:** Comparison of time course of OIRD from clinical observation and model prediction for buprenorphine, morphine, and fentanyl




**Source:** Adapted from Applicant's PK/PD modeling report: Page 64-72, Figure 15-17.

*Reviewer's comments: The PK/PD model of buprenorphine, morphine and fentanyl were based on the literature (Table 2), and the model diagnostics could not be reproduced by the reviewer due to unavailability of data.*

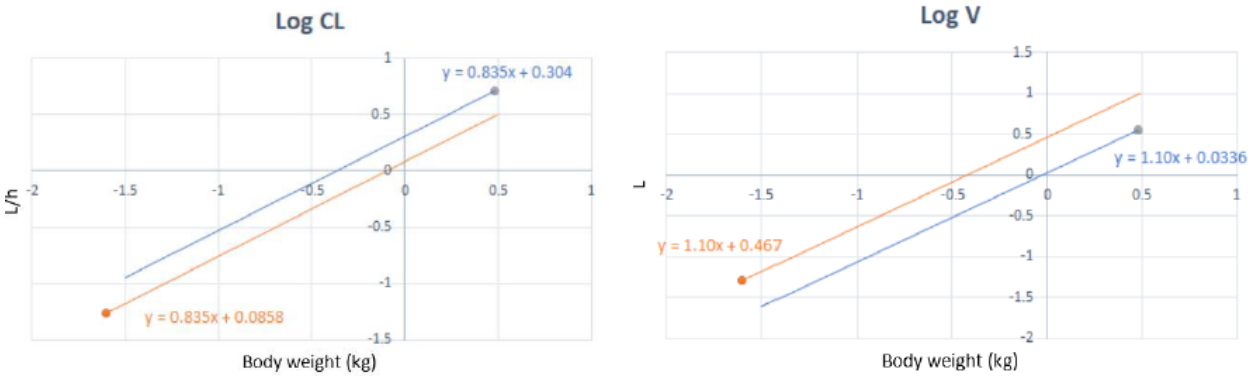
- *The PK/PD model of buprenorphine overpredicted the buprenorphine-induced ventilatory depression during the first 100 min of opioid exposure (Figure 4A), but reasonably predicted later phase (beyond 100 min) of ventilation.*
- *The PK/PD model of morphine reasonably predicted mean ventilation for 200 ug and 400 ug naloxone treatment groups (subject received naloxone doses at 30 mins after morphine administration).*

- *The PK/PD model of fentanyl reasonably predicts ventilation after fentanyl 0.15 mg/70 kg dose, but underpredicts the ventilatory depression after fentanyl 0.3 mg/70 kg dose during later phase (beyond 30 minutes) (Figure 4C).*

*Overall, these PK/PD models have some level of inadequacy to predict OIRD but do provide informative trends regarding treatment effects. For more details on the reviewer's evaluation on these PK/PD models, please refer to Reviewer analysis section - Evaluation of the applicant's population PK/PD model for opioids.*

Considering PK data was available from two animal species, the PK data of fentanyl 0.1 mg/kg IV was also used to support allometric scaling of carfentanil PK to predict PK in human subjects. As a first step, non-compartmental PK parameters (CL and V) were derived from the available animal PK data. The PK parameters of fentanyl available in mouse, rabbit and human were used to identify the allometric exponents (0.83 for CL and 1.1 for V), which was then applied to scale PK parameters of carfentanil from animal to human. For the allometric coefficients (y-intercept), the regression line was passed through the points (x-axis: bodyweight, y-axis: CL or V) relative either to the mouse or rabbit data (**Figure 5**). This resulted in two different sets of PK parameters i.e., Scenario-1 showing carfentanil half-life of 5 h based on mouse data (CL: 42.3 L/h and V: 308 L); and Scenario 2 showing carfentanil half-life of 1 h based on rabbit data (CL: 69.9 L/h and V: 114 L). Due to the uncertainty in human PK predictions, simulations were run with both scenarios to evaluate the sensitivity of differences in half-lives of approximately 1 hour and 5 hours for carfentanil. Other PK parameters were assumed to be similar between fentanyl and carfentanil and scaled accordingly. For the PD model, a binding kinetic model was used, as per FDA recommendation (Github FDA, 2021), due to possibility that carfentanil may unbind slowly from the MOP receptor like buprenorphine. The validation of the PK-PD model was not conducted due to lack of carfentanil human clinical data.

**Figure 5:** Carfentanil allometric scaling of clearance and volume of distribution based on mouse and rabbit data as well as fentanyl allometric exponent (log-log scale) according to scenario 1 (orange) and scenario 2 (blue).

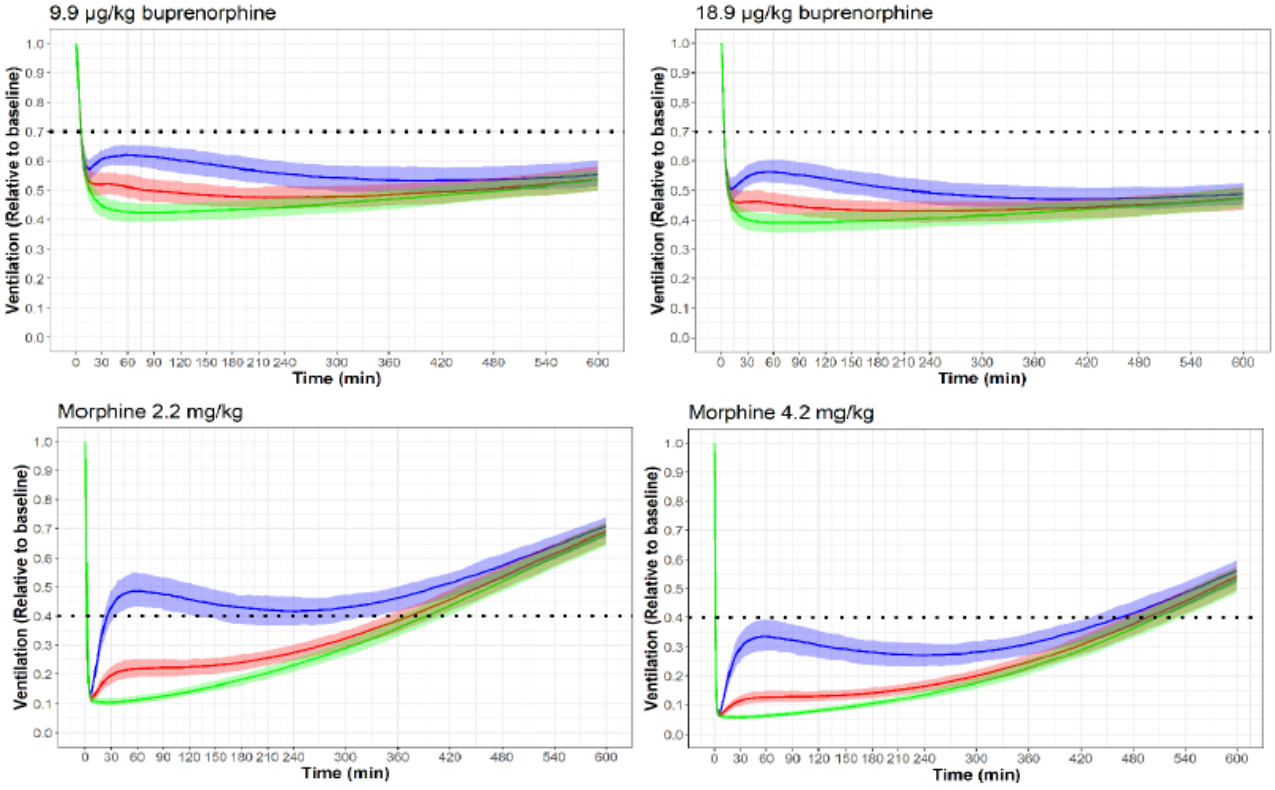


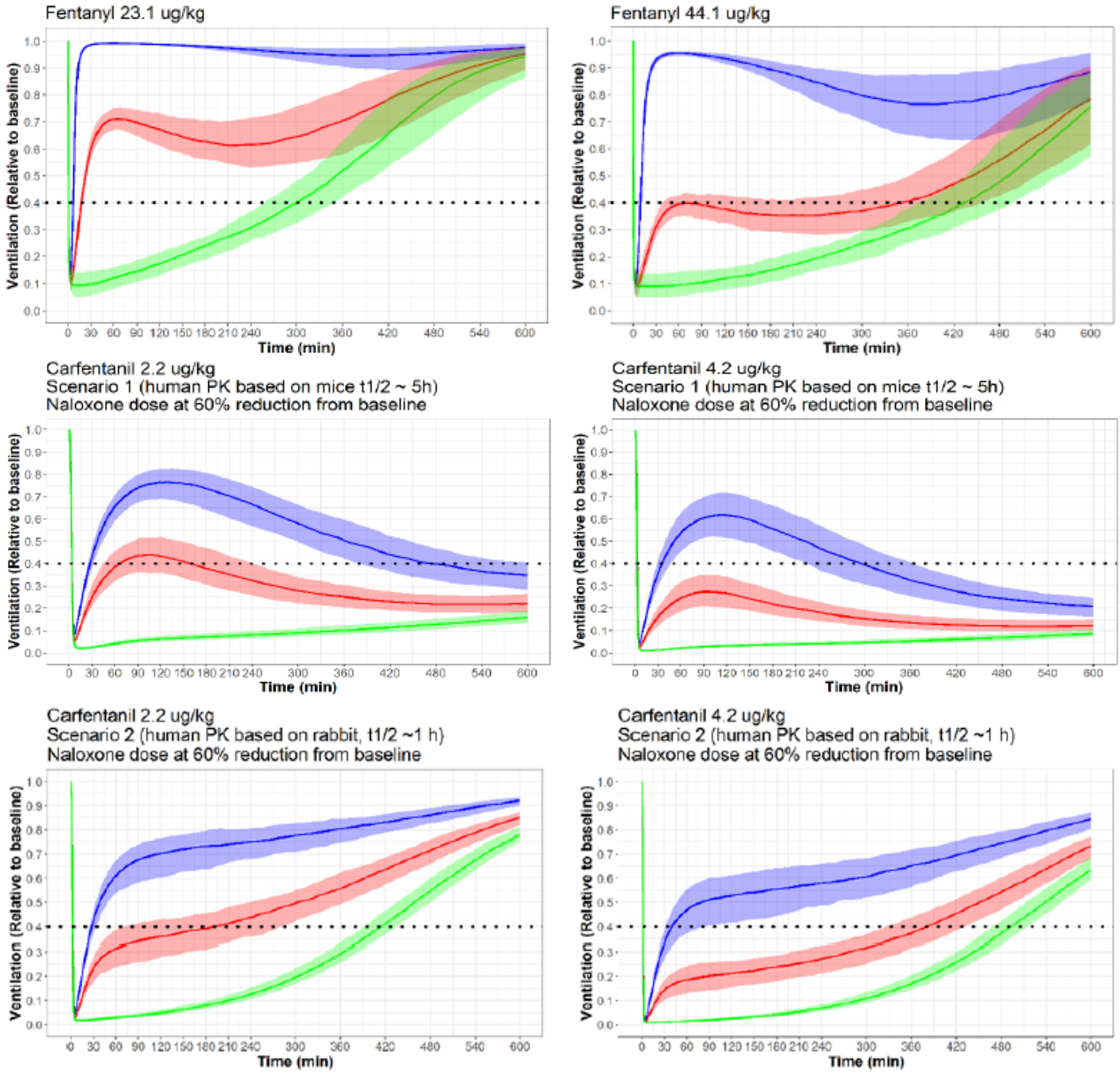

**Source:** Applicant's PK/PD modeling report: Page 71, Figure 21.

The results from the PK/PD simulations as follows:

- **Impact of NAI on OIRD:** The PK/PD simulations of single NAI on reversal of OIRD was shown in **Figure 6** and summarized in **Table 4**, which showed that NAI 10 mg administration resulted in higher percentage of subjects recovered back to the rescue thresholds (40%, 70%, or 85% baseline ventilation) with faster return when compared to naloxone 2 mg.
- **Impact of second NAI dose:** Second dose of NAI 10 mg expedited ventilation recovery by reducing rescue time when compared to single dose, with larger percentage of subjects recovered to at least 85% of baseline with longer time to renarcotization (**Figure 7** and **Table 5**).
- **Impact of prior NAI exposure:** Administration of NAI 10 mg at each timepoint prior to highest fentanyl and carfentanil doses administration (i.e., -60, -30, -15, and -5 minutes) prevent rapid and profound opioid-induced respiratory depression (**Figure 8** and **Table 6**).

**Figure 6:** Effects on ventilation (relative to baseline) for opioid-induced respiratory depression (median and 90% confidence interval of the median) by NAI 10 mg (blue), NAI 2 mg (red), and no naloxone (green)





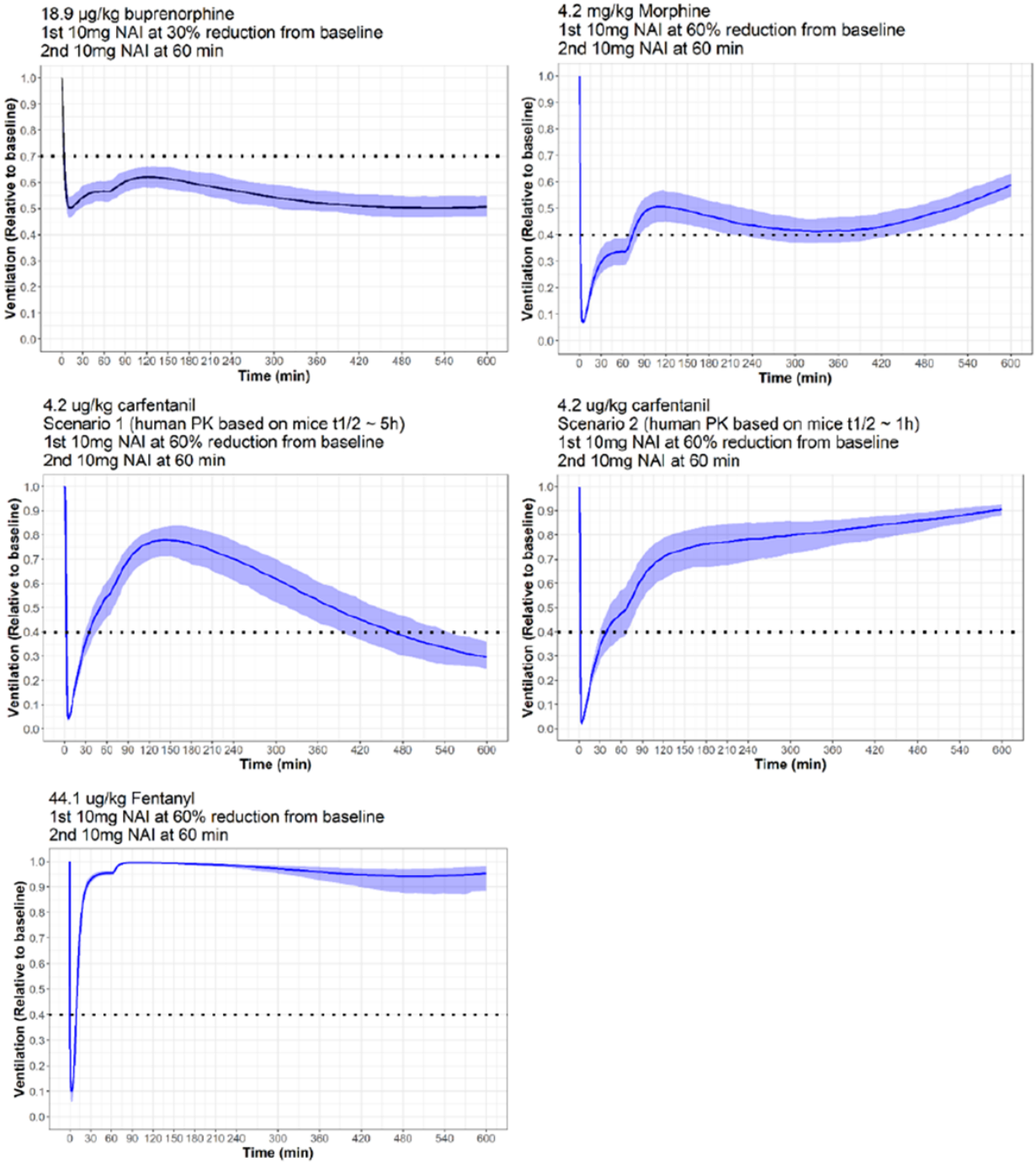

**Source:** Applicant's Clinical Summary: Page 26, Figure 2.7.2.2.3.3-1.

**Table 4**: Summary of the percentage of subjects who recovered to ventilation thresholds and rescue times after naloxone auto-injector administration

| Opioid (IV) | Opioid Dose | Recovery Ventilation Threshold | % Subjects who Recovered to Threshold (of those subjects who received NAI), Median [90% CI] | | Rescue Time (min), Median [90% CI] | |
|---|---|---|---|---|---|---|
| | | | NAI 2 mg | NAI 10 mg | NAI 2 mg | NAI 10 mg |
| Buprenorphine | 9.9 µg/kg | 40% | 71.1 [62.99 - 78.03] | 69.75 [61.39 - 78.01] | 200.25 [97.5 - 263.84] | 16.15 [8.4 - 279.4] |
| | | 70% | 16.95 [11 - 24.11] | 25.15 [17.39 - 32.61] | 339.9 [46.5 - 476.11] | 25.95 [16.36 - 41.62] |
| | | 85% | 4.6 [1.2 - 8.61] | 10.7 [5.99 - 16.11] | NC | NC |
| Buprenorphine | 18.9 µg/kg | 40% | 62.5 [54.89 - 70.51] | 62.3 [53.8 - 70.21] | 212.1 [84.5 - 286.86] | 17.3 [8.6 - 268.62] |
| | | 70% | 9.8 [5.4 - 15.11] | 16.5 [10.99 - 23.11] | 370 [40.88 - 504.05] | 23.7 [15.98 - 48.1] |
| | | 85% | 2.15 [0 - 4.4] | 6.2 [2.2 - 10.5] | NC | NC |
| Morphine | 2.2 mg/kg | 40% | 94 [90.67 - 98] | 97 [93.86 - 99] | 351.35 [312.77 - 385.01] | 21.9 [18.18 - 30.83] |
| | | 70% | 48.5 [37.4 - 55.03] | 58 [49 - 65.03] | 506.8 [480.79 - 529.82] | 413.9 [264.69 - 477.62] |
| | | 85% | 13.1 [8 - 19.62] | 20 [14 - 28] | NC | NC |
| Morphine | 4.2 mg/kg | 40% | 77 [69 - 83] | 83 [78 - 89] | 450.9 [422.06 - 477.07] | 161.8 [29.8 - 365.07] |
| | | 70% | 21 [14.95 - 27] | 29 [21.95 - 37.1] | 540.65 [514.99 - 563.08] | 477.9 [288.23 - 526.33] |
| | | 85% | 4 [1 - 7] | 6 [3 - 11] | NC | NC |
| Fentanyl | 23.1 µg/kg | 40% | 95.8 [92.5 - 99] | 100 [98.9 - 100] | 16.7 [14.8 - 18.7] | 6.4 [5.8 - 6.8] |
| | | 70% | 75.5 [68.8 - 81.92] | 100 [98.9 - 100] | 31.95 [28 - 37.9] | 8.8 [8 - 9.4] |
| | | 85% | 61.7 [54.2 - 71.3] | 100 [98.9 - 100] | NC | NC |
| Fentanyl | 44.1 µg/kg | 40% | 72 [65.28 - 79.41] | 99 [97.8 - 100] | 36.2 [29.2 - 45.81] | 9 [8.4 - 9.8] |
| | | 70% | 54.25 [45.18 - 63.51] | 98.9 [96.8 - 100] | 311.8 [220.55 - 383.42] | 13.4 [12.4 - 14.6] |
| | | 85% | 45.95 [37.17 - 54.3] | 93.6 [88.8 - 97.9] | NC | NC |
| Carfentanil Scenario 1, $T_{½}$ ~5 hrs | 2.2 µg/kg | 40% | 54.5 [46.5 - 62.01] | 81 [73.98 - 87] | 26 [22 - 30.23] | 19.85 [17.8 - 22.8] |
| | | 70% | 26.3 [19.19 - 34.33] | 58 [49 - 65.32] | 48.6 [41.8 - 56.43] | 42.45 [39 - 47.01] |
| | | 85% | 12.1 [7 - 17.35] | 38 [29.96 - 47.05] | NC | NC |
| Carfentanil Scenario 1, $T_{½}$ ~5 hrs | 4.2 µg/kg | 40% | 37 [30 - 46] | 68 [59.95 - 75] | 28.2 [23.59 - 33.6] | 22 [19.09 - 24.61] |
| | | 70% | 15 [9.96 - 22.05] | 43 [34.28 - 52] | 50.45 [41.4 - 59.9] | 45 [39.79 - 49.2] |
| | | 85% | 6 [3 - 11] | 26.3 [20 - 34.05] | NC | NC |
| Carfentanil Scenario 2, $T_{½}$ ~1 hr | 2.2 µg/kg | 40% | 98 [95 - 100] | 99 [97.95 - 100] | 165.6 [55.99 - 266.11] | 24.8 [22.1 - 30.22] |
| | | 70% | 81 [75 - 87] | 91.9 [87 - 95] | 417.7 [360.81 - 453.61] | 78.75 [57.4 - 192.11] |
| | | 85% | 51 [42.88 - 59] | 73 [65.28 - 81] | NC | NC |
| Carfentanil Scenario 2, $T_{½}$ ~1 hr | 4.2 µg/kg | 40% | 91 [86 - 95] | 96 [92 - 99] | 338.5 [277.43 - 389.6] | 34.75 [27.09 - 57.44] |
| | | 70% | 57 [48 - 65] | 76 [68.95 - 82] | 474.9 [431.74 - 507.18] | 175.35 [68.53 - 320.04] |
| | | 85% | 25 [18 - 31] | 50.25 [40.38 - 58] | NC | NC |

**Source:** Applicant's Clinical Summary: Page 28, Table 2.7.2.2.3.3-2.

**Figure 7:** Effect of a second dose of NAI 10 mg on time course of ventilation (relative to baseline) for opioid-induced respiratory depression (median and 90% confidence interval of median)




**Source:** Applicant's Clinical Summary: Page 30, Table 2.7.2.2.3.4-1.

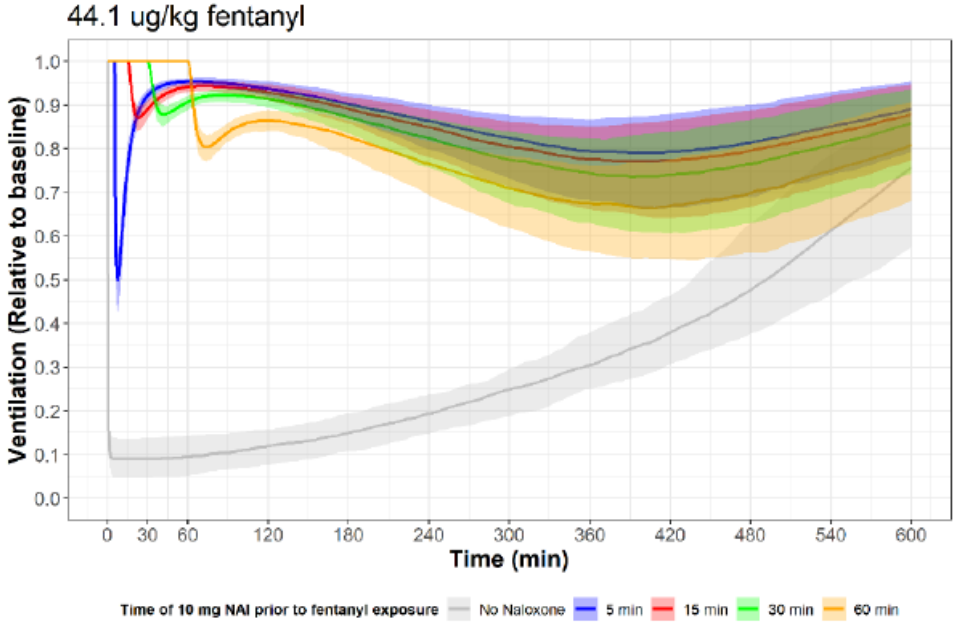
**Table 5**: Renarcotization time by second NAI 10 mg at 60 minutes following opioid-induced respiratory depression

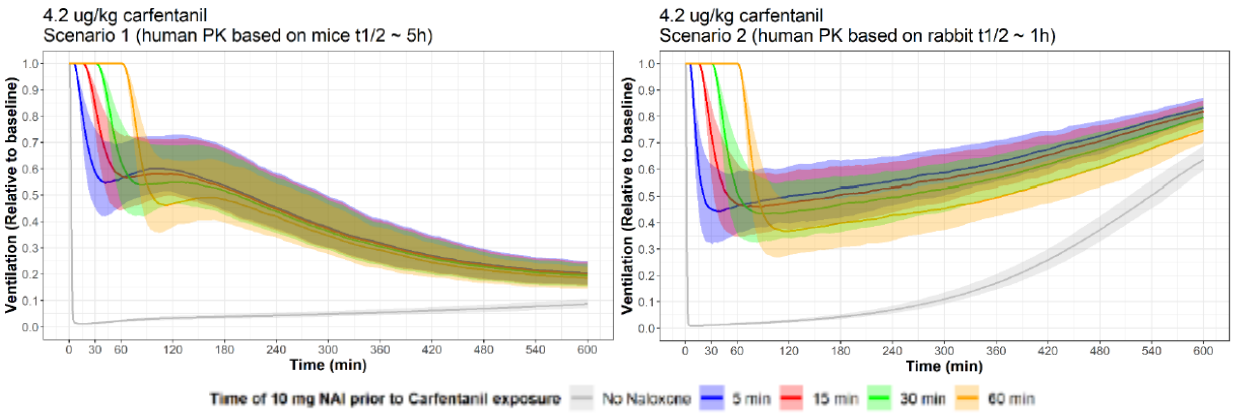
| Opioid IV Dose | # of 10 mg NAI | % subjects who recovered back to above 85%*, Median [90% CI] | % subjects who experienced renarcotization**, Median [90% CI] | Time to renarcotization (min)***, Median [90% CI] |
|---|---|---|---|---|
| Buprenorphine 18.9 ug/kg | 1 | 6.2 [2.2 – 10.5] | 66.7 [28.42 – 100] | 183.65 [102.76 – 298.98] |
| | 2 | 11.7 [6.5 – 16.8] | 69 [45.4 – 90.9] | 258.8 [177.5 – 340.3] |
| Morphine 4.2 mg/kg | 1 | 6 [3 - 11] | 25 [0 - 55.67] | 121.65 [66.94 - 229.07] |
| | 2 | 12 [7 - 18] | 37.5 [14.25 - 62.5] | 190 [143.72 - 301.66] |
| Fentanyl 44.1 ug/kg | 1 | 93.6 [88.8 - 97.9] | 51.2 [41.88 - 60.53] | 155.5 [135.2 - 177.21] |
| | 2 | 100 [98.9 - 100] | 39.9 [31.2 - 48.52] | 303.7 [279.6 - 338.18] |
| Carfentanil 4.2 ug/kg Scenario 1 | 1 | 26.3 [20 - 34.05] | 90.25 [78.27 - 100] | 296.2 [242.32 - 352.31] |
| | 2 | 41.2 [33 - 48] | 81.8 [72.06 - 91.72] | 340.65 [295.39 - 390.62] |
| Carfentanil 4.2 ug/kg Scenario 2 | 1 | 50.25 [40.38 - 58] | 4.3 [0 - 10.91] | 289.8 [189.16 - 418.57] |
| | 2 | 67 [59 - 74] | 4.2 [0 - 7.53] | 334.2 [218.6 - 438.98] |

* Among subjects who received naloxone dose; ** Among subjects who recovered back above 85% of baseline; *** If % subject who experienced renarcotization was zero per simulation, it was excluded to calculate statistical summary of the time of renarcotization

**Source:** Adapted from Applicant's PK/PD modeling report: Page 93-99, Table 31, 33, 35, 37.

**Figure 8**: Ventilation time course (relative to baseline) of different naloxone auto-injector administration times prior to opioid exposure (median and 90% confidence interval of median)






**Source:** Adapted from Applicant's PK/PD modeling report: Page 100-102, Figure 30-31.

**Table 6:** Summary of maximum ventilation suppression and time to reach maximum ventilation suppression following different NAI 10 mg injection times prior to opioid exposure

| | | | | Median [90% CI] | |
|---|---|---|---|---|---|
| **Opioid (IV)** | **Opioid Dose** | **NAI Dose (mg)** | **Time of NAI Administration Prior to Opioid (min)** | **Max Ventilation Suppression (Relative to Baseline)** | **Time from Opioid Exposure to Max Ventilation Suppression (min)** |
| Fentanyl | 44.1 µg/kg | 0 | NA | 0.09 [0.05 - 0.14] | 9.9 [9 - 10.9] |
| | | 10 | 5 | 0.49 [0.42 - 0.56] | 2.6 [2.4 - 2.7] |
| | | 10 | 15 | 0.83 [0.8 - 0.86] | 8.9 [7.7 - 10.1] |
| | | 10 | 30 | 0.84 [0.81 - 0.86] | 12.7 [10.9 - 15.2] |
| | | 10 | 60 | 0.77 [0.73 - 0.8] | 13.3 [11.5 - 15.2] |
| Carfentanil Scenario 1, $T_{½}$ ~5 hrs | 4.2 µg/kg | 0 | NA | 0.01 [0.01 - 0.01] | 15.8 [15.59 - 16.3] |
| | | 10 | 5 | 0.54 [0.42 - 0.69] | 38.9 [32.5 - 46.43] |
| | | 10 | 15 | 0.55 [0.43 - 0.71] | 54.05 [44.7 - 88.3] |
| | | 10 | 30 | 0.53 [0.41 - 0.68] | 55.3 [45.98 - 78.1] |
| | | 10 | 60 | 0.46 [0.35 - 0.63] | 50.65 [42.6 - 59.8] |
| Carfentanil Scenario 2, $T_{½}$ ~1 hr | 4.2 µg/kg | 0 | NA | 0.01 [0.01 - 0.01] | 10 [9.7 - 10.3] |
| | | 10 | 5 | 0.42 [0.31 - 0.56] | 29.35 [22 - 43.61] |
| | | 10 | 15 | 0.45 [0.34 - 0.57] | 62.65 [46.58 - 83.67] |
| | | 10 | 30 | 0.42 [0.32 - 0.54] | 65.2 [50.48 - 86.3] |
| | | 10 | 60 | 0.36 [0.26 - 0.48] | 57.9 [45.2 - 59.8] |

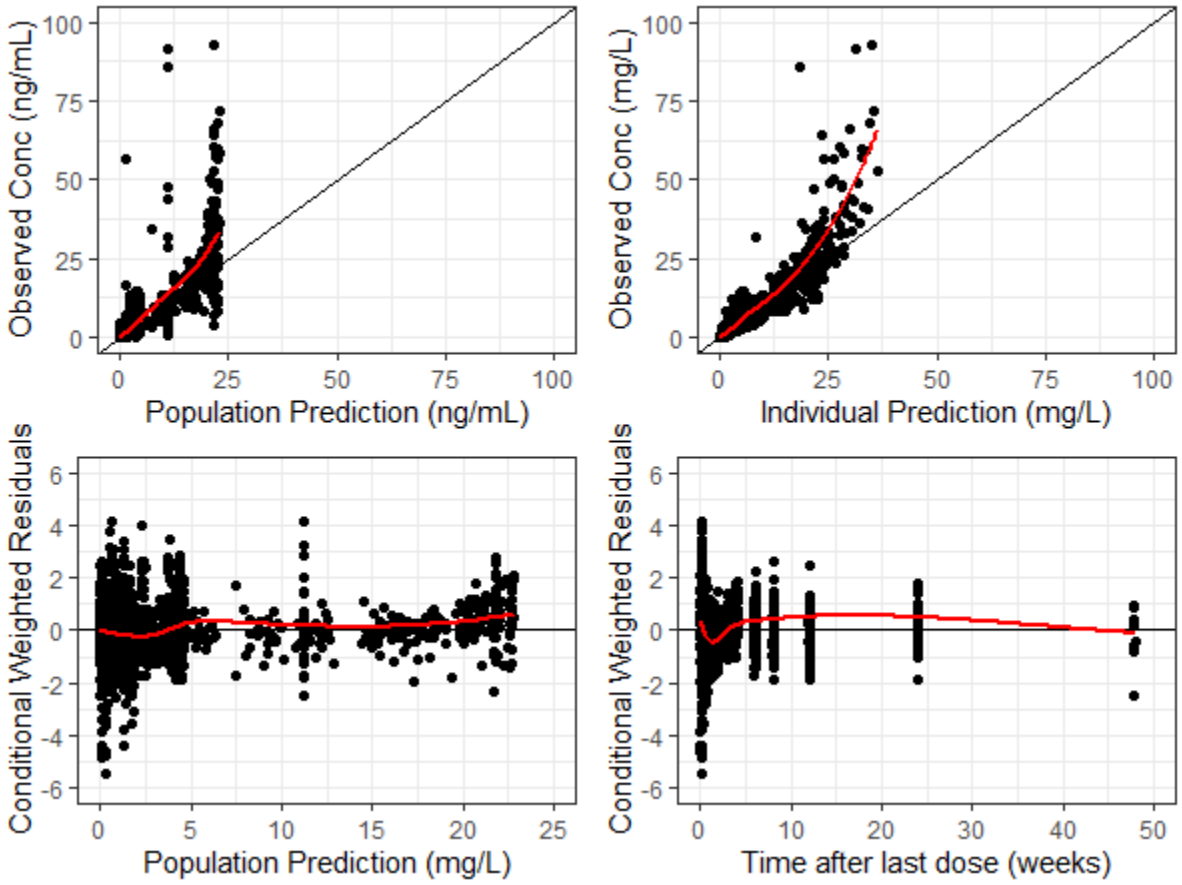
**Source:** Applicant's Clinical Summary: Page 33, Table 2.7.2.2.3.5-1.

## REVIEWER'S ANALYSIS

### Applicant's population PK model evaluation

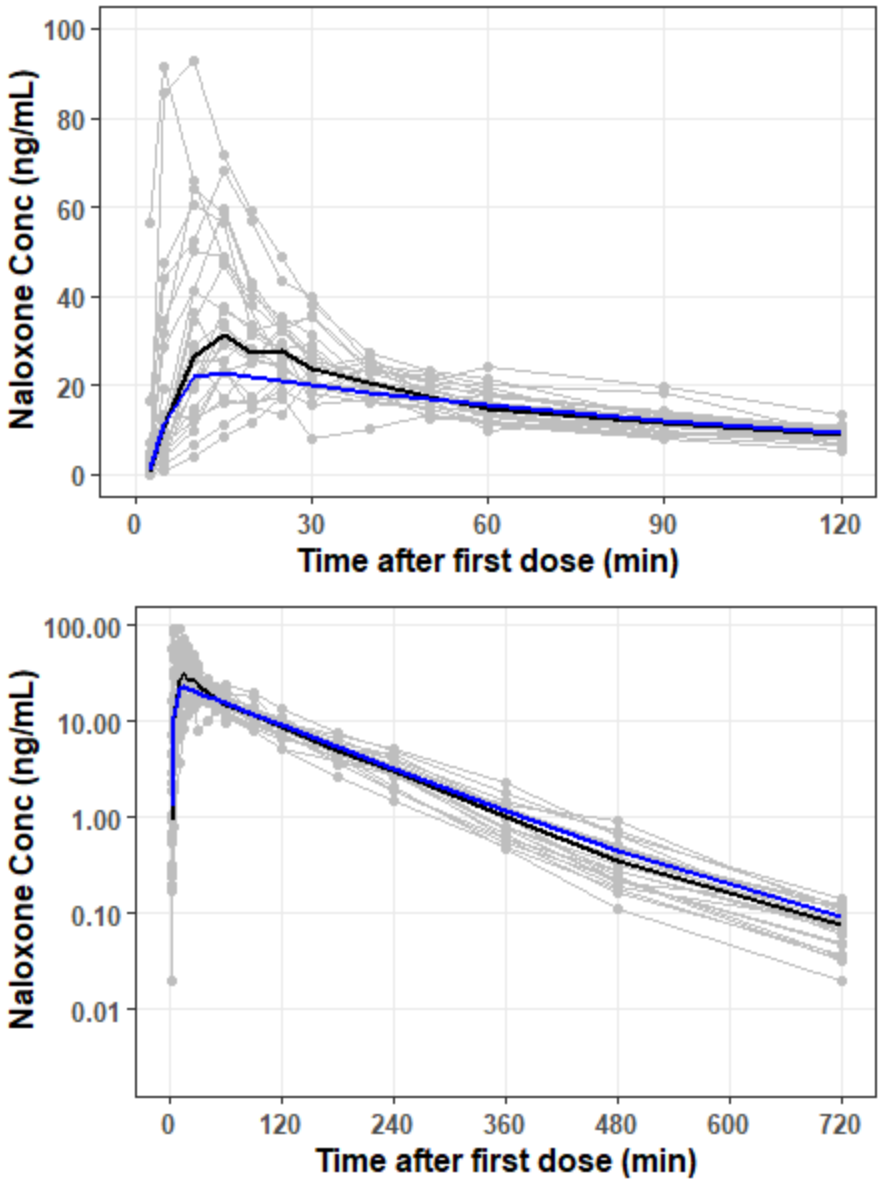
The reviewer was able to run the applicant's final PK model and obtained similar results. Model diagnostics for naloxone are shown in **Figure 9** and **Figure 10**, respectively. Overall, lower $C_{max}$ (35%) and lower AUC (8%) was predicted by the model as compared to the observed data. The underprediction in $C_{max}$ was related to unaccounted more-than-dose-proportional increase in Cmax in the PK model. More than dose proportional increase in $C_{max}$ was observed in Study KA-900DV-002 (dose normalized geometric mean ratio [90% CI] for $C_{max}$ between 10 mg and 2 mg was 1.21 [1.07,1.37]) and Study KA-900DV-05A (dose normalized geometric mean ratio [90% CI] for $C_{max}$ between 2 mg and 0.4 mg was 1.24 [1.04,1.49]). The clinical relevance of the underpredicted $C_{max}$ is further discussed in Reviewer's analysis section - Applicant's population PK/PD simulation evaluation.

**Figure 9:** Goodness-of-fit plots of applicant's population PK model for naloxone.




**Source**: Reviewer's analysis

**Figure 10:** Comparison of the model-predicted median PK profiles with observed data during the first 2 hours (top plot) and the first 12 h (bottom plot) after the NAI 10 mg administration.




Blue and black lines represented model-predicted and observed median of the data. Grey and red solid circle represents observations.
**Source**: Reviewer's analysis

**Evaluation of the applicant's population PK/PD model for opioids**

The PK/PD model of buprenorphine, morphine, fentanyl and carfentanil were based on the literature (Table 2), and the model diagnostics could not be reproduced by the reviewer due to unavailability of data. However, the literature was reviewed for the adequacy of these PK/PD models to describe the PK and PD (i.e., OIRD) of these opioids, and is described below:

**Buprenorphine**: The PK-PD model of buprenorphine on OIRD is a three-compartment buprenorphine PK model with PD model of combined effect-compartment and receptor kinetics model with linear transduction function. The model was developed using data of 44 healthy subjects (age range 19 - 30 years) from an adaptive naloxone dose-selection trial following IV administration of buprenorphine 0.2 mg/70 kg and 0.4 mg/70 kg. The PK/PD parameters of the model were estimated with reasonable precision (RSE ≤ 50%) with higher RSE for the random effects on central volume of distribution (71% RSE) and intercompartmental clearance (51% RSE). The model diagnostics (goodness-of-fit plots, observed vs. population prediction for individuals, and external VPC) provided in the literature suggested that the PK/PD model of buprenorphine is reasonable to describe buprenorphine-induced respiratory depression.

**Morphine**: The mechanistic PK-PD model of morphine on OIRD is a three-compartment morphine PK model with PD model of combined effect-compartment and receptor kinetics model with linear transduction function. The model was developed using data of 24 healthy subjects (age range 19 - 27 years) who received morphine 0.15 mg/kg IV followed by placebo (n=8), 200 ug naloxone IV (n=8) or 400 ug naloxone IV (n=8) at 30 minutes after morphine administration. The PK/PD parameters of the model were estimated with reasonable precision (RSE ≤50%). The model diagnostics were not provided for the PK model. For the PD, the model diagnostics (goodness-of-fit plots, and data fits for individuals) provided in the literature suggested that the PK/PD model of morphine is reasonable to describe morphine-induced respiratory depression.

**Fentanyl**: The mechanistic PK-PD model of fentanyl on OIRD is a two-compartment fentanyl PK model with PD model of effect compartment link model with a fractional Emax PD model. The model was developed using data of 24 healthy subjects (age range 19 - 27 years) who received fentanyl dose of 0.075 mg, 0.15 mg, 0.2 mg, 0.3 mg and 0.5 mg/70 kg. The PK/PD parameters of the model were estimated with reasonable precision (RSE ≤ 50%) with higher RSE for shape parameter (74.6%) and EC50 random effects (66% RSE). The model diagnostics were not provided for the PK model. For the PD, the model diagnostics (data fits for three individuals) provided in the literature suggested that the PK/PD model of fentanyl is reasonable to describe fentanyl-induced respiratory depression.

The applicant provided **Figure 4** to show the validity of the above-mentioned PK/PD models of opioids. Overall, these PK/PD models have some level of inadequacy to predict OIRD but do provide informative trends regarding treatment effects.

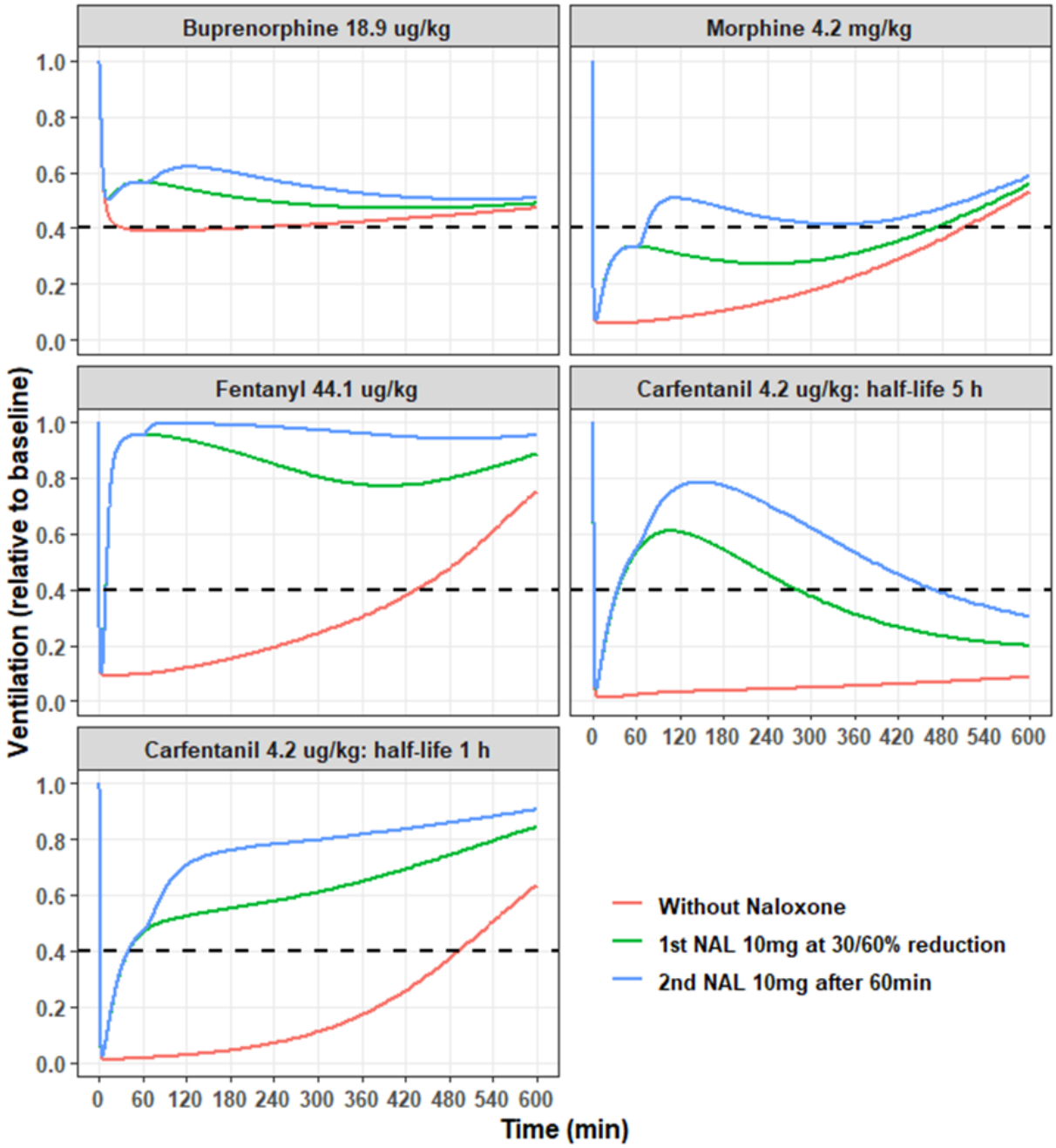
**Carfentanil**: Considering limited human PK and PD data on carfentanil, the PK model was developed based on animal data and the PK information available from fentanyl. In terms of animal data, the PK available in African green monkey after IV/SC administration was not utilized as carfentanil bioavailability was not available for these routes, and thus PK data of carfentanil given IV in mouse and rabbit was utilized. As only two animal species were available for allometric scaling of carfentanil from animal to human, the applicant relied on fentanyl animal data to derive allometric scaling factor for CL and V considering carfentanil is a fentanyl

analog with similar lipophilicity. The PK model also assumed similar structure, intercompartmental clearance (3.51 L), and drug distribution (Vc = 12%*V) as fentanyl. The applicant's analysis, as also described in the result section of the applicant analysis, resulted in two PK scenarios differing in carfentanil half-life. In scenario 1, carfentanil showed half-life of ~5 h, which was similar to a carfentanil human case report, in which carfentanil half-life of 5.7 h was reported, based on 3 PK samples taken up to 52 h after hospital admission, in a 34-year male admitted with depressed level of consciousness and in respiratory failure after recreational exposure to carfentanil (Uddayasankar et al, 2018). In scenario 2, carfentanil showed half-life of ~1 h, similar to a literature in which carfentanil half-life of 42-51 min was reported (Minkowski et al, 2012). In this study, low dose (mean dose ~0.05 ug/kg) of carfentanil was given to 23 cocaine users (mean age 33.8) and 15 healthy subjects (mean age 43.9) and PK was measured up to 90 minutes post-opioid exposure (Minkowski et al, 2012). Therefore, limited evidence are available from human PK data to support both PK scenarios, described by the applicant. Due to the uncertainty of human PK, these two scenarios can evaluate the sensitivity of differences in half-lives of approximately 1 hour and 5 hours on carfentanil-induced respiratory depression. For the PD model, a binding kinetic model was used, as per FDA recommendation (Github FDA, 2021), due to possibility that carfentanil may unbind slowly from the MOP receptor like buprenorphine. The validation of the PK-PD model was not conducted due to lack of carfentanil human clinical data.

**Applicant's population PK/PD simulation evaluation**

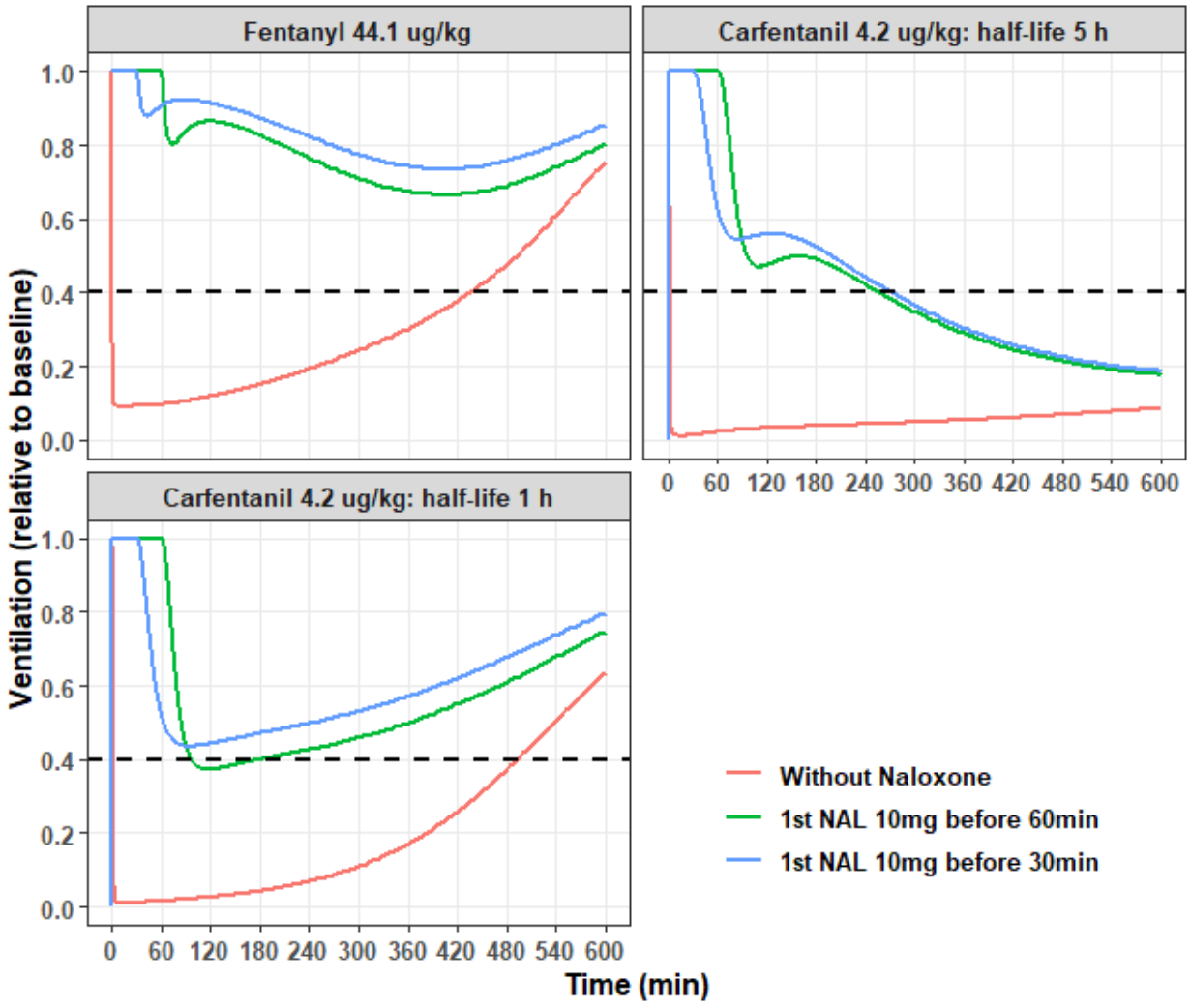
The reviewer also reproduced the applicant's PK/PD simulations with a focus on naloxone's reversal effect on the highest opioid doses and obtained similar results (**Figure 11** and **Figure 12**). Overall, the results suggested that naloxone 10 mg administration will result in higher percentage of subjects recovered back to the rescue thresholds (40%, 70%, or 85% baseline ventilation) with faster return when compared to Naloxone 2 mg. Second naloxone 10 mg dose at 60 minutes post-opioid exposure would expedite ventilation recovery. Administration of naloxone 10 mg at 5, 15, 30, or 60 minutes prior to fentanyl or carfentanil exposure can prevent rapid and profound opioid-induced respiratory depression.

**Figure 11:** Effects on ventilation (relative to baseline) for opioid-induced respiratory depression (median) by first and second dose of NAI 10 mg




**Source**: Reviewer's analysis

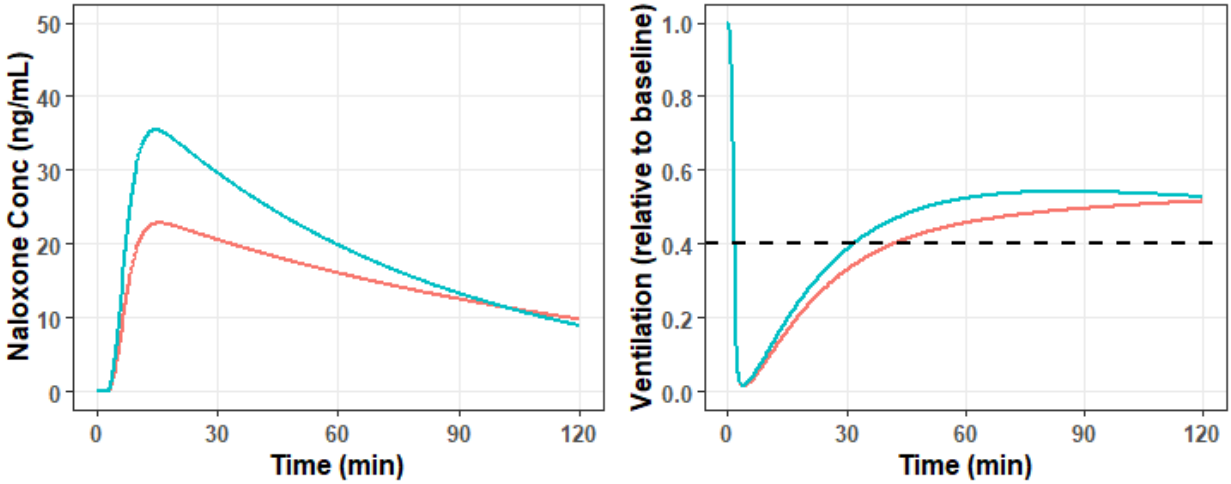
**Figure 12:** Median ventilation time course (relative to baseline) of different NAI administration times prior to opioid exposure




**Source**: Reviewer's analysis

As mentioned above in the reviewer's pop PK model evaluation section, the applicant's PK model underpredicted Cmax and AUC of naloxone by 35% and 8% respectively. The impact of lower Cmax on the reversal of OIRD was evaluated using PK/PD simulations. The PK model of NAI was modified to account for 35% decrease in Cmax and the resulting concentrations were then used to drive its PD effect on carfentanil-induced respiratory depression (**Figure 13**). The highest dose (4.2 ug/kg) of carfentanil assuming half-life of 1 h was used in the PK/PD simulations. The results suggested that ventilation returns to 40% baseline in 31.6 min using modified PK/PD model, while it takes 41.8 mins for the same using the original PK/PD model. Overall, the reviewer's sensitivity analysis suggested that applicant's simulation could provide a reasonable understanding of reversal effect of NAI on OIRD.

**Figure 13:** Impact of lower Cmax (~35%) of NAI 10 mg on naloxone's PK (left plot) and PD [i.e., carfentanil 4.2 ug/kg induced median respiratory depression assuming carfentanil half-life of 1 hour] (right plot).




Red and blue line indicate naloxone's PK and PD effect driven by original and modified PK/PD model respectively.
**Source**: Reviewer's analysis

The above-mentioned findings are based on the "reversal of opioid-induced respiratory depression" endpoint and have limitations due to various assumptions. For instance, this study assumed that metabolites of opioids are inactive and will not play a role in the duration or degree of respiratory depression. The studies did not consider known drug interactions (e.g., benzodiazepine-opioid or alcohol-opioid) that could influence respiration. Also, the delayed naloxone administration after onset of hypoxia or severe acute hypoxemia and subsequent naloxone resistance was not considered in the model. Lastly, the model did not account for biological factors such as chemoreceptors that influence the ventilation response to changes in oxygen and CO2 levels (e.g., hypoxic environments) and genotypic variations of enzymes that influence opioid metabolism

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