CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215457Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review and Division Summary Review

Date	February 28, 2022
From	Jennifer Nadel, MD (Primary Clinical Reviewer) Celia Winchell, MD (Cross Discipline Team Leader) Rigoberto Roca, MD (Division Director)
Subject	Cross-Discipline Team Leader Review and Summary and Cross-Discipline Team Leader Review
NDA #	215457
Applicant	Kaleo, Inc.
Date of Submission	August 31, 2021
PDUFA Goal Date	February 28, 2022
Proprietary Name	N/A
Established or Proper Name	Naloxone Hydrochloride Autoinjector10 mg
Dosage Form	10 mg IM/SC autoinjector
Applicant Proposed Indications/Populations	(b) (4)
Regulatory Action	*Approval*

Recommended Indications/Populations	For use by military personnel and chemical incident responders for: • Emergency treatment of patients 12 years of age and older where use of high-potency opioids such as fentanyl analogues as a chemical weapon is suspected. • Temporary prophylaxis of respiratory and/or central nervous system depression in military personnel and chemical incident responders entering an area contaminated with high-potency opioids such as fentanyl analogues.

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DMEPA 1 = Division of Medication Error Prevention and Analysis 1
DPV II = Division of Pharmacovigilance II
DPT-N = Division of Pharmacology/Toxicology for Neuroscience
DEPI II = Division of Epidemiology II
CDRH = Center for Devices and Radiological Health
OMEPRM = Office of Medication Error Prevention and Risk Management
OPDP = Office of Prescription Drug Promotion
OSE = Office of Surveillance and Epidemiology

1. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The Department of Defense (DoD) reports that the availability of synthetic opioids, such as fentanyl and its derivatives, is a significant threat as a chemical weapon. They have reported in meeting background information to the Division that, "A military need exists to quickly reverse adverse effects resulting from exposure to highly potent opioids. The onset of respiratory depression creates a critical need to rapidly deliver an adequate dose of a medical countermeasures (MCM), such as naloxone, to reverse an opioid's effects. Prompt delivery of a high dose MCM, with a sufficient duration of action and ability to mitigate adverse effects from highly potent opioid agents is paramount for soldiers to complete their mission and/or wait until a transition to a higher echelon of medical care to receive follow-on care." They also stated that, "The MCM will be administered to non-opioid dependent, healthy individuals with few or no underlying medical conditions who have been exposed to ultra-potent synthetic opioids."

The DoD has identified a need for a 10 mg naloxone autoinjector product to be used by military personnel in the event of a military attack, terrorist attack, or some other mass casualty type of event where highly potent opioids may be present. They also want a product that can be given for prophylaxis prior to opioid exposure (e.g., when responding to a contaminated area) and that can be used to treat opioid exposure or overdose. The DoD partnered with the drug company kaleo to produce this product. The Applicant has provided PK/PD modeling data indicates that this product may be useful in reversing high potency opioids in certain situations. Additionally, the modeling data indicate there may be a benefit to using this product prophylactically. Higher doses of naloxone (e.g., 10 mg via the intramuscular [IM] route) may be more effective in reversing certain opioid overdoses (e.g., carfentanil) which has been demonstrated through PK/PD modeling. However, modeling has shown that the timing of the dose of naloxone is much more critical than the dose of naloxone given. Realistically, administration of naloxone before or immediately upon appearance of symptoms is only possible in the scenario envisioned by the DoD.

There are FDA-approved treatment options for opioid overdose including naloxone hydrochloride (HCl) as well as the community-use naloxone products. The currently available opioid overdose reversal products are not specifically indicated for the DoD's indicated need. There is currently one approved and available community-use naloxone product, Narcan Nasal Spray (NNS) 4 mg IN (intranasal). Evzio (both 0.4 mg and 2 mg intramuscular [IM] autoinjector) is not currently marketed. The recently approved Kloxxado 8 mg IN and ZIMHI 5 mg IM/SC prefilled syringe are not currently marketed. Other generic products supplied pre-filled syringes (without needles) are marketed as well. The DoD notes that intranasal products cannot be used while wearing personal protective equipment and prefers auto-injectors for ease of administration by service members, and none of the available products provide the 10 mg IM dose sought by the DoD for military use.

There are no clinical studies or clinical data to support the 10 mg naloxone autoinjector product. Given the lack of clinical data, the Applicant is

relying on PK/PD modeling. The modeling has indicated that higher-dose naloxone products may be more effective in reversing certain opioid overdoses. However, modeling has shown that the timing of the dose of naloxone is much more critical than the dose of naloxone given in treatment of overdose from highly-potent opioids such as carfentanil; unless treatment is given immediately on onset of symptoms, no amount of naloxone is likely to avert fatal respiratory depression when high doses of carfentanil are given.

The Applicant provided literature, PK data, and PK/PD modeling data to support the safety and effectiveness of 10 mg naloxone for prophylaxis and treatment of opioid overdose from highly potent opioids. The target patient population will active duty military, who are expected to be healthy adults without opioid dependence. The efficacy of this 10 mg naloxone product is supported by a scientific bridge between the proposed product and the reference product Narcan 2 mg injection through a pharmacokinetic (PK) study KS-900DV-002. The pharmacokinetic data demonstrated that a single dose of 10 mg naloxone IM injection for the proposed product, results in greater naloxone concentrations at all critical time points including earlier time points (e.g., 2.5, 5 min post-dose). The PK/PD modeling supports the conclusion that this product, if given prior to or immediately upon exposure to opioids (when respiration is 90% of baseline), can be effective in preventing many deaths associated with exposures to high potency opioids.

(b) (4)

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Exposure to opioids may result in respiratory and CNS depression. The DoD is concerned that some high potency opioids could be weaponized. • The DoD has identified a need for a 10 mg naloxone autoinjector product to be used by military personnel in the event of a military attack, terrorist attack, or some other mass casualty type of event where highly potent opioids may be present.	• PK/PD modeling data indicates that this product may be useful in reversing high potency opioids in certain situations. Modeling data indicates there may be a benefit to using this product prophylactically
Current Treatment Options	• The current treatment options do not have the indications that the DoD is seeking in their new product. • Naloxone HCl is approved for opioid overdose and is used via the IV/IM/SC route and the approved dose is 0.4 mg to 2 mg. This product is typically used in the healthcare setting.	There are FDA-approved treatment options for opioid overdose. There may be a role for naloxone products with a higher dosage, than what is already approved, for unusual situations such as those envisioned by the DoD.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• There is currently one approved and available community-use naloxone product, Narcan Nasal Spray (NNS) 4 mg IN (intranasal). • Evzio (both 0.4 mg and 2 mg intramuscular [IM]) is not currently marketed. The recently approved Kloxxado 8 mg IN and ZIMHI 5 mg IM/SC are not currently marketed.	High-dose naloxone products may be more effective in reversing certain opioid overdoses (e.g., carfentanil) which has been demonstrated through PK/PD modeling. However, modeling has shown that the timing of the dose of naloxone is much more critical than the dose of naloxone given. Realistically, administration of naloxone before or immediately upon appearance of symptoms is only possible in the scenario envisioned by the DoD.
Benefit	• The efficacy of this product is supported by a scientific bridge between the proposed product and the reference product Narcan 2 mg injection through a pharmacokinetic (PK) study KS-900DV-002. The pharmacokinetic data demonstrated that a single dose of 10 mg naloxone IM injection for the proposed product, results in greater naloxone concentrations at all critical time points including earlier time points (e.g., 2.5, 5 min post-dose). • Given that this product has different indications than the reference product, it is also supported by PK/PD modeling data. • The safety and efficacy of this product for pediatric patients 12 years and older is supported by literature review. • There are no clinical efficacy data for this product to assess its efficacy in treating overdoses from high-potency synthetic opioids	The Applicant provided literature, PK data, and modeling data to support the safety and effectiveness of 10 mg naloxone for prophylaxis and treatment of opioid overdose from highly potent opioids. The target patient population will include healthy adult active military service members.
Risk and Risk Management	• The safety profile of naloxone in healthy, non-opioid-dependent individuals is well known. • There is literature to support the safety of naloxone doses exceeding the proposed dose for this product in adults and pediatrics down to 12 years old. • Recurrent respiratory and central nervous system depression with duration of action of certain opioids, may exceed duration of action of naloxone • Naloxone administration causes withdrawal symptoms in opioid	Approval of this product would provide an additional approved naloxone product. This would be the first naloxone and first opioid antagonist specifically indicated to treat overdose by highly potent opioids such as fentanyl and its analogues. This would be the first product indicated for prophylaxis against opioid overdose.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	dependent individuals. Precipitated withdrawal may be severe and occasionally serious, and the risk increases with higher doses of naloxone. • A larger bolus of naloxone has a greater risk of precipitating withdrawal in opioid-dependent patients. This is not expected to occur in active duty military personnel but should nevertheless be communicated.	In opioid dependent individuals, naloxone-precipitated withdrawal may be severe and occasionally serious. This is not expected to occur in active-duty military personnel but should nevertheless be communicated.

2. Background

2.1 Product Information

Naloxone is a nonselective opioid receptor antagonist, with the greatest affinity for the mu-opioid receptor. If immediately administered, naloxone can reverse the life-threatening effects of an opioid overdose and prevent hypoxia-associated injury and death. Naloxone has been approved for commercial use since 1971. There are approved drug products containing the active ingredient naloxone in the United States (**Error! Reference source not found.**). Notably, only the products highlighted in gray are currently *available.* The autoinjector products are no longer marketed, and Kloxxado and Zimhi are not yet launched.

Table 1 Current Approved Naloxone Treatment Options

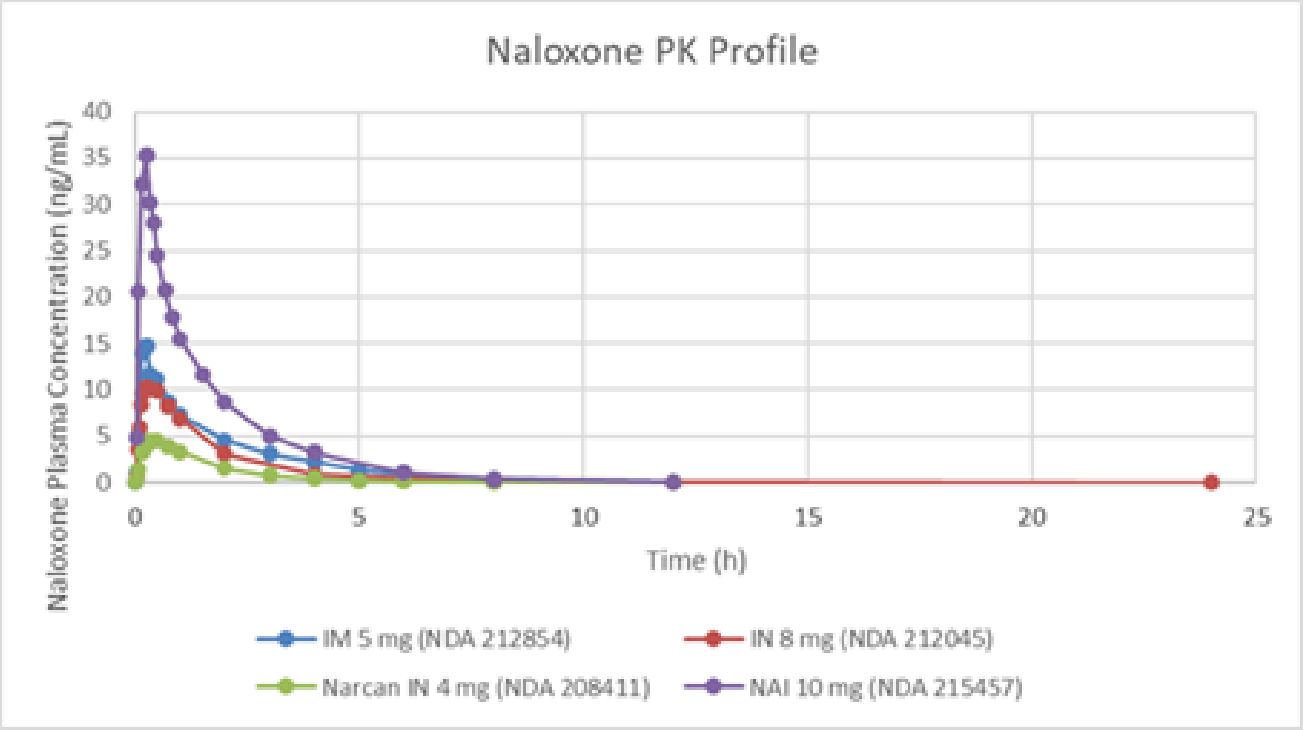
Drug Product Name	NDA	Approval Date	Dose Form	Dose	Route[1]
Narcan	016636	4/13/1971	Solution for injection (generics also supplied as pre-filled syringes)	0.2-2 mg	IV, IM, SC
EVZIO	205787[2]	4/3/2014	Autoinjector	0.4 mg	IM, SC
Narcan Nasal Spray	208411	11/18/2015	Nasal Spray	4 mg	IN
EVZIO	209862[3]	10/19/2016	Autoinjector	2 mg	IM, SC
Narcan Nasal Spray	208411 S-001[4]	1/24/2017	Nasal Spray	2 mg	IN
Kloxxado	212045[5]	4/29/2021	Nasal Spray	8 mg	IN
ZIMHI	212854[6]	10/15/21	Intramuscular injector	5 mg	IM, SC

Evzio, Narcan nasal spray, Kloxxado, and ZIMHI are approved with the same indication for community use. Naloxone is included as an active ingredient in several products in combination with opioid ingredients for the treatment of opioid dependence. It is generally included in these products to deter abuse of the opioid component.

[1] Currently available routes include intravenous (IV), intramuscular (IM), subcutaneous (SC), and intranasal (IN)
[2] This product was replaced by the Sponsor with a 2 mg product using the same device.
[3] This product is not currently marketed by the Sponsor and is listed as Discontinued in the Orange Book.
[4] This product was never marketed by the Sponsor and has never been available for sale since the approval date.
5 This product is not yet launched.
[6] This product is not yet launched.

Evzio (owned by the Applicant) was initially approved as a 0.4 mg dose, which was replaced following approval of a 2 mg IM (intramuscular) dose of naloxone. Kaleo is not currently marketing either Evzio dose. Narcan Nasal Spray was initially approved as a 4 mg dose, followed by approval of a 2 mg dose. The 2 mg dose was never marketed. The 8 mg IN (intranasal) naloxone product Kloxxado was approved in 2021. It is not available for purchase at the time of this review. ZIMHI is a 5 mg IM/SC (subcutaneous) product which was also approved in 2021 and is also not available for purchase at the time of this review. ZIMHI is currently the highest dose of naloxone approved. Figure 1 shows a comparison of the pharmacokinetic (PK) profiles for naloxone 10 mg NAI, ZIMHI, Kloxxado, and Narcan Nasal Spray. As the two Evzio products were withdrawn from the market, they are not included. Naloxone 10 mg produces the highest levels of naloxone measured in the blood stream during the PK studies used as part of the NDA submission. All products show very fast elevation to peak naloxone concentration level. All of four of the products have PK profiles exceeding the exposure associated with 0.4 mg naloxone IM, considered an adequate dose for treatment of typical opioid overdose.

Figure 1 Comparison of PK Profiles for 10 mg NAI (NDA 215457), ZIMHI (NDA 212854), Kloxxado (NDA 212045), and Narcan Nasal Spray (NDA 208411)



The product is identical to the Evzio products, except

- it is formulated to a drug concentration of 25 mg/mL
- Per DoD requirements, it does not include the electronic prompt system (audible voice prompts and light emitting diodes) that provide visual and audible cues during the

injection process that is included in the Evzio products. The prompt system is separate from the functionality of the autoinjector itself.

2.2 Therapeutic Context: Opioid Overdose and Naloxone

Opioid overdose is characterized by life-threatening respiratory and central nervous system (CNS) depression that, if not immediately treated, may lead to significant morbidity and mortality due to irreversible hypoxic injury. The DoD notes that high-potency opioids could potentially be used as chemical weapons and result in mass casualty situations.
Clinical efficacy trials of medications to treat opioid toxicity present significant logistical and ethical challenges, as already-approved naloxone-containing products are available for treatment of opioid overdose, which, if not immediately treated, could result in substantial morbidity and mortality. The Division has previously determined that it is not necessary to conduct clinical efficacy trials with novel naloxone products intended for treatment of typical opioid toxicity, as effective doses have been established. The evidence of efficacy of a new formulation or route of administration of naloxone has been based on a demonstration of adequate systemic naloxone levels in relative bioavailability studies which compare the systemic exposure of naloxone from the new product to an approved product. However, the effective dose for treating toxicity that might occur in a mass casualty situation, where a highly potent product has, for example, been aerosolized or introduced into the water supply, is not established and this application therefore relies on PK/PD modeling of the effects of both naloxone and certain specific opioids.

The Applicant's proposed indications are the following:

(b) (4)

Only the first two uses (as re-worded in the Division's proposed labeling) are discussed in this review.

2.3 Summary of Presubmission Regulatory Activity

NDA 205787, EVZIO 0.4 mg, was approved on April 3, 2014. NDA 209862, EVZIO 2 mg, was approved on October 19, 2016. See those reviews in DARRTS for further information on

the regulatory activity related to those submissions. The studies for these applications and for this new NDA were all conducted under IND 112292.

For this new NDA with a 10 mg product there have been several meetings and communications with the Sponsors (DoD and Kaleo). The key points from each meeting are summarized below:

- December 13, 2018, Type B Meeting (PIND 141770) with the Department of Defense (DoD). DoD was looking for a manufacturer/Sponsor to partner with for the development of a 10 mg naloxone HCl autoinjector to immediately treat exposures to ultra-potent opioids. This product is a Public Law 15-92 priority drug for the DoD. The DoD's stated purpose of the meeting was to obtain Agency guidance and feedback to further inform their regulatory strategy for the rapid development of a 10 mg naloxone HCl autoinjector for use as a medical countermeasure (MCM) against ultra-potent opioid threats. The DoD's proposed indication was, (b) (4) At the meeting the Sponsor was given advice regarding the 505(b)(2) pathway, PREA, and nonclinical requirements. The intended patient population was discussed as well, with the Sponsor stating that their primary interest is having this product available for the active-duty population.
- February 24, 2020, Type B Meeting. The DoD had partnered with Kaleo and planned use the EVZIO device for the planned 10 mg product. In the backgrounder package, Kaleo had changed the DoD indication (b) (4) This was specifically discussed at the meeting. Kaleo agreed to adopt the DoD proposed indication (under PIND 141770). It was discussed that the proposed NDA would be a new NDA and not a supplement to the previous EVZIO NDAs. The possibility of expedited review was discussed. The Sponsor was also given advice regarding pediatric requirements.
- July 7, 2020, an Advice Letter was sent in response to questions sent by Kaleo regarding the proposed bioavailability study.
- September 4, 2020, Kaleo applied for Fast Track designation. The proposed indication for their product at that time was, (b) (4) The request was denied as the Sponsor had not provided adequate evidence of efficacy that their product, NAI 10 mg, would be able to reverse a life-threatening overdose of highly potent synthetic opioids.
- February 1, 2021, Kaleo made a second request for Fast Track designation. In this submission the Sponsor outlined a plan to conduct PK/PD[7] studies as part of the development plan in order to further investigate the efficacy of the product for the proposed indication. Fast Track designation was granted.

[7] Pharmacokinetic pharmacodynamic

- September 20, 2021, agreed pediatric study plan (PSP) was submitted.

3. Product Quality

The drug substance, drug product, process/facilities, and microbiology review teams all recommend approval. Other than the manufacturing site for final product assembly (see below), all manufacturing sites were recommended for approval based on inspectional history. The following recommendations from the Executive Summary are reproduced verbatim from the review:

> **I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY**
> CMC recommends approval of this application based on drug substance, drug product, manufacturing and microbiology reviews. There will be postmarketing requirements from the drug product reviewer. See the drug product summary below for details.
> The proposed shelf life of 24 months is acceptable when stored at controlled room temperature 15°C - 25°C (59°F - 77°F).

Please see the full review available in DAARTS for further details. The CMC postmarketing recommendations (PMRs) are listed in the Postmarketing Recommendations section as well as the approval letter.

4. Center for Devices and Radiological Health (CDRH)

The CDRH review did not identify concerns and recommends approval for the DoD's intended uses. Please see the full review available in DAARTS for further details. The Facilities and Quality Systems review recommended inspection of (b) (4) facility for final product assembly, device performance testing. The following is reproduced verbatim from the CDRH review:

> (b) (4) is responsible for quality control of incoming device components and sub-assemblies and final finished product assembly, packaging and labeling, device performance quality control testing, maintenance of the device master record and execution of device history records.

An inspection of the (b) (4) site was completed and CMC has classified the inspection findings as voluntary action indicated.

5. Nonclinical Pharmacology/Toxicology

The non-clinical review did not identify concerns precluding approval for the DoD's intended uses. Drug formulation, specifications (drug substance and drug product), and elemental impurities are acceptable. Leachable assessment demonstrated that compounds are below the 5 mcg/day threshold. Local toxicity study in rabbits resulted in a slight increase is edema (Grade 0 to Grade 1) between control and 10 mg naloxone groups with no changes in erythema.

Please see the full review available in DAARTS for further details. The nonclinical PMRs are listed in the Postmarketing Recommendations section as well as the approval letter.

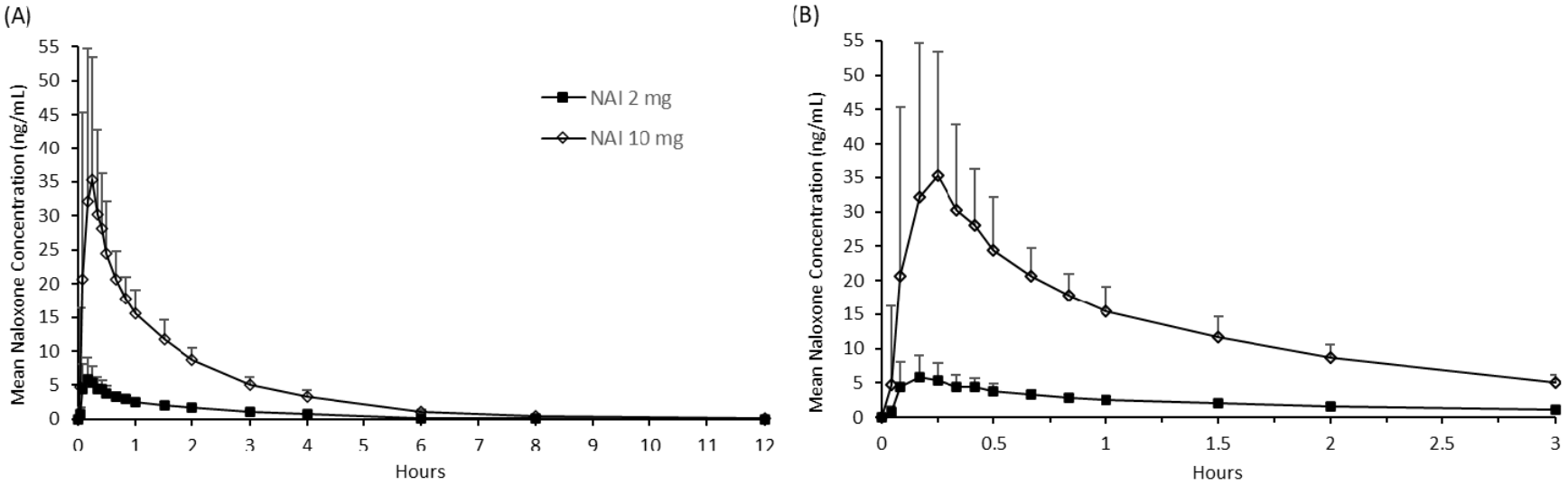
6. Clinical Pharmacology

The clinical pharmacology review was a joint review by the clinical pharmacology team and the Division of Applied Regulatory Science (DARS) team. The clinical pharmacology program included one pharmacokinetic study, and a sponsor-conducted modeling/simulation.

Study KA-900DV-002: PK of NAI 10 mg and dose proportionality study between NAI 2 mg and NAI 10 mg

- Phase 1 R, SD, 2-way CO dose proportionality study in 24 healthy volunteers
- Treatment: injection in the anterolateral aspect of the thigh; 48-hour washout period
  - Test: NAI 10 mg
  - Reference: NAI 2 mg
- PK sampling**:** pre-dose and at 2.5, 5, 10, 15, 20, 25, 30, 40, and 50 min, and 1, 1.5, 2, 3, 4, 6, 8, and 12 h post-dose
- PK parameters (free (unconjugated) naloxone): Cmax, tmax, AUC0-t, AUC0-inf, partial AUCs (0-2.5 min, 0-5 min, 0-10 min, and 0-15 min), and t1/2
- The figure and tables below illustrate the findings of this study

Figure 2 Mean (±SD) Free Naloxone Plasma Concentration (A) 12-hour and (B) 3-hour Time Profiles (KA-900DV-002)



Source: KA-900DV-002 Figure 14.2.1.1

Table 2 Summary of Naloxone Pharmacokinetic Parameters and Dose Proportionality Results (KA-900DV-002, N=24)

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 3 Summary of Naloxone Exposure During the Early Absorption Phase (KA-900DV-002, N=24)

Treatment	Statistic	$AUC_{0\text{-}2.5min}$ (ng.h/mL)	$AUC_{0\text{-}5min}$ (ng.h/mL)	$AUC_{0\text{-}10min}$ (ng.h/mL)	$AUC_{0\text{-}15min}$ (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

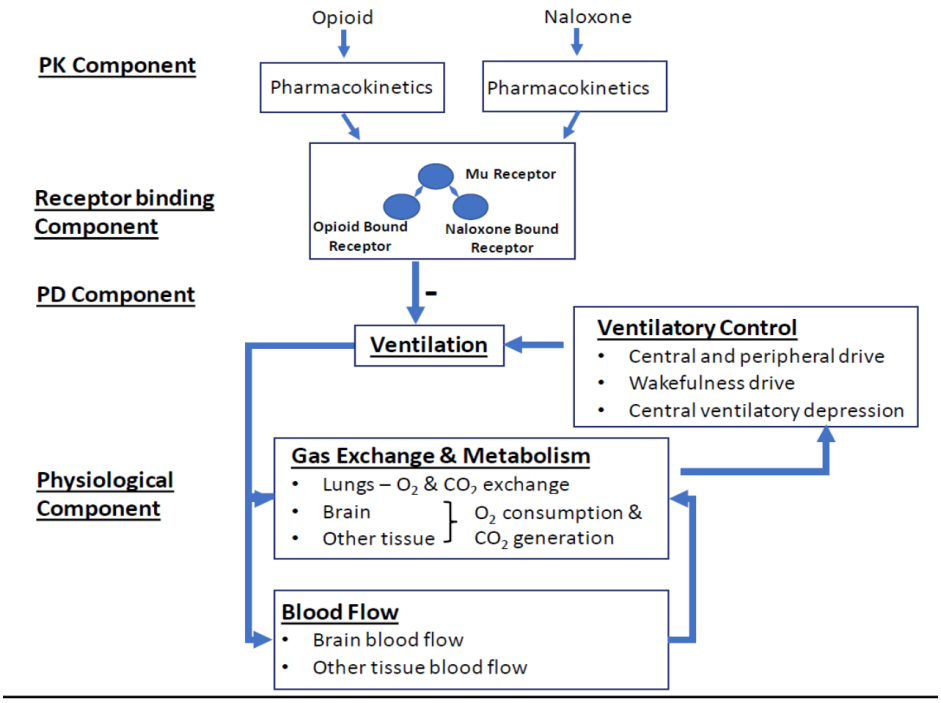
KA-910DV-002: PK-PD modeling simulation to predict reversal or delay of ventilatory depression in lethal doses of a variety of opioids, including morphine, buprenorphine, fentanyl and carfentanil

The Applicant's modeling and simulation is described in full in the clinical-pharmacology review. The limitations of the modeling are also described in that review. The clinical team, and the consultants from the Pulmonary and Critical Care division, had significant reservations about how to interpret the endpoint used in the Applicant's model. Therefore, the Division of Applied Regulatory Science (DARS) conducted their own modeling using the PK data and applying more clinically-interpretable endpoints. The slides below describe the difference between the Applicant's modeling and DARS approach, which the clinical team finds more relevant and interpretable. More detail may be found in the Clinical Pharmacology review in DARRTS.

Key Differences Between DARS and Sponsor's Model

	DARS Model	Sponsor Model
Simulated Conditions	• Poikilocapnic (breathing room air) • Isohypercapnic	• Isohypercapnic (end-tidal CO2 partial pressure fixed)
Endpoints	• **Cardiac arrest** • **Brain hypoxia (brain PO2 < 20 mm Hg)** • Minute ventilation	• Minute ventilation
Carfentanil PK model	Fentanyl PK model adjusted to fit Minkowski et al. 2011	Animal model extrapolated to human
Opioid inhalation route considered?	Yes	No
Model Validation	Independent clinical data used for calibration and validation from a series of fentanyl derivatives	No strict separation between calibration and validation

Overall DARS Model Structure



Independent validation (predict new data not used during model calibration)

- New in vitro receptor binding data
- New animal data (hypoxia-induced cardiac arrest)
- New clinical data (minute ventilation, arterial O2 and CO2 partial pressures, CO2 response slope) for fentanyl, alfentanil, sufentnail, and remifentanil

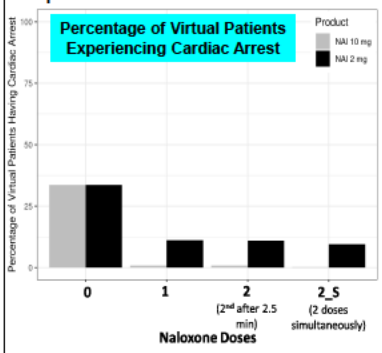
To address the specific scenario of an aerosolized opioid in a mass casualty situation, the DARS model included the following features:

- Assumed inhalation exposure of opioids
- Simulations assumed 1st dose of naloxone was given 1 min after the minute ventilation dropped to 40% of baseline due to opioid overdose
- Different **fentanyl** and **carfentanil** overdose scenarios were evaluated
  - Sponsor's low, medium, and high overdose scenarios
  - Body weight 70 kg assumed
- Key results summarized for simulated population
    - Percentage of patients having cardiac arrest (not recovering)
    - Median (IQR) time brain $pO_2 < 20$ mmHg

The slides reproduced below summarize the findings. See the Clinical Pharmacology review for greater detail.

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Fentanyl 1.617mg (sponsor "medium" dose)
Population Simulations:



Brain Hypoxia Time

Time Brain PO2 is <20 mm Hg (min)		
Naloxone Dose	NAI 10 mg *Median [IQR]*	NAI 2 mg *Median [IQR]*
0	0 (0-NR)	0 (0-NR)
1	0 (0-1.2)	0 (0-2.6)
2 (2nd dose after 2.5 min)	0 (0-1.2)	0 (0-2.6)
2_S (2 dose simultaneously)	0 (0-0.6)	0 (0-1.9)

NR Not Rescued (due to cardiac arrest)

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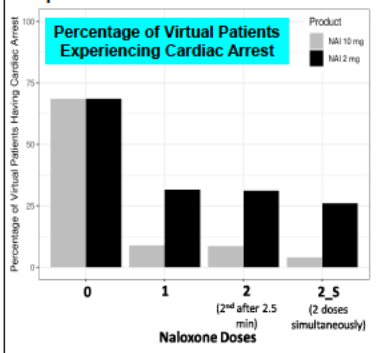
Fentanyl 3.087mg (sponsor "high" dose)
Population Simulations:



Brain Hypoxia Time

Time Brain PO2 is <20 mm Hg (min)		
Naloxone Dose	NAI 10 mg *Median [IQR]*	NAI 2 mg *Median [IQR]*
0	NR (9.3-NR)	NR (9.3-NR)
1	1.8 (0-3.2)	2.8 (0-NR)
2 (2nd dose after 2.5 min)	1.8 (0-3.2)	2.8 (0-NR)
2_S (2 dose simultaneously)	1.3 (0-2.6)	2 (0-NR)

NR Not Rescued (due to cardiac arrest)

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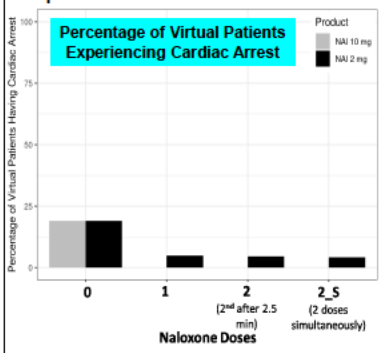
Carfentanil 0.014mg (sponsor "low" dose)
Population Simulations:



Brain Hypoxia Time

Time Brain PO2 is <20 mm Hg (min)		
Naloxone Dose	NAI 10 mg *Median [IQR]*	NAI 2 mg *Median [IQR]*
0	NR (NR-NR)	NR (NR-NR)
1	0 (0-0)	0 (0-NR)
2 (2nd dose after 2.5 min)	0 (0-0)	0 (0-8.2)
2_S (2 dose simultaneously)	0 (0-0)	0 (0-6.6)

NR Not Rescued (due to cardiac arrest)

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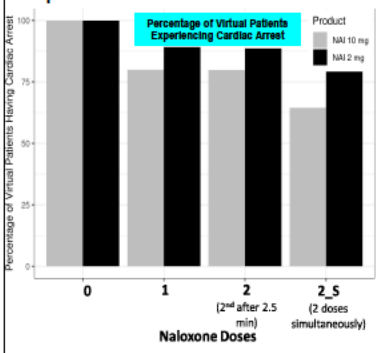
Carfentanil 0.154mg (sponsor "medium" dose)
Population Simulations:



Brain Hypoxia Time

Time Brain PO2 is <20 mm Hg (min)		
Naloxone Dose	NAI 10 mg *Median [IQR]*	NAI 2 mg *Median [IQR]*
0	NR (NR-NR)	NR (NR-NR)
1	NR (NR-NR)	NR (NR-NR)
2 (2nd dose after 2.5 min)	NR (NR-NR)	NR (NR-NR)
2_S (2 dose simultaneously)	NR (4.3-NR)	NR (NR-NR)

NR Not Rescued (due to cardiac arrest)

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Considerations for Carfentanil

- At carfentanil median overdose (0.154 mg), NAI 10 mg rescued more patients than NAI 2 mg, but the majority still experienced cardiac arrest
  - Similar pattern seen for carfentanil high overdose (0.294 mg)
- To see if earlier dosing could save more patients, we explored a faster dosing strategy: naloxone was given 1 min after minute ventilation drops to 90% of baseline
- Such early dosing strategy may be possible within the context of use of the NAI 10 mg product (military personnel under chemical attack, first responders under mass casualty situations, etc.)

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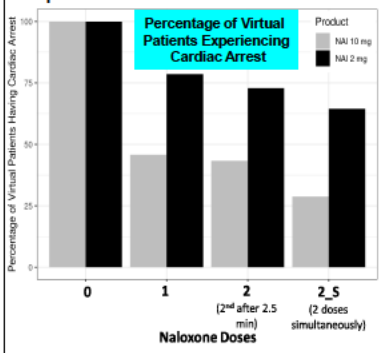
Carfentanil 0.154mg (sponsor "medium" dose)
Population Simulations:



Brain Hypoxia Time

Time Brain PO2 is <20 mm Hg (min)		
Naloxone Dose	NAI 10 mg *Median [IQR]*	NAI 2 mg *Median [IQR]*
0	NR (NR-NR)	NR (NR-NR)
1	4.9 (1.6-NR)	NR (NR-NR)
2 (2nd dose after 2.5 min)	4.6 (1.5-NR)	NR (5.4-NR)
2_S (2 dose simultaneously)	3.3 (0-NR)	NR (3.2-NR)

NR Not Rescued (due to cardiac arrest)

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1st dose of naloxone given 1 min after minute ventilation reaching 90% of baseline

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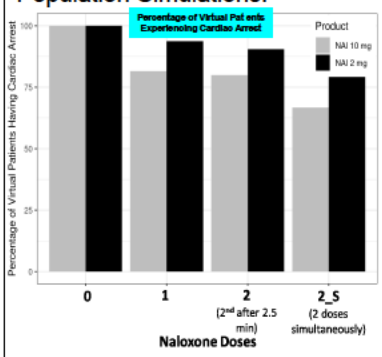
Carfentanil 0.294mg (sponsor "high" dose)
Population Simulations:



Brain Hypoxia Time

Time Brain PO2 is <20 mm Hg (min)		
Naloxone Dose	NAI 10 mg *Median [IQR]*	NAI 2 mg *Median [IQR]*
0	NR (NR-NR)	NR (NR-NR)
1	NR (NR-NR)	NR (NR-NR)
2 (2nd dose after 2.5 min)	NR (NR-NR)	NR (NR-NR)
2_S (2 dose simultaneously)	NR (4.3-NR)	NR (NR-NR)

NR Not Rescued (due to cardiac arrest)

23

1st dose of naloxone given 1 min after minute ventilation reaching 90% of baseline

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Prophylactic Naloxone Administration

- Simulation in previous slides assumed the 1st dose of naloxone was given 1 min after the minute ventilation dropped to some level of baseline due to opioid overdose
- In subsequent slides we simulated scenarios where the NAI 10 mg was given 5 min or 30 min prior to expected opioid exposure
- Only the high overdose scenarios for fentanyl and carfentanil were tested

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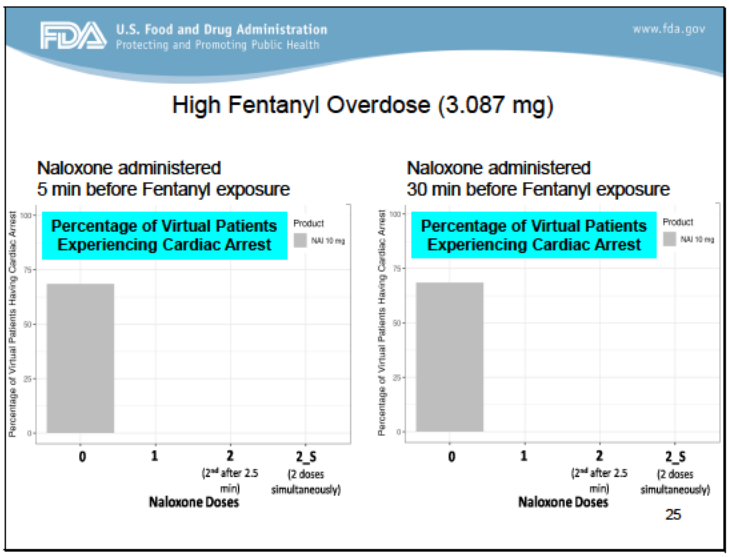

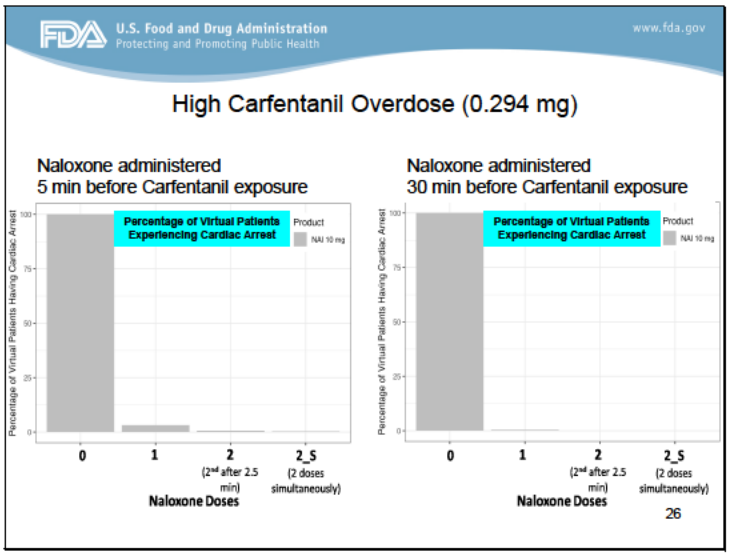

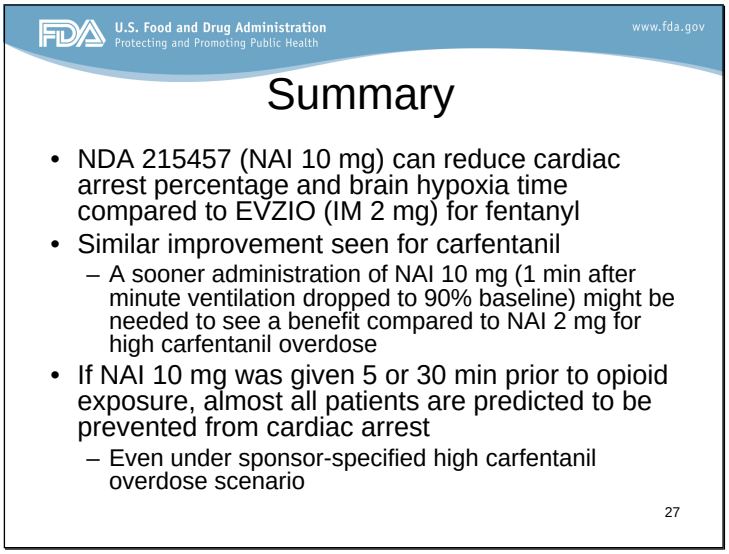

Conclusion by the clinical pharmacology and DARS team:

(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 and 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 [in the scenarios modeled]. 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.

7. Clinical Microbiology

The proposed product is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for this application.

8. Clinical/Statistical- Efficacy

Based on the modeling and simulation discussed above, the proposed naloxone formulation is predicted to achieve reversal in >90% of patients for the high fentanyl and low carfentanil overdose scenarios assuming administration 1-min after baseline ventilation <40% and opioid exposure via inhalation.

Earlier administration of the naloxone (1-min after baseline ventilation < 90%) is predicted to rescue >50% of patients for the median carfentanil overdose scenario.

Prophylactic administration of NAI 10 mg can prevent almost all patients from having cardiac arrest, including the high carfentanil overdose scenario.

Timing of administration of naloxone, route of opioid exposure, and amount of opioid are the main contributors to effectiveness of the intervention.

9. Safety

The Applicant is relying upon the Agency's previous findings of safety and efficacy of Adapt Pharma's Narcan (NDA 16636). They are also cross-referencing Evzio (naloxone HCl, NDA 205787 and NDA 209862), owned by the Applicant. The Applicant performed one relative bioavailability study in healthy volunteers, Study KS-900DV-002.

There were no major safety findings and no new safety signals in the PK study. There were no deaths or serious adverse events (SAE). There were no severe adverse events (AE) or any discontinuations due to an AE. There were no dropouts or discontinuations. There were seven TEAEs reported in five subjects who received NAI 10 mg. There were no AEs reported in subjects after receiving 2 mg NAI. The AEs that did occur were considered mild by the Investigator and resolved.

Table 4 Number and Percentage of Subjects with Treatment-Emergency Adverse Events

System Organ Class Preferred Term	Treatment, n (%)	
	2 mg Naloxone (NAI 2 mg) N = 24	10 mg Naloxone (NAI 10 mg) N = 24
Total Number of Subjects Experiencing ≥ 1 TEAE	**0**	**5 (20.8)**
General Disorders and Administration Site Conditions	**0**	**4 (16.7)**
Feeling Hot	0	3 (12.5)
Injection Site Pain	0	1 (4.2)
Nervous System Disorders	**0**	**1 (4.2)**
Headache	0	1 (4.2)
Skin and Subcutaneous Tissue Disorders	**0**	**1 (4.2)**
Rash erythematous	0	1 (4.2)

Source: Clinical Summary page 52
Data source: KA-900DV-002 (Table 14.3.1.2)
Abbreviations: N = number of subjects exposed to treatment; n = number of subjects with observation; NAI = naloxone auto- injector; TEAE = treatment-emergent adverse event
A subject is only counted once per treatment group in the 'Total Number of Subjects Experiencing ≥ 1 TEAE' row. A subject with more than 1 preferred term event in a System Organ Class is only counted once for that System Organ Class.

Adverse Events of Special Interest

Given the increase in concentration for the naloxone formulation for this new 10 mg product, the Agency was concerned about the possibility of tissue injury or necrosis from this product. The Applicant was required to conduct nonclinical studies prior to initiating the human clinical study. There was sufficient evidence of safety, and the clinical study was allowed to procced. Please see the nonclinical review for a full discussion of the findings. Because of this concern, however, the Applicant was required to evaluate and monitor for potential local reactions at the injection site. As part of the protocol, these evaluations were conducted by assessment of injection sites for pain, tenderness, erythema, induration, and bruising immediately prior to dosing (to establish baseline) and then at multiple times post dose. Findings of injection site reactions were planned to be recorded as adverse events. The injection site reactions were graded according to the toxicity grading scale for local reactions to injectable product as found in the *Guidance for Industry: Toxicity Grading Scale for Healthy adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials*. One subject reported injection site pain and injection site tenderness immediately after administration of NAI 10 mg. Both events code to the preferred term of injection site pain and were graded mild (Grade 1) according to the Guidance.

Summary of Safety

The safety for this high-dose naloxone product is based primarily on the Agency's prior findings for Narcan (naloxone hydrochloride) solution for injection. As mentioned in the background section, there is literature to support the safety of doses of naloxone higher than 10 mg. The Applicant has submitted a literature review and the Agency is also aware of previous studies which demonstrate the safety of high dose naloxone in individuals without opioid-dependence.

10. Pediatrics

The Applicant submitted a request to defer studies in pediatric patients less than 12 years old which was agreed upon prior to NDA submission. The plan to study this product in younger aged patients is discussed in the agreed upon pediatric study plan (PSP).

The Applicant submitted a pediatric assessment to support the efficacy and safety of the 10 mg dose in pediatric patients 12 years and older, consistent with that described in the PSP, for which the Division of Pediatric and Maternal Health (DPMH) was consulted to review the adequacy of the assessment.

The DPMH review was conducted by Ndidi Nwokorie, MD with secondary concurrences by Mona Khurana, MD and John J. Alexander, MD, MPH.

Dr. Nwokorie concluded that:

> Kaleo, Inc. demonstrated through its PK/PD analysis that this product may reverse high potency opioids in certain situations in the adult population when given immediately. The Applicant's analyses further suggest that this product may be beneficial prophylactically when entering an environment with suspected aerosolized ultra-potent opioids. Thus, kaleo, Inc. has established an effective dose of its product, naloxone autoinjector, to reverse the effects of high-potency opioids. Given that this product is expected to produce greater exposures of naloxone and the risks of high dose naloxone are unknown, this reviewer searched the literature for evidence supporting the pediatric safety of the proposed 10 mg dose injectable. The literature supporting the safe use of 10 mg naloxone in the pediatric population is limited and a literature search yielded 3 recent publications. However, these published reports demonstrate that pediatric patients have been exposed to high doses of naloxone with no reported adverse events. There is a theoretical concern that a larger bolus of naloxone may precipitate withdrawal in opioid-dependent patients. There are some pediatric patients who may be opioid dependent, particularly older adolescents with a substance abuse disorder. Administration of naloxone in such patients could theoretically result in an acute withdrawal syndrome. However, in mass casualty situations, where there is known or suspected exposures to high-potency opioids, adolescents exposed to such threats could benefit from this higher naloxone dose where rapid higher plasma concentration of the naloxone would be beneficial in reversing the opioid overdose and thus increase the probability of survival. In such situations the risks of an acute withdrawal syndrome, which is manageable with appropriate care, is outweighed by the potential prevention of death from the ultra-potent opioid exposure. Likewise, there may be civilian responders younger than 18 years of age who may be deployed into a mass casualty situation with known or suspected ultra-potent opioid exposure who would benefit from this novel naloxone product.

DPMH recommends approval of this application in the proposed indication in pediatric patients ages 12 and older and provided pediatric labeling recommendations. The use of this product in ages less than 12 years old will be evaluated post-approval.

This application was discussed at a meeting of the Pediatric Review Committee (PeRC) on January 25, 2022, and the plan was agreed upon. The Applicant had requested a deferral for pediatric patients from birth to less than 12 years of age and conducted an assessment for pediatric patients 12 to less than 17 years of age. Additional modeling and simulation data will be needed to support the safety of the 10mg dose in patients < 12 years of age. In addition, if the modeling and simulation identify exposures that would suggest a safety issue, there may be a need to conduct additional nonclinical studies. Only adult responders are anticipated to administer this product in a military context or to use it prophylactically before responding to a contaminated scene, but victims may be under age 12. Therefore, post-marketing studies to evaluate safety in younger patients will be required under PREA.

11. Labeling

The package insert for this product largely follows the labeling for other naloxone products. The Division recommended minor changes to the wording of the indications to limit the product to use by the military and certain other responders to chemical attacks (e.g., DHS personnel).

The new indication is as follows:

> For use by military personnel and chemical incident responders for:
>
> - Emergency treatment of patients 12 years of age and older where use of high-potency opioids such as fentanyl analogues as a chemical weapon is suspected.
> - Temporary prophylaxis of respiratory and/or central nervous system depression in military personnel and chemical incident responders entering an area contaminated with high-potency opioids such as fentanyl analogues.

The warnings and precautions were reordered and reworded to emphasize the risk of precipitated withdrawal, which is the key concern with this product should it be used in patients physically dependent on opioids. This is not expected to occur in active duty military personnel but should nevertheless be communicated. Language (b) (4) was removed (b) (4).

Certain instructions were proposed for inclusion in labeling that are better communicated in institutional policies. For example, the proposed label included the instruction to inspect the product for damage periodically and to request a replacement if needed (b) (4). These statements were omitted. Certain claims (b) (4)

[redacted] were deleted because of lack of support.

12. Postmarketing Recommendations

The following will be included as PMRs under PREA in the action letter.

4228-1: Conduct allometric scaling of PK/PD models of naloxone-opioid interaction to establish the minimal effective dose of naloxone HCl required to reverse respiratory depression induced by fentanyl and carfentanil ages birth to less than 12 years old.

Draft Protocol Submission:	03/2022
Final Protocol Submission:	04/2022
Trial Completion:	10/2022
Final Report Submission:	04/2023

4228-2 Conduct a juvenile animal toxicology study in rats to support clinical dosing in pediatric patients from birth to less than 12 years of age. This study will evaluate the effects of naloxone on the developing central nervous system, endocrine, and reproductive system.

Draft Protocol Submission:	07/2022
Final Protocol Submission:	10/2022
Study Completion:	10/2023
Final Report Submission:	02/2024

The following PMRs will be required under FDAAA.

4228-3 Conduct a GLP in vitro genetic toxicology Ames assay testing the potential for the naloxone degradant, [redacted], to induce points mutations.

Draft Protocol Submission:	04/2022
Final Protocol Submission:	06/2022
Study Completion:	09/2022
Final Report Submission:	01/2023

4228-4 Conduct a GLP in vitro genetic toxicology study characterizing the potential of the naloxone degradant, [redacted] to induce chromosomal damage.

Draft Protocol Submission:	04/2022
Final Protocol Submission:	06/2022
Study Completion:	09/2022

Final Report Submission:	01/2023

4228-5 Conduct a GLP repeat-dose toxicology study of at least 14 days duration in a single species to characterize the toxicologic potential of the naloxone degradant, (b) (4)

Draft Protocol Submission:	08/2022
Final Protocol Submission:	11/2022
Study Completion:	07/2023
Final Report Submission:	11/2023

4228-6 Perform structural identification of the specified unknown impurities observed at relative retention time (RRT) of (b) (4) The chemical structures of these impurities should be confirmed using physical and chemical techniques such as elemental analysis, mass spectrometry (MS), nuclear magnetic resonance (NMR) spectroscopy, ultraviolet (UV) spectroscopy, infrared (IR) spectroscopy, X-ray crystallography, and other tests (e.g., functional group analysis, derivatization, complex formation).

Draft Protocol Submission:	04/2022
Final Protocol Submission:	07/2022
Study Completion:	07/2023
Final Report Submission:	09/2023

4228-7 Conduct a study in order to provide product stability and leachables data through the proposed shelf-life for three batches of to-be-marketed (TBM) drug product stored at both inverted and horizontal orientations. Manufacture these batches at the commercial site and collect stability data including leachables determination at multiple stability time-points per the testing frequency recommended in ICH Q1A(R2).

Draft Protocol Submission:	04/2022
Final Protocol Submission:	07/2022
Interim Report (Batch #1)	09/2024
Interim Report (Batch #2)	09/2025
Study Completion:	07/2026
Final Report Submission:	09/2026

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

/s/

JENNIFER L NADEL
02/28/2022 02:39:12 PM

CELIA J WINCHELL
02/28/2022 02:41:06 PM

RIGOBERTO A ROCA
02/28/2022 02:53:05 PM