DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 8, 2024

TO: To Whom It May Concern

FROM: Zachary Dezman, MD, MS

SUBJECT: Addenda to Clinical Review for New Drug Application #218590 ZURNAI (nalmefene injection)

APPLICATION/DRUG: NDA 218590 ZURNAI

The table describing the Benefits-Risk Dimensions (Table 1) in the submitted Clinical Review dated August 7, 2024, for NDA 218590 ZURNAI (nalmefene injection) contained a typographical error. The following table has the corrected text (highlighted).

Table 1 Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• There were 106,699 drug overdose deaths in 2021 in the United States, resulting in an age-adjusted rate of 32.4 per 100,000 persons.[13] • Around 80% of these drug overdose deaths involved an opioid.[13] • From 2001 to 2021, almost 630,000 people have died from a drug overdose.[13] • On average, 230 Americans die every day from opioid overdoses.[13]	Opioid overdose and death continue to be a public health crisis and a leading cause of death in the US. While nalmefene hydrochloride can reverse the acute opioid intoxication of a patient, patients require emergency department evaluation afterwards, and receiving nalmefene hydrochloride is not a permanent solution for opioid abuse, misuse, and addiction.
Current Treatment Options	• There are a number of currently approved and available community-use nalmefene hydrochloride and naloxone hydrochloride products.[8] • EVZIO (both 0.4 mg and 2 mg intramuscular [IM/SC]) were discontinued.[14] • NARCAN Nasal Spray (NNS) and Revive, both 4 mg IN (intranasal) are considered safe for non-prescription use.[15, 16] • Anecdotally, some overdoses have required multiple administrations of standard doses of naloxone. It is not known whether these represent failures of the products approved for use in the community, the increasing prevalence of synthetic opioids (e.g., fentanyl and analogs), or co-ingestions without mu-opioid receptor activity (e.g., xylazine).	Patients and advocates have been clear in their desire for a broad array of opioid reversal products, including a multiple doses and routes of administration. While there are a number of FDA-approved treatment options available to treat opioid overdose, there are currently no approved autoinjector products on the market.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The efficacy of this product for community use is supported by a scientific bridge between the proposed product (ZURNAI, 1.5 mg delivered in 0.5 mL via IM/SC injection) and the reference product, REVEX, administered as 1.0 mg IM/SC, as shown in the pharmacokinetic (PK) study NAL 1005. • The pharmacokinetic data demonstrated that a single dose of ZURNAI results in the same or greater systemic nalmefene hydrochloride concentration compared to the reference product REVEX given 1.0 mg IM. This includes earlier time points that are most relevant to the immediate treatment of opioid overdose (e.g., 0-5 min post-dose), as demonstrated in the pharmacodynamic study NAL 1005. • The efficacy and safety of this product has not been shown in the entire pediatric age range (i.e., there is no data for those from birth to 12 years of age). • There are no clinical efficacy data for this product to assess its efficacy in treating overdoses from synthetic opioids. • There are no comparative efficacy data between this product and other approved opioid reversal products for community use.	The Applicant provided literature and PK data to support the effectiveness of ZURNAI for the proposed indication intended for community use for those 12 years and older. The application contains no evidence that this product will result in improved outcomes in reversing synthetic opioids compared to other approved products.
Risk and Risk Management	• There is literature and modelling data to support the safety of nalmefene hydrochloride doses similar to the proposed dose for this product in adults and in the children 12 years and older. • Nalmefene hydrochloride administration causes withdrawal symptoms in opioid dependent individuals. Precipitated withdrawal may be severe and if left untreated, it can lead to dehydration, electrolyte abnormalities, and renal failure. These products are intended to save the lives of persons who use illicit opioids, but they may be less accepting and less likely to use products that frequently	The Applicant has not provided data to describe the frequency of precipitated opioid withdrawal in patients who are treated with the proposed device and have opioid dependence. Based on evidence from the literature and other Applicants/NDAs, we would expect the current application to have safety on-par with existing opioid reversal products. Future trials may provide additional insight.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	precipitate withdrawal. • Similar to naloxone hydrochloride, there are reports of patients suffering from noncardiogenic pulmonary edema after receiving nalmefene hydrochloride.[17] • Proposed product labeling includes language about the serious risks of precipitating acute opioid withdrawal. There are no comparative safety data between this product and other currently available reversal products to inform prescribing decisions.	Approval of this product would provide an additional approved opioid reversal product and would be the only autoinjector available to civilian use.

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/

ZACHARY D DEZMAN
08/08/2024 02:19:01 PM
Addenda to Clinical Review for NDA 218590

RIGOBERTO A ROCA
08/08/2024 02:23:43 PM

CLINICAL REVIEW

Application Type	505(b)(2)
Application Number	NDA 218590
Priority or Standard	Priority
Submit Date	February 7th, 2024
Received Date	February 7th, 2024
PDUFA Goal Date	August 7th, 2024
Division/Office	Anesthesia, Addiction Medicine, and Pain Medicine/Office of Neuroscience
Reviewer Name	Zachary Dezman, MD, MS, MS
Review Completion Date	8/7/2024
Established/Proper Name	Nalmefene hydrochloride
Proposed Trade Name	ZURNAI
Applicant	Purdue Pharmaceuticals
Dosage Form	Injection: 1.5 mg/0.5 mL nalmefene (base) solution in a pre-filled auto-injector. Each ZURNAI Auto-Injector delivers 1.5 mg nalmefene (base) injection (0.5 mL).[1]
Applicant Proposed Dosing Regimen	<u>Initial Dosing [1]:</u> The recommended dose of ZURNAI Auto-Injector in adults and pediatric patients aged 12 years and older is 1.5 mg delivered by intramuscular or subcutaneous injection into the anterolateral aspect of the thigh, through clothing if necessary. <u>Repeat Dosing:</u> Seek emergency medical assistance as soon as possible after administration of the first dose of ZURNAI Auto-Injector. The requirement for repeat doses of ZURNAI Auto-Injector depends upon the amount, type, and route of administration of the opioid being antagonized. If the patient responds to ZURNAI Auto-Injector and subsequently relapses back into respiratory depression before emergency assistance arrives, administer an additional dose of ZURNAI Auto-Injector using a new auto-injector and continue surveillance of the patient. If the desired response is not obtained after 2 to 5 minutes, administer an additional dose of ZURNAI Auto-Injector using a new auto-injector. If there is still no response and additional doses are available, administer additional doses of ZURNAI Auto-Injector every 2 to 5 minutes using a new ZURNAI Auto-Injector with each dose until emergency medical assistance arrives.

	Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance.
Applicant Proposed Indication/Population	ZURNAI is indicated for the emergency treatment of known or suspected opioid overdose induced by natural or synthetic opioids in adults and pediatric patients aged 12 years and older, as manifested by respiratory and/or central nervous system depression. ZURNAI is intended for immediate administration as emergency therapy in settings where opioids may be present. ZURNAI is not a substitute for emergency medical care.[1]
Recommendation on Regulatory Action	Approval
Recommended Indication/Population (if applicable)	[Patients suffering from] known or suspected opioid overdose induced by natural or synthetic opioids in adults and pediatric patients aged 12 years and older

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(b) (4)

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Glossary

AC	advisory committee
AE	adverse event
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
CRF	case report form
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
FIRD	Fentanyl-induced respiratory depression
IND	Investigational New Drug Application
IM/SC	intramuscular/subcutaneous
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
Perc	Pediatric Review Committee
PK	pharmacokinetics
PMC	Postmarketing commitment
PMR	Postmarketing requirement
PREA	Pediatric Research Equity Act
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Nalmefene hydrochloride is a nonselective opioid receptor antagonist, with the greatest affinity for the mu receptor. Nalmefene hydrochloride antagonizes opioid effects by competing for the mu, kappa, and sigma opiate receptor sites in the central nervous system (CNS).

Purdue Pharmaceutical (Applicant) has submitted an application in support of a single-use drug-device combination product intended for the emergency treatment of patients with apparent opioid overdose in community settings.[2] Each drug-device product contains one fixed dose of 1.5 mg of nalmefene hydrochloride in 0.5 mL of solution. The drug solution contains magnesium chloride (b) (4). The device is a fixed-dose, (b) (4), disposable autoinjector that can deliver an intramuscular or subcutaneous injection of the active substance (Figure 1, below). This device was originally developed under (b) (4), is marketed under the tradename (b) (4), and has been used (predominantly) in one previously approved product, (b) (4)

To administer a dose, the user takes off the safety seal and cap, and presses the needle guard to the patient's anterolateral thigh. Once the needle guard has been depressed far enough, the autoinjector is triggered and the dose is administered. The needle guard then re-extends and locks into position, covering the needle. The viewing window should appear orange, confirming the dose has been injected.

The Applicant plans to rely on the previous findings of efficacy and safety for the reference product, REVEX (NDA 20459) via the 505(b)(2) pathway.[5] The results of a pharmacokinetic (PK) trial (NAL 1005) and a PD trial (NAL 1004) were submitted in support of this application.[2] These trials were conducted with the reference standard (ANDA 212955),[6] as the relied-upon listed drug (LD), REVEX (NDA 20459),[5] was discontinued not for reasons of efficacy or safety.[7]

There are many approved opioid reversal products based on naloxone hydrochloride and nalmefene hydrochloride , with intranasal or intravascular routes of administration, which can be purchased with a prescription or over-the-counter (Section 2.2) The current application was awarded Priority review based upon the continued loss of life due to the opioid crisis (Section 1.4), the request of patients and advocates for an array of products with many routes of administration be made available (Section 2.1), and the lack of intramuscular or subcutaneous injection products for opioid reversal since EVZIO (NDA 205787 and NDA 209862) was withdrawn (section 2.2).[8]

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided studies that detail the PK, PD, and safety of their product in healthy volunteers. They did not submit a clinical trial demonstrating efficacy, instead relying on previous FDA findings on REVEX (nalmefene hydrochloride, NDA 20459) as a part of a 505(b)(2) application.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Overdose is a major problem in the United States, being the cause of more than 100,000 unintentional deaths in 2021.[9] The Centers for Disease (CDC) data indicates that opioids were involved in more than 75% of all drug overdose deaths. Overdose can occur in patients, the household contacts of a patient prescribed opioids by unintentional exposure, or through intentional misuse and abuse of licit and illicit opioids. Opioid overdose is characterized by life-threatening respiratory and central nervous system depression that may lead to significant morbidity and mortality due to irreversible hypoxic injury. Death due to overdose from most opioids may be preventable with the immediate administration of an opioid antagonist such as naloxone. Nalmefene hydrochloride is known to be an effective treatment for suspected opioid overdose if an adequate dose is administered in time. There are currently three nalmefene hydrochloride products for opioid overdose in the United States: two ANDAs marketed for intravenous injection (IV)[6, 10] and one 2.7 mg intranasal drug-device product (OPVEE).[11] There are also eight approved and marketed naloxone hydrochloride products for opioid overdose, spanning an array of doses (3mg-10mg), routes of administration (IN, IM/SC), and patient populations (in-hospital, community use, and military).

ZURNAI is a drug-device combination product designed to deliver 1.5 mg of nalmefene hydrochloride in 0.5 mL solution of in a single-use pre-filled autoinjector by (b) (4).[2] The product is used by unwrapping the needle cap and pressing the device upon the anterolateral thigh of the patient suffering from an opioid overdose. As the needle guard is depressed and the needle enters the IM/SC compartments, the device automatically injects the active substance. (b) (4)

Purdue Pharmaceuticals [Applicant] submitted this New Drug Application (NDA) proposing to use the 505(b)(2) regulatory pathway. The indication sought for ZURNAI is "ZURNAI Auto-Injector is an opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose induced by natural or synthetic opioids in adults and pediatric patients aged 12 years and older, (b) (4) (b) (4)[1]

The Applicants has chosen to support their efficacy claim by relying on the Agency's prior findings of efficacy for approved nalmefene hydrochloride products.[6] (b) (4) (b) (4) (b) (4) Given the recent re-entry of nalmefene hydrochloride to the market, there is little literature on the safety and efficacy of nalmefene hydrochloride in the current era of illicit fentanyl

use. The current evidence largely reflects the use of naloxone hydrochloride, which shows the large majority of opioid overdoses do not require high doses or multiple doses of reversal agents (i.e., either two doses of 2mg IV, or two doses of 4mg IN), with few receiving 8 mg of naloxone hydrochloride or more.[5-12] Nonetheless, patients and advocates have been clear in their desire for a broad array of opioid reversal products, including a range of doses and routes of administration. While there are a number of FDA-approved treatment options for opioid overdose, there are currently no approved autoinjector products on the market. Furthermore, evidence derived from clinical trials and data submitted by other Applicants, we would expect the current application to have a safety and efficacy on-par with existing opioid reversal products.[11, 12]

Table 1 Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• There were 106,699 drug overdose deaths in 2021 in the United States, resulting in an age-adjusted rate of 32.4 per 100,000 persons.[13] • Around 80% of these drug overdose deaths involved an opioid.[13] • From 2001 to 2021, almost 630,000 people have died from a drug overdose.[13] • On average, 230 Americans die every day from opioid overdoses.[13]	Opioid overdose and death continue to be a public health crisis and a leading cause of death in the US. While nalmefene hydrochloride can reverse the acute opioid intoxication of a patient, patients require emergency department evaluation afterwards, and receiving nalmefene hydrochloride is not a permanent solution for opioid abuse, misuse, and addiction.
Current Treatment Options	• There are a number of currently approved and available community-use nalmefene hydrochloride and naloxone hydrochloride products.[8] • EVZIO (both 0.4 mg and 2 mg intramuscular [IM/SC]) were discontinued.[14] • NARCAN Nasal Spray (NNS) and Revive, both 4 mg IN (intranasal) are considered safe for non-prescription use.[15, 16] • Anecdotally, some overdoses have required multiple administrations	Patients and advocates have been clear in their desire for a broad array of opioid reversal products, including a multiple doses and routes of administration. While there are a number of FDA-approved treatment options available to treat opioid overdose, there are currently no approved autoinjector products on the market.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	of standard doses of naloxone. It is not known whether these represent failures of the products approved for use in the community, the increasing prevalence of synthetic opioids (e.g., fentanyl and analogs), or co-ingestions without mu-opioid receptor activity (e.g., xylazine).	
Benefit	• The efficacy of this product for community use is supported by a scientific bridge between the proposed product (ZURNAI, 1.5 mg delivered in 0.5 mL via IM/SC injection) and the reference product, REVEX, administered as 1.0 mg IM/SC, as shown in the pharmacokinetic (PK) study NAL 1005. • The pharmacokinetic data demonstrated that a single dose of ZURNAI results in the same or greater systemic naloxone hydrochloride concentration compared to the reference product REVEX given 1.0 mg IM. This includes earlier time points that are most relevant to the immediate treatment of opioid overdose (e.g., 0-5 min post-dose), as demonstrated in the pharmacodynamic study NAL 1005. • The efficacy and safety of this product has not been shown in the entire pediatric age range (i.e., there is no data for those from birth to 12 years of age). • There are no clinical efficacy data for this product to assess its efficacy in treating overdoses from synthetic opioids. • There are no comparative efficacy data between this product and other approved opioid reversal products for community use.	The Applicant provided literature and PK data to support the effectiveness of ZURNAI for the proposed indication intended for community use for those 12 years and older. The application contains no evidence that this product will result in improved outcomes in reversing synthetic opioids compared to other approved products.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• There is literature and modelling data to support the safety of nalmefene hydrochloride doses similar to the proposed dose for this product in adults and in the children 12 years and older. • Nalmefene hydrochloride administration causes withdrawal symptoms in opioid dependent individuals. Precipitated withdrawal may be severe and if left untreated, it can lead to dehydration, electrolyte abnormalities, and renal failure. These products are intended to save the lives of persons who use illicit opioids, but they may be less accepting and less likely to use products that frequently precipitate withdrawal. • Similar to naloxone hydrochloride, there are reports of patients suffering from noncardiogenic pulmonary edema after receiving nalmefene hydrochloride.[17] • Proposed product labeling includes language about the serious risks of precipitating acute opioid withdrawal. There are no comparative safety data between this product and other currently available reversal products to inform prescribing decisions.	The Applicant has not provided data to describe the frequency of precipitated opioid withdrawal in patients who are treated with the proposed device and have opioid dependence. Based on evidence from the literature and other Applicants/NDAs, we would expect the current application to have safety on-par with existing opioid reversal products. Future trials may provide additional insight. Approval of this product would provide an additional approved opioid reversal product and would be the only autoinjector available to civilian use.

1.4. Patient Experience Data

Several sources of patient experience data were used to inform this review (Table 2). A Patient-Focused Drug Development Meeting relating to Opioid Use Disorder (OUD) was held on April 17th, 2018. The meeting featured the experience of patients with OUD, guided by moderators. From the summary report:[18]

> Page 5: "Participants described 'being a prisoner' to opioid withdrawals often accompanied by nausea, vomiting, and uncontrollable muscle spasms. Participants also offered insight on opioid 'cravings,' or desire to use. They highlighted the relationship between craving and anxiety and stressed that cravings are more than a physical liking for a substance. Cravings were described as 'the act of doing it, preparing it, consuming it, the immediate relief afterwards.' Participants also stressed that cravings may last well beyond acute withdrawal and can be triggered unpredictably."
>
> Page 5: "They described the added challenges to maintaining recovery due to the intensity of withdrawal and craving, the significant pain or mental health needs, and their own difficulty in coming to terms with their illness."
>
> Page 7: "Meeting participants referred to the symptoms of opioid withdrawal as feeling 'drug sick.' Throughout the large-group discussion participants highlighted avoiding the feeling of being 'drug sick' during opioid withdrawals often hindered their recovery. One participant shared, 'Always the withdrawals drove me back to opioids.' Another participant described the 'unsurmountable' challenges of opioid withdrawal stating, "Opioid use sort of drove my daily activities as I would be drug sick if I didn't [obtain opioids]." During meeting discussion individuals described opioid withdrawal in vivid detail in the statements below:
>
> - 'The feeling of these bugs like crawling underneath my skin and chewing their way through my body.'
> - 'Skin crawls where you can't lay still…your body just jerks. You feel like a cat on a hot tin roof.'"
>
> Page 7: "In-person and web participants also highlighted the intense emotional impacts of opioid withdrawal. Participants shared that withdrawal also led to anxiety, depression, low self-esteem, and, at times, suicidal ideation. One participant highlighted this concept, stating, '[Without opioids] I seemed just completely useless and worthless, weak, and pathetic.' Meeting participants also noted that due to their past dependence on opioids, OUD affects how they experience anxiety. One participant highlighted this

> concept, stating, 'For the addict mind [anxiety] is resemblance of withdrawal symptoms. My mind will tell my body that I need drugs to manage the anxiety.'"

Public comments submitted to the docket described a similar impact of OUD, opioid dependence, and opioid withdrawal on individuals, consistent with those discussed at the meeting. These included opioid withdrawal, opioid cravings, and other health effects. For example, one commenter described [cravings and withdrawal] "an intense mental desire to secure the drug at all cost."

A FDA Reagan-Udall meeting was held on March 8th and 9th of 2023 regarding the current management of opioid overdose.[19] Patient advocates and addiction medicine specialists contributing to the meeting requested greater involvement of persons who use drugs in the development of opioid reversal products, as that community will be the primary users and beneficiaries of these product. The patient advocates recognized that opioid overdose is life-threatening and a greater immediate risk than precipitated opioid withdrawal. However, as a public health matter, we should be cognizant of the risk of decreased acceptance of opioid-overdose reversal products by persons who use drugs if the only available products are likely to drive them into opioid withdrawal.

As a solution, patient advocates requested there be a wide array of reversal products be made available. They ask for an array of fixed-dose devices (3 mg and up) or adjustable devices that can provide a range of doses. Products should also cover all routes of administration (IM, SC, IV, IN, etc.).

Table 2 Patient Experience Data Relevant to this Application

☐	The patient experience data that was submitted as part of the application include:		Section where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
	☐	Patient reported outcome (PRO)	
	☐	Observer reported outcome (ObsRO)	
	☐	Clinician reported outcome (ClinRO)	
	☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	☐	Observational survey studies designed to capture patient experience data	

	☐		Natural history studies	
	☐		Patient preference studies (e.g., submitted studies or scientific publications)	
	☐		Other: (Please specify)	
☒	Patient experience data that were not submitted in the application, but were considered in this review:			
		☒	Input informed from participation in meetings with patient stakeholders	Section 1.4
		☒	Patient-focused drug development or other stakeholder meeting summary reports	Section 1.4
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

Opioid overdose is a syndrome of decreased awareness, bradycardia, and bradypnea coming about from the exposure to opioids. Untreated, opioid overdose can lead to life-threatening respiratory failure, permanent hypoxic injury, and death. Outside of children and infants, where they are often due to unintentional exposure to the caregiver's methadone or buprenorphine,[20] most opioid overdoses in the United States are due to illicit opioids. However, they may also occur due to medication errors, drug-drug interactions, or other concomitant illnesses in patients being treated with opioids for pain. There were 106,699 such drug overdose deaths in the United States in 2021.[13] Overdose deaths have increased over the last 20 years, with the age-adjusted rate of drug overdose deaths increasing from 6.8 per 100,000 persons in 2001, to 32.4 per 100,000 persons in 2021.

In 2015 illicit fentanyl and fentanyl analogs manufactured overseas began to appear on the American illicit drug market. Much of it is manufactured in Mexico and China and pressed into pills and sold as oxycontin.[21] It is also sold as a powder either mixed with, or passed off as, heroin.[22] The potency and uneven quality of street preparations of illicit fentanyl led to rapid increases in fatal and non-fatal opioid overdoses,[23] leading to the largest drop in US life expectancy before the COVID pandemic.[24] Today much of the illicit opioids sold contain fentanyl or are mostly fentanyl and nearly all opioid fatal and nonfatal opioid overdoses involve fentanyl.[25] Fentanyl is increasingly being mixed with stimulants like cocaine and methamphetamine or sedating agents like xylazine and nitazenes.[26-28]

Because naloxone hydrochloride was approved before nalmefene hydrochloride (1971 and 1995, respectively) and nalmefene hydrochloride was off the market from 2017 to 2023, many of the currently available opioid-reversal products contain naloxone. There is a resulting relative paucity of evidence on nalmefene hydrochloride compared to naloxone, especially in children 12 and under (see sections 8.8.3 and 12). However, there are trials comparing nalmefene hydrochloride and naloxone hydrochloride.[12, 29-32] This review will present and extrapolate evidence from naloxone hydrochloride to nalmefene hydrochloride when appropriate.

Nalmefene hydrochloride and naloxone hydrochloride have similar chemical structures (See Figures 2 and 3). Both naloxone hydrochloride and nalmefene hydrochloride antagonize opioid effects by competing for the mu, kappa, and sigma opiate receptor sites in the central nervous system. Both substances effectively and rapidly reverse opioid overdose symptoms if given shortly (<2-3 minutes) after the development of symptoms.[33] One important difference is that the duration of action of nalmefene hydrochloride (10.8 hours) is longer than naloxone hydrochloride (90 minutes) The difference in duration of action may provide a theoretical benefit to patients receiving nalmefene hydrochloride having a decreased possibility of relapse (i.e., "renarcotization") compared to those receiving naloxone. Co-prescribing opioid reversal products (again, largely naloxone hydrochloride products) when prescribing opioids is considered a best practice,[34] and increased access to naloxone hydrochloride has been shown to prevent opioid overdose deaths.[35] Administration of these opioid reversal drugs is not a substitute for emergency care and patients receiving nalmefene hydrochloride or naloxone hydrochloride should be transported to an emergency department.

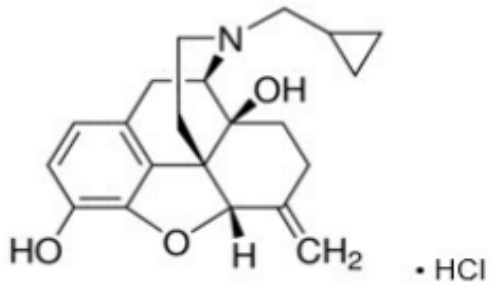


Figure 2. Chemical structure of nalmefene hydrochloride [Source: adapted from approved label for OPVEE, NDA 217470][11]

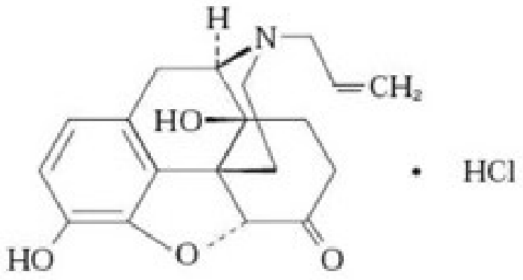


Figure 3. Chemical structure of naloxone hydrochloride [Source: adapted from approved label for EVZIO, NDA 209862][14]

While nalmefene hydrochloride administration has only mild effects in opioid-naïve persons, it can cause opioid withdrawal in persons with opioid dependence. Opioid withdrawal is characterized by generalized pain or achiness, chills, nausea, vomiting, diarrhea, diaphoresis, insomnia, tremors, anxiety, restlessness, piloerection, yawning, and mydriasis. The risk of a patient with OUD developing opioid withdrawal after reversal is dose-dependent.[36] Uncomplicated opioid withdrawal is very uncomfortable but, in of itself, it is not life-

threatening for most adults. However, if untreated, it can lead to life-threatening complications like dehydration, kidney injury, and electrolyte imbalances. Opioid withdrawal can lead to life-threatening seizures in children and infants,[37] and the development of withdrawal is one of the largest barriers to decreasing substance use among people who use drugs.[38, 39]

2.2. Analysis of Current Treatment Options

Injectable nalmefene hydrochloride (REVEX) was approved by FDA in 1995 (NDA 020459)[5] and is indicated for complete or partial reversal of opioid drug effects and management of known or suspected opioid overdose (Table 3). Nalmefene hydrochloride is available as a sterile solution for IV, IM and SC administration. Nalmefene hydrochloride was supplied in two concentrations: 100 μg/ml dosage strength for postoperative opioid depression with initial dose 0.25 μg/kg followed by 0.25 μg/kg incremental doses at 2-5 minutes intervals until desired degree of opioid reversal is obtained and 1 mg/ml dosage strength with initial dose for non-opioid dependent patients is 0.5 mg/70 kg, may be followed with second dose of 1 mg/70 kg 2-5 minutes later. Generic versions of nalmefene hydrochloride are currently available, one of which was licensed by the current Applicant and used in the development of the current product.[6, 10] OPVEE, a drug-device combination nasal spray delivering 2.7 mg of nalmefene hydrochloride via the Aptar device, was approved for the treatment of respiratory depression secondary to opioid overdose in the community in 2023.[11]

There are many currently approved naloxone hydrochloride-containing products that are also indicated for opioid overdose in various settings (Table 3). Naloxone hydrochloride (NARCAN, NDA 16636)[40] was approved in April 1971 and is available for subcutaneous, intramuscular, and intravenous use for the complete or partial reversal of opioid depression, including respiratory depression, induced by natural and synthetic opioids. NARCAN is also indicated for diagnosis of suspected or known acute opioid overdosage. Naloxone hydrochloride has been incorporated in a number of drug and drug-device products since that time (Table 3, below). When naloxone hydrochloride is administered by IV, the onset of action is generally apparent within 2 minutes; the onset of action is slightly less rapid when it is administered by SC or IM injection. Naloxone hydrochloride product labels recommend initial doses of 0.4 mg to 2 mg naloxone hydrochloride by the IM or IV route of administration, followed by repeat doses up to a total dose of 10 mg. There is no maximum dose of naloxone; A practitioner is cautioned to consider alternative causes for a patient's presentation once 10 mg has been administered.

Table 3. Summary of Treatment Armamentarium Relevant to Proposed Indication

Product (s) Name	Year of Approval	Route and Frequency of Administration	Efficacy Information	Other Comments
Approved treatments containing nalmefene hydrochloride				
REVEX (NDA 20459, generics listed below) [5]	1995	IV:0.5 to 2.0 mg IM/SC: I mg.	IV: within 2 to 5 minutes IM/SC: within 5-15 minutes	Discontinued in 2014 not for safety or efficacy reasons. Safety and efficacy in pediatric patients has not been established.
ANDA 212955 [6]	2023	IV:0.5 to 2.0 mg IM/SC: I mg. Generics available	IV: within 2 to 5 minutes IM/SC: within 5-15 minutes	Held by Purdue Pharma, used in the development of the current market application
ANDA 216007 [10]	2023	IV:0.5 to 2.0 mg IM/SC: I mg. Generics available	IV: within 2 to 5 minutes IM/SC: within 5-15 minutes	Held by Chengdu Shuode Pharmaceutical
OPVEE (NDA 217470)[11]	2023	2.7 mg nasal spray		Approved as prescription for 12 y/o and older, as of 7/2023
Approved treatments containing naloxone hydrochloride				
NARCAN (NDA 16636, generics/ANDAs available)	1971	Injection for IV, IM, SC. Available concentrations: 0.02 mg/mL, 0.4mg/mL, and 1 mg/mL	Onset of action is apparent within two minutes	Approved for use in entire pediatric range.
NARCAN (NDA 208411)	2015	4mg nasal spray	Onset of action is apparent within two minutes	Non-prescription as of 3/2023
KLOXXADO (NDA 212045)	2021	8mg nasal spray	Onset of action is apparent within two minutes	Prescription
ZIMHI NDA 212854	2021	5mg prefilled syringe IM/SC		Prescription
RiVIVE (NDA 217722)	2023	3mg nasal spray	Onset of action is apparent within two minutes	Non-prescription as of 7/2023
REZENOPY (NDA 215487)	2024	10 mg nasal spray	Onset of action is apparent within two minutes	Prescription
Currently Not Marketed				
EVZIO (NDA 205787)	2014	Autoinjector 0.4 mg IM/SC		Not currently marketed [41]

EVZIO (NDA 209862)	2016	Autoinjector 2mg IM/ SC		Not currently marketed [41]
Rapid Opioid Countermeasure System (NDA 215457)	2022	10mg autoinjector		Approved for treatment or prophylaxis against opioid exposure for military and mass casualty events, available via the military but not on the civilian market.[42]

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

REVEX (Nalmefene hydrochloride injection) was approved by the FDA in 1995.[5, 7] The manufacturing and distribution of REVEX® were discontinued for business reasons by Baxter Healthcare Corporation in 2008. The FDA determined that REVEX was not withdrawn from sale for reasons of safety or effectiveness in 2017.[7] Two ANDAs for nalmefene hydrochloride were approved in 2023, one of which was to the current Applicant.[6, 10] OPVEE, which delivers 2.7 mg of nalmefene hydrochloride via a intranasal spray device, was approved in May 2023.[11]

3.2. Summary of Presubmission/Submission Regulatory Activity

The Division held a Type B PIND meeting with the Applicant during the pre-IND stage of development on June 19, 2018. The topics discussed that were relevant to this clinical review were how to apply for Fast Track designation, how to pick a relevant reference drug (and how to address the unique pediatric and reproductive concerns related to nalmefene hydrochloride), how to choose and create the data needed to support the device portion of their application (specifications [including needle length], reliability testing, storage, human factors).

On June 3rd, 2020, the Applicant requested a Type C meeting. The Agency further clarified how to bridge to the Agency's prior finding of nalmefene hydrochloride's safety and efficacy, provided initial guidance on the Applicant's choice of using an autoinjector for their product, and described the data that would be needed to be submitted to support the addition of $MgCl_2$ (an excipient new to the IM/SC route of administration). The Agency stressed the importance of the initial resuscitation period (i.e., 0-5 and 0-10 minutes after administration) and provided guidance on how the Applicant may demonstrate their product has overcome known issues with 1) the onset of action of nalmefene hydrochloride and 2) the generally slow onset of IM/SC injections. The Agency provided guidance on the safety of the Applicant's fentanyl-induced respiratory depression (FIRD) protocol.

There was an end-of-phase 1 meeting held on October 4th, 2021. The Agency requested the Applicant's FIRD model be revised for safety. The Applicant discussed some of the changes they enacted in their FIRD protocol to provide more reliable results (See Section 6.2 for more on this point). It was stated that the Agency did not agree the proposed study in healthy recreational opioid users, NAL 1004, would adequately explore issues related to precipitated withdrawal. Other topics of discussion included proposed nonclinical animal tolerance/toxicology studies, labelling,

The Office of Pharmaceutical Quality held a separate end-of-Phase 1 meeting with the Applicant on March 31st, 2022. The conversation revolved around how to provide the appropriate data for their product's stability, extractable/leachables, and reliability.

At the pre-NDA meeting on November 2nd, 2023, the Applicant largely discussed how to divide and present the data within the NDA and confirmed the process to apply for Priority Review and the 505(b)(2) pathway.

3.3. Foreign Regulatory Actions and Marketing History

ZURNAI has not been marketed in the United States or abroad. However, nalmefene hydrochloride is marketed in the European Union as SELINCRO, an 18 mg oral formulation of nalmefene hydrochloride for the indication of reduction of alcohol consumption in adult patients with alcohol dependence who have a high drinking risk level, without physical withdrawal symptoms and who do not require immediate detoxification.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The OSI review is complete, and they had no concerns.

4.2. Product Quality

The leachables/extractables data provided by the Applicant was incomplete. Based on the data already provided by the Applicant, the team felt likelihood of the missing data being the cause for a denial of approval was low. They recommended a post marketing requirement (see their review for more details).

4.3. Clinical Microbiology

No concerns as of the date of this report.

4.4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology team moved for approval. There were no concerns related to the active substance. While this is a new route of administration for $MgCl_2$, $MgCl_2$ has been administered intravenously (a higher-risk method of administration) for decades and the dose administered in ZURNAI is relatively low. There were no concerns related to local tolerability of the injection based on the submitted nonclinical data.

The Pharmacology/Toxicology team did notice what appears to be a discrepancy in the animal data presented in the proposed label and REVEX, specifically the factor of safety as calculated from the NOAEL.[6] The difference in between labels requires clarification, but given the safety factor is between 15x (REVEX label) and 645x (Applicant's proposed label), the team felt there low likelihood of this data changing the approvability of the product (once provided), so the clarification could be done via a post-marketing requirement.

4.5. Clinical Pharmacology

This product underwent a long development cycle, and this submission contains data from several studies: NAL 1002 (Parts 1 and 2), NAL 1003, NAL 1004, and NAL 1005. The first part of NAL 1002 is a pilot formulation study. NAL 1002 Part 2 is a small PD pilot study where the Applicant developed their FIRD model of opioid overdose and recovery. The Applicant further refined their FIRD protocol and added PK monitoring in NAL 1003. NAL 1004 is the final, well-developed PD FIRD study demonstrating the ability of the product to perform at early time points after administration. NAL 1005 is the PK study that provides the pharmacological bridge to the agency's prior findings of efficacy of nalmefene hydrochloride.

Note that NAL 1002 (Parts 1 and 2) and NAL 1003 did not utilize the final product or the final active substance. We chose to include summaries of these initial studies because they shaped the final product and the trial protocols for NAL 1004 and NAL 1005. The data generated by NAL 1002 (Parts 1 and 2) and NAL 1003 were not included in the integrated assessments of safety and efficacy of the final product (Sections 7.3 and 8.10, respectively). The Applicant states NAL 1002 Part 1, NAL 1002 Part 2, and NAL 1003 were conducted in compliance with Good Clinical Practices.[2] A single Financial Disclosure statement submitted by the Applicant on the part of all study investigators (Please see Section 13.2 Financial Disclosure).

4.6. NAL 1002 Part 1 – Development of the Product

4.6.1. Study Overview and Objective

NAL 1002 Part 1 was conducted to guide the initial development of the product, to evaluate the impact of a range of REVEX formulations administered via various routes, and determine the impact of these factors on nalmefene hydrochloride exposure in subjects. The Applicant included formulations containing magnesium chloride (b) (4)

4.6.2. Study Design, Population, and Endpoints

NAL 1002 Part 1 was an open-label, single-center crossover study among healthy subjects. The study endpoints were subjects' serum exposure of nalmefene hydrochloride at regular timepoints over the study period to describe the uptake and excretion of the drug.

4.6.3. Study Results

The Applicant determined a nalmefene hydrochloride solution containing between 0.47 % and 1.41% $MgCl_2$ increased exposures in the critical early administration period (0-10 minutes), similar to exposures generated by administering twice the dose. These results guided the Applicant to decide to pursue a product that would dispense 1.5 mg nalmefene hydrochloride in 0.5 mL of injection volume containing 0.94% $MgCl_2$.

4.7. NAL 1002 Part 2 – Development of the Fentanyl-Induced Respiratory Depression Protocol

4.7.1. Study Overview and Objective

Applicant built internal expertise and refined the execution of their fentanyl-induced respiratory depression (FIRD) model of opioid overdose during NAL 1002 Part 2.

4.7.2. Study Design, Population, and Endpoints

NAL 1002 Part 2 was an open-label, single-center crossover study among healthy subjects who had experience with opioids (See Appendix 13.2, NLA 1002 Inclusion and Exclusion Criteria).[43] Subjects were then given an intravenous infusion of fentanyl until their respiratory rate was approximately 50% of their baseline rate before given an opioid reversal treatments: NARCAN 4mg IN, the study formulation of nalmefene hydrochloride and $MgCl_2$, or placebo. The subjects' respiratory rate in response to the treatment was followed throughout the trial.

4.7.3. Study Results

The Applicant developed the FIRD procedure they used in NAL 1004 and demonstrated increasing dose of nalmefene hydrochloride administered decreased the mean time to resolution of respiratory depression. Note the increases in respiratory rate seen in all arms at time zero is considered artifact and attributed to the stimuli of treatment administration and led to improvements in the study protocol (see Section 6.2.2 Efficacy Results – Secondary and other relevant endpoints).

4.8. NAL 1003 - Pilot Pharmacodynamics in Fentanyl-Induced Respiratory Depression

4.8.1. Study Overview and Objective

The objective of NAL 1003 was to study the onset and time course of the reversal FIRD protocol piloted in NAL 1002 Part 2 following administration of opioid reversal agents. The opioid reversal agents used in NAL 1003 were REVEX (nalmefene hydrochloride, the LD) 1 mg IM, naloxone hydrochloride 2 mg IM, and NARCAN (naloxone hydrochloride) 4 mg IN. Note NAL 1003 did not utilize the to-be-marketed drug or play a direct role in the development of the Applicant's product.

4.8.1. Study Design, Population, and Endpoints

NAL 1003 was a single center, randomized, single-blind, 6-period crossover study in healthy adult subjects with a history of prior opioid exposure. After the subjects were consented and screened, the treatment phase consisted of three treatments administered in replicate (i.e., six phases total): Nalmefene hydrochloride (comparator product to REVEX) 1 mg IM anterolateral thigh, Naloxone hydrochloride 2 mg IM anterolateral thigh, and NARCAN 4 mg, IN. The objective of the study was to compare the onset and time course of reversal of the Applicant's FIRD model following administration of the three opioid antagonists.

4.8.2. Study Results

The mean ventilation of subjects improved in response to all the interventions. Note the baseline median minute ventilation of the subjects in this trial was 10 L/min. Subjects receiving naloxone hydrochloride products in NAL 1003 recover to a minute ventilation between 6.0-7.5 L/min, close to the 5.0-7.5 L/min baseline minute ventilation seen in adults.[44] Also note the baseline median minute ventilation of subjects seen in NAL 1002 Part 1 was between 7.0-7.5 L/min (Figures 8 and 9). The difference in baseline ventilation rates would have to be further clarified before this data could be used to support any subsequent application.

4.9. NAL 1004 – Pharmacodynamics of the Applicant Product in Fentanyl-Induced Respiratory Depression

4.9.1. Study Design

Overview and Objective

The objective of the pharmacodynamic trial NAL 1004 was to demonstrate the efficacy of the final, to-be-marketed drug-device product in a FIRD model.

Trial Design

NAL1004 was a Phase 1 open label, single-center, randomized, two-treatment, four-period, crossover study utilizing the developed FIRD model, followed by administration of either the to-be-marketed 1.5 mg nalmefene hydrochloride in autoinjector(NAI) IM or NARCAN 4 mg IN, in healthy, opioid-experienced adult subjects (See Appendix 13.3, NLA 1004 Inclusion and Exclusion Criteria).

Study Endpoints

The prespecified primary endpoint was the change in minute ventilation at 5 minutes after the administration of the opioid antagonist. The secondary endpoints included following: the change in minute ventilation from nadir at 2.5, 10, 15, 20, and 90 minutes after opioid antagonist was administered. The maximal or highest minute ventilation after administration of reversal agent, and the time to maximal minute ventilation, at these same timepoints. Along with these pharmacodynamic parameters, the standard pharmacokinetic parameters of C_{max} and AUC were calculated.

Protocol Amendments

There were a number of protocol amendments.[2] The Applicant increased the study size to allow for comparisons between arms that are appropriately powered and could account for multiplicity, added local tolerance inspections at the site of treatment injection, added clarifications for the dosing of fentanyl, enacted the revisions to the FIRD protocol as stated in Section 6.2, and added additional stopping criteria based on vital signs and ECG criteria.

4.9.2. Study Results

Compliance with Good Clinical Practices

Applicant attests study NAL 1004 was conducted in compliance with Good Clinical Practices (See 5.3.4 NAL 1004 Study Report Body).[2]

Financial Disclosure

There is a single Financial Disclosure statement submitted by the Applicant on the part of all the study investigators. Please see Financial Disclosure Section 13.2.

Table of Demographic Characteristics

Table 10 (below) describes the population of subjects who were enrolled in NAL 1004 and received at least one dose of the study drug.

Table 4. Summary of Demographic and Baseline Characteristics of Randomized Safety Population in NAL 1004 (n=24) [Source: Adapted from Table 11-2, Summary of Demographic and Baseline Characteristics, page 57, 5.3.4.1 NAL 1004 Clinical Study Report)[2]

Characteristics	Statistics	Overall (N=24)
Age (years) at Baseline [1]	n	24
	Mean (SD)	39.1 (7.60)
	Median	39.5
	Min, Max	24, 52
Age Group		
18≤Age<35	n (%)	8 (33.3)
35≤Age<50	n (%)	13 (54.2)
50≤Age<55	n (%)	3 (12.5)
Age≥55	n (%)	0 (0.0)
Sex		
Male	n (%)	22 (91.7)
Female	n (%)	2 (8.3)
Ethnicity		
Hispanic or Latino	n (%)	5 (20.8)
Not Hispanic or Latino	n (%)	19 (79.2)
Race		
White	n (%)	10 (41.7)
Black or African American	n (%)	11 (45.8)
Native Hawaiian or Other Pacific Islander	n (%)	0 (0.0)
Asian	n (%)	0 (0.0)
American Indian or Alaska Native	n (%)	0 (0.0)
Multiple	n (%)	3 (12.5)
Other	n (%)	0 (0.0)
Height (cm) at baseline	n	24
	Mean (SD)	175.46 (7.726)
	Median	175.50
	Min, Max	159.5, 191.5
Weight (kg) at baseline	n	24
	Mean (SD)	81.11 (10.373)
	Median	82.00
	Min, Max	63.5, 100.4
BMI (kg/m^2) at baseline [2]	n	24
	Mean (SD)	26.35 (2.498)
	Median	26.30
	Min, Max	22.3, 30.4
Birth Control		
Yes	n (%)	24 (100.0)
No	n (%)	0 (0.0)

Patient Disposition

The Applicant used the following terminology to describe the disposition of the subjects throughout their product development program (Table 11, below).

Table 5. Definitions of Subject Dispositions in NAL 1004, and NAL 1005. [Source: Section 9.7.1.1 Analysis Populations, page 44, Clinical Study Report][2]

Population	Description
Enrolled	The group of subjects who provide informed consent.
Randomized safety population	The group of subjects who are randomized and receive at least 1 dose of the study drug.
Full analysis population	All subjects who are randomized, receive study drug and have at least 1 valid pharmacodynamics (PD) measurement
Eligible analysis set	Subjects/periods who are randomized, receive study drug, have at least 1 valid PD measurement, and their OIRDs are worse than baseline for MV and TCO_2. Note: baseline and OIRD for MV and TCO_2 may be different. Therefore, eligible analysis set for each PD parameter and period may be different.

Forty-one subjects were enrolled into NAL 1004. Of those, fourteen completed the first treatment period and thirteen of those fourteen were qualified to complete the second treatment. Seven of the forty-one subjects were screen failures, two withdrew from the study, one did not return to the facility after being consented, one was a screen failure based on a low respiratory rate just prior to fentanyl infusion, and sixteen failed through the qualification process on the day of the first treatment period.

Twenty-seven subjects were enrolled into the second treatment period. Fourteen were from Part 1 (above) and previous studies conducted by the Applicant. Twenty-four were randomized and twenty-two completed the study. The disposition of the subjects participating in NAL 1004 is shown in Table 12 (below). Note the difference between the Enrollment and Safety populations was three subjects (Table 12).

Table 6. Subject Enrollment and Disposition [Source: Adapted from Table 10-2 Subjects Enrollment (Enrolled Population), page 53, NAL 1004 Clinical Study Report][2]

Disposition	Statistics	Enrolled Overall (N=41)	Enrolled Overall (N=27)	Randomized Safety Overall (N=24)
Number of Subjects Completed Study	n (%)	14 (34.1)	22 (81.5)	22 (91.7)
Number of Subjects Discontinued (Including Screening Failures)	n (%)	27 (65.9)	5 (18.5)	2 (8.3)
Reasons for Early Termination				
Withdrawal by subject	n (%)	2 (4.9)	2 (7.4)	1 (4.2)*
Significant worsening of condition as judged by the Investigator at any point during the active treatment period	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse Event	n (%)	0 (0.0)	1 (3.7)	1 (4.2)
Pregnancy	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol Deviation	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Noncompliance with study drug	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Rescue medication/s required beyond protocol allowance	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Related to the COVID-19 pandemic	n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Screen Failure	n (%)	7 (17.1)	0 (0.0)	0 (0.0)
Other: Administrative-No Show	n (%)	1 (2.4)	0 (0.0)	0 (0.0)
Other: Backup Not Used	n (%)	0 (0.0)	1 (3.7)	0 (0.0)
Other: I/E Criteria Not Met	n (%)	1 (2.4)	1 (3.7)	0 (0.0)
Other: Qualification Failure	n (%)	16 (39.0)	0 (0.0)	0 (0.0)

Protocol Violations/Deviations

The Applicant reported 25 protocol deviations: 19 sample time collection deviations, two fentanyl infusions were terminated early, two assessments were not completed and one assessment was completed late, and one subject was lost to follow up.[2]

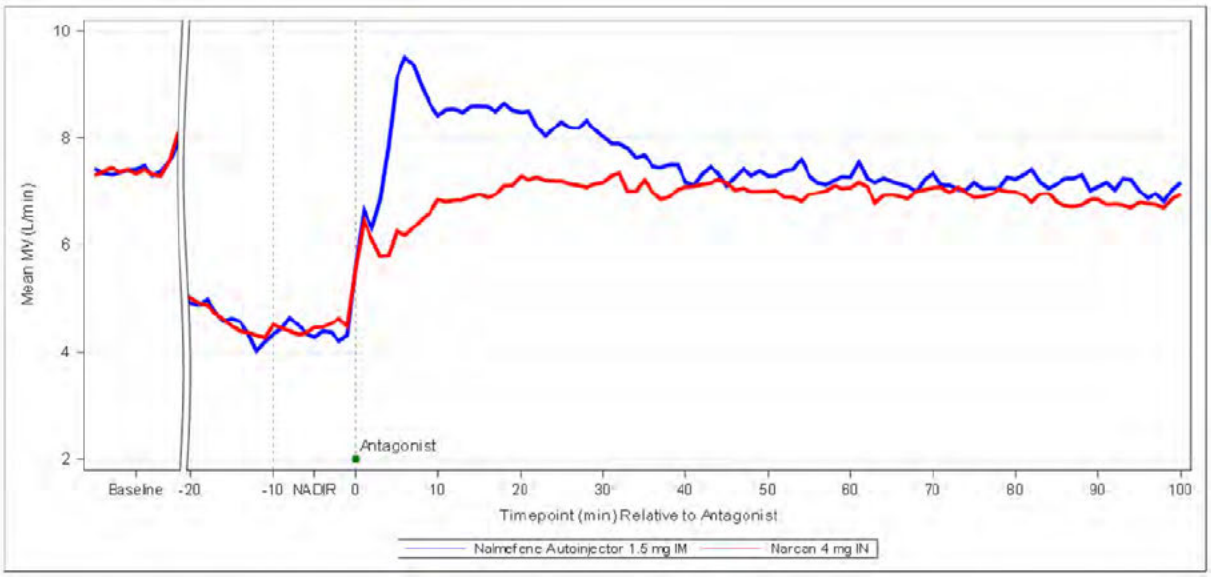
Treatment Compliance, Concomitant Medications, and Rescue Medication Use

There were no issues of treatment compliance. The past medical and surgical history of subjects were largely distant traumatic injury or minor ailments and related surgical corrections (e.g., history of hemorrhoids and subsequent removal). Concomitant medications (i.e., medications administered to subjects outside of the study drugs) were atropine and acetaminophen and related to AEs experienced by subjects.

Efficacy Results – Primary Endpoint

The primary evidence of efficacy produced by this pharmacodynamic trial is shown in Figure 11 (below). Figure 11 shows the average of subjects' minute ventilation profiles of subjects,

stratified by treatment received. Each individual profile was smoothed over one minute, with the resulting profiles averaged over time to create Figure 11.



Baseline is defined as Median of MV during 10 minutes before the start of fentanyl loading infusion. NADIR is defined as Median of MV between -10 minutes and -5 minutes before Antagonist.

Eligible Subject/Period is defined as NADIR worse than baseline.

Figure 4. Mean Smoothed (1-min Median) Profiles of Minute Volume (L/minute), Stratified by Treatment Arm (Eligible Analysis Population)[Source: Figure 11-1, page 60, NAL 1004 Clinical Study Report][2]

Much like described in Section 6.2.2, the left-hand portion of the figure is the baseline minute ventilation. Note the baseline average minute ventilation for both arms is between 7 and 8 L/min, more consistent with expected values for adults at rest.[44] After the break, after the administration of fentanyl as a part of the FIRD model and just prior to the administration of the opioid antagonists, the subjects have stabilized at a mean minute ventilation of 4-5 L/min. Around time zero we see the same small peak in ventilation associated with stimulation of administration of the study drug, followed by the pharmacological effect of the drug in the following minutes.

Efficacy Results – Secondary and other relevant endpoints

The secondary endpoints of NAL 1004 included the change in minute ventilation from nadir to pre-specified time points after the study treatment was administered. Table 13 (below) shows the characteristics of FIRD reversal observed in NAL 1004, stratified by study treatment. This data provides supportive evidence of efficacy (b) (4)

(b) (4)

Table 7. Descriptive Summary of Minute Ventilation Reversal Observed in NAL 1004 [Source: Table 11-5, page 69, NAL 1004 Clinical Study Report][2]

		MV (L/min)	Change in MV (L/min) from NADIR at							
Treatment	Statistics	NADIR	Baseline	2.5 min	5 min	10 min	15 min	20 min	30 min	90 min
Overall Nalmefene Autoinjector 1.5 mg IM	n	23	23	23	23	23	23	23	23	23
	Mean (SD)	4.33 (1.123)	2.92 (1.254)	2.00 (1.284)	4.42 (2.033)	3.97 (1.755)	4.15 (1.990)	4.00 (2.176)	3.62 (1.820)	2.74 (1.519)
	SEM	0.234	0.262	0.268	0.424	0.366	0.415	0.454	0.379	0.317
	Median	4.53	2.40	2.05	3.95	4.25	3.80	3.60	3.45	2.30
	Min, Max	2.2, 6.1	0.9, 5.9	0.0, 4.7	0.3, 9.4	0.1, 6.9	0.4, 8.3	0.8, 8.8	0.8, 7.8	0.8, 6.5
Overall Narcan 4 mg IN	n	24	24	24	24	24	24	24	24	24
	Mean (SD)	4.41 (1.080)	3.02 (1.022)	1.67 (1.046)	2.03 (0.992)	2.57 (1.364)	2.79 (1.328)	3.11 (1.610)	2.92 (1.357)	2.55 (0.994)
	SEM	0.221	0.209	0.213	0.203	0.278	0.271	0.329	0.277	0.203
	Median	4.45	2.90	1.25	1.95	2.22	2.60	3.03	2.88	2.46
	Min, Max	2.3, 7.8	1.1, 5.0	0.3, 4.0	0.2, 3.4	0.5, 5.5	0.4, 5.3	0.0, 8.1	0.5, 5.6	0.5, 4.7

SD = Standard Deviation; SEM = Standard Error;
NADIR is defined as Median of MV between -10 and -5 -minutes before the start of the Antagonist.
The data for overall treatment period is calculated as the average of available data from individual periods.
Eligible Subject/Period is defined as NADIR worse than baseline

Along with these pharmacodynamic parameters, the standard pharmacokinetic parameters of C_{max} and AUC were calculated (Table 14 [ZURNAI] and fifteen [NARCAN 4 mg IN])

Table 8. Pharmacokinetic Parameters of ZURNAI Observed in NAL 1004 (Full Analysis Population)[Source: Table 11-9, page 84, NAL 1004 Clinical Study Report][2]

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

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

Table 9. Pharmacokinetic Parameters of NARCAN 4 mg IN Observed in NAL 1004 (Full Analysis Population)[Source: Table 11-10, page 85, NAL 1004 Clinical Study Report][2]

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

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

Dose/Dose Response

The Applicant tested one dose in each arm of NAL 1004.

Durability of Response

The pharmacological effect of both study treatments lasted to the end of data collection (one hundred minutes).

4.10. NAL 1005 – Bridging Biopharmaceutical Study

4.10.1. Study Design

Overview and Objective

The objective of NAL1005 was to establish a scientific bridge between a single dose of the final, to-be-marketed ZURNAI autoinjector containing 1.5 mg nalmefene hydrochloride and a single 1.0 mg IM administration of REVEX LD per the 505(b)(2) development pathway.

Period 3 was a substudy nested within in the overall NAL 1005 study design to characterize the PK of nalmefene hydrochloride 1.0 mg IV bolus administration. The nalmefene hydrochloride IV PK data was utilized to conduct simulations of systemic exposure following repeat doses of nalmefene hydrochloride IV bolus. Reviewer note: This substudy also provides the data needed to compare the safety of the Applicant product to the published literature (see Section 8).

Trial Design

NAL1005 was a Phase 1 single-center, open-label, randomized, single-dose, 2-treatment, 2-

period, 2-way crossover study in healthy adult subjects. An additional third period for a third treatment (1.0 mg IV REVEX) was conducted in a subset of the general NAL 1005 study population. Section 13.4 lists the inclusion and exclusion criteria used for NAL 1005.

Study Endpoints

The primary study endpoint of NAL 1005 was the plasma concentrations of nalmefene hydrochloride with time, allowing for the calculation of the standard PK parameters for each treatment. Secondary objectives included the safety of the study drugs were assessed using recorded AEs, clinical laboratory test results, vital signs, SpO2, physical examinations, and conventional 12-lead ECGs and local tolerability.

The primary endpoint of the nested substudy was to characterize the PK (PK) of nalmefene hydrochloride following nalmefene hydrochloride 1.0 mg intravenous bolus administration. Secondary objectives included the assessment of the safety and tolerability of nalmefene hydrochloride 1.0 mg intravenous bolus administration.

Statistical Analysis Plan

NAL 1005 assessed the pharmacokinetic parameters of ZURNAI in comparison to nalmefene hydrochloride injection. For $AUC_{0-2.5}$ minutes, AUC_{0-5} minutes, AUC_{0-10} minutes, AUC_{0-15} minutes, AUC_{0-20} minutes, AUC_{0-30} minutes, AUC_t and C_{max}, a 90% confidence interval for the PK metrics were to be constructed to compare Test (nalmefene hydrochloride autoinjector) and Reference (nalmefene hydrochloride injection). This confidence interval was to be derived from the appropriate statistical model using PROC MIXED SAS® procedure with the Log PK metrics as dependent variables and treatment, sequence and period as fixed effect and subject within sequence as random effect.

Protocol Amendments

There were two protocol amendments. The first was an amendment to allow the study physician to dose patients with study drug prior to knowing the subject's serum phosphate levels. The second protocol amendment allowed for the addition of the nested substudy relating to 1 mg IV REVEX.

4.10.2. Study Results

Compliance with Good Clinical Practices

Applicant attests study NAL 1005 was conducted in compliance with Good Clinical Practices (See 5.3.1.2 NAL 1005 Study Report Body).[2]

Financial Disclosure

There is a single Financial Disclosure statement submitted by the Applicant on the part of all the study investigators. Please see Financial Disclosure Section 13.2.

Patient Disposition

There were a total of sixty subjects enrolled, twenty-four of whom were randomized, and twenty who completed the study. One subject had a positive drug abuse screen at check-in for their second treatment period and was discontinued from receiving additional study drug. They had already received one dose of REVEX 1 mg IV. There were no safety concerns at follow up.

A second subject had an elevated BUN at check in for their second period. They had received one 1.0 mg dose of REVEX during their first period of participation. They were discontinued from receiving additional study drug and had no safety concerns at follow-up.

A third subject completed study period 1 and 2 (ZURNAI and REVEX), but did not return for participation in period 3 (NARCAN). This subject was deemed lost to follow up as they did not complete the follow-up safety procedures.

A fourth subject was discontinued because of an error in PK serum sampling during their first period. They completed all the follow-safety procedures.

All twelve subjects who were enrolled into the IV REVEX substudy completed the substudy.

Protocol Violations/Deviations

There were several protocol deviations. One was a miscommunication on the timing of local tolerability assessments. The protocol was to do the assessment within 5 minutes of administration, the assessments were actually recorded within 10 minutes of administration. The blood draws used to measure the serum exposures were not all timed correctly to allow for the calculation of PK parameters. These specific blood draws were excluded from the final analysis as adjudicated by an independent reviewer. We do not believe these protocol violations create a concern about the overall interpretability or validity of the study's results.

Table of Demographic Characteristics

The demographics of the population included in the final analysis of NAL 1005 is shown in Table 16 (below).

Table 10. Summary of Demographic Data of NAL 1005 Subjects (Randomized Safety Population) [Source: Adapted from Table 11-1, page 38, NAL 1005 Clinical Study Report)[2]

		Overall N = 24
Age (years)	Mean ± SD	35.8 ± 10.0
	Range (min – max)	21 - 55
Age Groups (years)	< 18	0 (0.0%)
	18 - 40	17 (70.8%)
	41 - 64	7 (29.2%)
	65 – 75	0 (0.0%)
	> 75	0 (0.0%)
Gender	Male	18 (75.0%)
	Female	6 (25.0%)
Ethnicity*	Hispanic or Latino	6 (25.0%)
	Not Hispanic or Latino	18 (75.0%)
Race*	American Indian or Alaska Native	0 (0.0%)
	Asian	2 (8.3%)
	Black or African American	12 (50.0%)
	Native Hawaiian or Other Pacific Islander	0 (0.0%)
	White	8 (33.3%)
	Multiple	2 (8.3%)
BMI (kg/m^2)	Mean ± SD	25.9 ± 2.4
	Range (min – max)	21.3 - 29.3
Height (cm)	Mean ± SD	171.5 ± 10.6
	Range (min – max)	150 - 191
Weight (kg)	Mean ± SD	76.5 ± 13.1
	Range (min – max)	54 - 99
Tobacco Users†	Yes	0 (0.0%)
	No	24 (100.0%)

* Categories based on FDA Guidance *Collection of Race and Ethnicity Data in Clinical Trials*, Issue Date: October 26, 2016.
† Defined as current tobacco user (having used tobacco- or nicotine-containing products within 30 days before initial dosing).
Reference Listing: L16.2.4.2, L16.2.4.3

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The subjects received study medications under direct observation from the study staff. Doses of administered drugs were verified by staff at the time of administration.

Efficacy Results – Primary Endpoint

Figure 12 and Table 17 (below) demonstrates the plasma profile of the drugs investigated in NAL 1005: the to-be-marketed product ZURNAI (1.5 mg nalmefene hydrochloride in 0.5 mL injection volume with 0.94% mgCl2) given IM/SC via the (b) (4) device, compared to 1.0 mg of the reference drug REVEX given IM/SC.[6] Table 18 shows the plasma profile of 1.0 mg of REVEX given IV compared to ZURNAI in the subjects participating in the substudy. Table 19 is taken from the approved REVEX label and lists the plasma profile for subjects given 1.0 mg of REVEX IV, stratified by age.

Figure 12 and Table 17 demonstrate that the autoinjector ZURNAI can produce nalmefene hydrochloride exposures in subjects higher than REVEX, the referenced drug, when administered as an IM/SC injection. Tables 18 and 19 demonstrate across studies that the early exposures of nalmefene hydrochloride (i.e., 0-10 min after administration) produced in subjects by ZURNAI approximate that of 1.0 mg of REVEX administered as an IV injection.

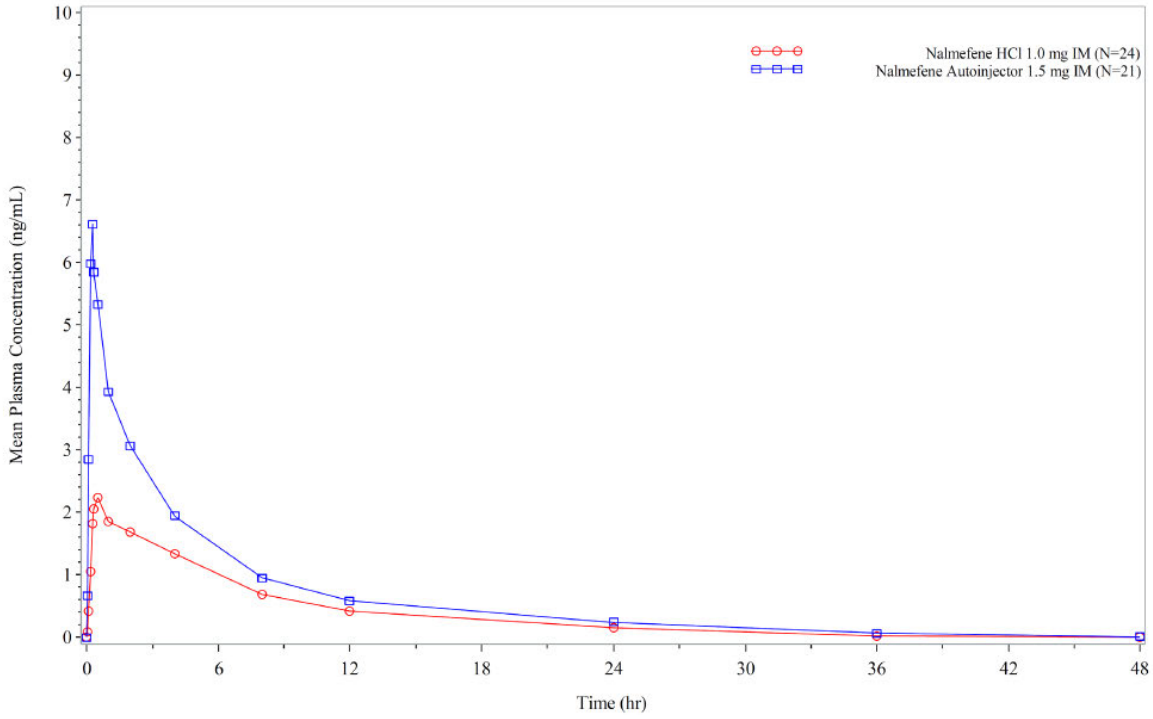


Figure 5. Mean Plasma Concentration with Time, Stratified by Study Drug [Source: Figure 11-1, page 41, NAL 1005 Clinical Study Report][2]

Table 11. Plasma Pharmacokinetic Values for ZURNAI vs Nalmefene Hydrochloride IM/SC (Full Analysis Population)[Source: Table 11-4, page 50, NAL 1005 Clinical Study Report][2]

		Geometric Least Squares Means		
Parameters	N (# subjects)	Nalmefene Autoinjector 1.5 mg IM	Nalmefene HCl 1.0 mg IM	Ratio %
C_{max}	24	7.512	2.387	314.7
$AUC_{0-2.5}$	14	0.009	0.002	383.9
AUC_{0-5}	20	0.036	0.008	450.1
AUC_{0-10}	23	0.320	0.047	687.2
AUC_{0-15}	23	0.836	0.151	552.0
AUC_{0-20}	23	1.331	0.312	426.5
AUC_{0-30}	24	2.273	0.647	351.0
AUC_t	24	28.384	16.036	177.0
AUC_{inf}	24	30.428	17.975	169.3

Table 12. Plasma Pharmacokinetic Values for ZURNAI vs Nalmefene Hydrochloride IV (Full Analysis Population)[Source: Adapted from Table 11-6, page 50, NAL 1005 Clinical Study Report][2]

Parameters	N (# subjects)	Nalmefene Autoinjector 1.5 mg IM	Nalmefene 1.0 mg IV Bolus
C_{max}	12	7.778	6.938
$AUC_{0-2.5}$	12	0.007	0.053
AUC_{0-5}	12	0.042	0.279
AUC_{0-10}	12	0.349	0.768
AUC_{0-15}	12	0.925	1.161
AUC_{0-20}	12	1.365	1.496
AUC_{0-30}	12	2.333	2.066
AUC_t	12	28.673	16.253
AUC_{inf}	12	31.007	18.223

Note: p-value is statistically significant if it is < 0.05.
Source: adam.adpp

Table 13. Mean Nalmefene Pharmacokinetic Parameters in Adult Males Following a 1 mg Intravenous Dose.[Source: Approved label for REVEX][6]

Parameter	Young, N=18	Elderly, N=11
Age	19 to 32	62 to 80
C_p at 5 min. (ng/mL)	3.7 (29)	5.8 (38)
V_{dss} (L/kg)	8.6 (19)	8.6 (29)
V_c (L/kg)	3.9 (29)	2.8 (41)
$AUC_{0\text{-}inf}$ (ng-hr/mL)	16.6 (27)	17.3 (14)
Terminal $T_{1/2}$ (hr)	10.8 (48)	9.4 (49)
Cl_{plasma} (L/hr/kg)	0.8 (23)	0.8 (18)

The pharmacokinetic parameters OPVEE nasal spray (2.7 mg nalmefene hydrochloride in 0.1 mL) are shown in Table 20. Note OPVEE has higher characteristics (C_{max} and AUC) than ZURNAI (Tables 17 and 18) and OPVEE was found to be safe and effective in 2023.[11]

Taken together, this evidence suggests the Applicant can rely upon the Agency's previous finding of efficacy in this 505(b)(2) application.

Table 14. Pharmacokinetic Parameters of OPVEE nalmefene hydrochloride nasal spray compared to nalmefene hydrochloride 1.0 mg IM/SC [Source: Table 3, Approved Label for OPVEE][11]

Parameter	OPVEE	Nalmefene IM
T_{max} (h)*	0.250 (0.0833-2.00)	0.33 (0.117-18.0)
C_{max} (ng/mL)†	10.4 (62.6)	1.50 (59.4)
$AUC_{0\text{-}2.5min}$ (ng-hr/mL)†	0.00763 (233)	0.00168 (186)
$AUC_{0\text{-}5min}$ (ng-hr/mL)†	0.0599 (201)	0.0102 (142)
$AUC_{0\text{-}10min}$ (ng-hr/mL)†	0.523 (124)	0.0639 (118)
$AUC_{0\text{-}15min}$ (ng-hr/mL)†	1.20 (94.2)	0.142 (98.6)
$AUC_{0\text{-}20min}$ (ng-hr/mL)†	1.89 (77.2)	0.228 (84.5)
$AUC_{0\text{-}30min}$ (ng-hr/mL)†	3.07 (60.4)	0.405 (69.2)
$AUC_{0\text{-}inf}$ (ng-hr/mL)†	40.6 (22.0)	16.8 (18.7)
F_{rel}†	0.806 (10.9)	NA
$T_{½}$ (h)†	11.4 (20.8)	10.6 (18.5)

NA Not applicable
* T_{max} presented as median (range)
† Arithmetic mean

Data Quality and Integrity

There are no concerns about the validity or integrity of the submitted data. There are alternative interpretations of the data produced by 1.0 mg IV REVEX substudy (Period 3) that are discussed in detail in Section 7.1.1, the Integrated Review of Effectiveness.

Dose/Dose Response

Only one dose was studied for each treatment arm in NAL 1005.

Durability of Response

The PK parameters for the study drugs were measured out to 48 hours after administration.

4.11. Synopsis of Clinical Pharmacology Team Review

Clinical Pharmacology believes the studies submitted by the Applicant provide the pivotal evidence of effectiveness. The Applicant proposed a pediatric study in the agreed initial pediatric study plan (iPSP) prior to the submission of this NDA, as follows: "Conduct a Pediatric Pharmacokinetic, Pharmacodynamic and Safety Study in Children From Birth to Less Than 12 Years of Age from an at-risk population". At the time of composing this review, the post-marketing requirements and commitments were still being finalized; hence, the final wording might be subject to change. Please see their review for additional details.

4.12. Devices and Companion Diagnostic Issues

The Center for Devices and Radiological Health had concerns related to the removability of the needle cap on the autoinjector: The mean and distribution of cap removal torques were acceptable as presented, but (b) (4) Because this is an application for a device intended to be used in a medical emergency, out of an abundance of caution, the CDRH team wanted to address this potential control issue via a post-marketing requirement.

4.13. Consumer Study Reviews

The Human Factors team had some additional labelling requests (See Section 10.1).

4.14. Office of Pharmacovigilance and Epidemiology

This application utilizes the (b) (4) autoinjector (developed by (b) (4)) which had been a part of one other approved product, (b) (4) . The patient population and use-case

for ZURNAI and (b) (4) are different: (b) (4) However, ZURNAI requires a higher level of reliability because it is intended to be a life-saving intervention used in emergencies and the potential cost of a device failure is high. We felt it worthwhile to examine the post-marketing experience of (b) (4) for potential safety signals and consulted the Office of Pharmacovigilance and Epidemiology to review FAERS reports related to the (b) (4) device used in the (b) (4) product.

(b) (4)

From the consult report:

- Device issues: 87% (n= 229) of cases reported device malfunction secondary to device issues. Reported device issues involved specific components of the autoinjector (e.g., needle, needle end/guard, viewing window) or other more general scenarios (e.g., no medication was released during injection, medication leaking from autoinjector, device exploded).
- User error: 13% (n=34) of cases in this case series reported device malfunction secondary to user error. Commonly reported user error scenarios included the following: users did not hold the autoinjector for/with sufficient duration or pressure, autoinjectors slipped during administration, or users did not realize (b) (4) is a single-use product.

From the individual case reports, the cases of device failures were from a broad and diverse

range of issues, each of which were low in number. This suggests none of the specific failure modes constituted a specific safety signal. Reports submitted to FAERS are voluntary, not automatic, so we cannot calculate incidence of errors directly. However, the consult states a total of 229 reports seems small given there have been (b) (4) units of (b) (4) sold.

Within the limits of how comparable (b) (4) and ZURNAI and their intended patient populations are, this post-marketing data is reassuring as it suggests there is not a device-specific safety signal.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

No clinical studies of efficacy were submitted in support of this 505(b)(2) application. This application relies on PK/PD data and the agency's previous findings of the efficacy of nalmefene hydrochloride.

5.2. Review Strategy

No clinical efficacy trials were conducted in support of this 505(b)(2) application. This application relies on PK/PD data and the agency's previous findings of the efficacy of nalmefene hydrochloride. The safety of the submitted product was assessed based on the safety evaluations completed as a part of the PK studies and the literature.

6. Review of Relevant Individual Trials Used to Support Efficacy

No clinical efficacy trials were conducted in support of this 505(b)(2) application. This application relies on PK/PD data and the agency's previous findings of the efficacy of nalmefene hydrochloride. The safety of the submitted product was assessed based on the safety evaluations completed as a part of the PK studies and the literature.

7. Integrated Review of Effectiveness

See Section 6, Review of Relevant Individual Trials Used to Support Efficacy.

8. Review of Safety

8.1. Safety Review Approach

The Applicant is relying on the Agency's previous findings of safety for the listed drug (LD) REVEX (nalmefene hydrochloride injection; NDA 020459). The Applicant has provided additional evidence of safety discussed derived (primarily) from NAL 1004 (pharmacodynamic study of ZURNAI to reverse FIRD in healthy subjects) and NAL 1005 (critical bridging pharmacokinetic study). As mentioned in Section 6. Review of Relevant Individual Trials Used to Support Efficacy, the study drugs administered in NAL 1002 Part 1/Part 2, NAL 1003, and NAL 1003 are not representative of the final product. Section 8 will only discuss safety signals observed in those product development trials in specific, relevant cases (e.g., the safety profile of an approved product like REVEX, NARCAN, or fentanyl should be comparable across trials).

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Across the entire drug development program, there were forty-seven subjects that were

enrolled and exposed to nalmefene hydrochloride. Of these, 44 were exposed to the Applicant's to-be-marketed product and completed NAL 1004 (n=23) and NAL 1005 (n=21)(Table 21).

Table 15: Summary of Subjects Exposed to the Study Drug (Safety Population)[Source: Table 5, page 23, 2.7.4 Summary of Clinical Safety][45]

	NAL1004	**NAL1005**			**Pooled**	
	Fentanyl/ NAI 1.5 mg IM	NAI 1.5 mg IM	Nalmefene HCl 1.0 mg IM	Nalmefene 1.0 mg IV Bolus	Pooled NAI 1.5 mg IM	Pooled Nalmefene
N	23	21	24	12	44	47

8.2.2. Relevant characteristics of the safety population:

The demographics and baseline characteristics of the safety population, stratified by study, is shown in Table 22 (below). The Applicant submitted a listing of the past medical history of subjects included in the safety population. The most common listings were classified as surgical procedures (10%, including wisdom tooth removal, tonsillectomy, tenoplasty, hemorrhoid removal) and injuries (6%, including gunshot wound, hand fracture, tibia, and wrist fractures). None of the conditions listed would impact the PK/PD or safety profile of the Applicant product. Note that none of the subjects in the safety population had a history of opioid abuse or dependence. The concomitant medications listed by the Applicant were generally non-prescription (acetaminophen) or were a form of female hormonal contraception. One subject received atropine during NAL 1004 (see Section 8.4).

Table 16. Summary of Demographic and Baseline Characteristics, Stratified by study (Safety Population)[Source: Adapted from Table 2, page 1675, Appendix 2 Integrated Summary of Tables and Listings][45]

		NAL1004			NAL1005			
Characteristics	Statistics	Fentanyl/ Nalmefene Autoinjector 1.5 mg IM (N=23)	Fentanyl/ Narcan 4 mg IN (N=24)	Total (N=24)	Nalmefene Autoinjector 1.5 mg IM (N=21)	Nalmefene HCl 1.0 mg IM (N=24)	Nalmefene 1.0 mg IV Bolus (N=12)	Total (N=24)
Age (years) at Baseline	n	23	24	24	21	24	12	24
	Mean (SD)	39.0 (7.75)	39.1 (7.60)	39.1 (7.60)	37.2 (9.76)	35.8 (10.05)	36.8 (11.13)	35.8 (10.05)
	Median	38.0	39.5	39.5	37.0	36.0	37.0	36.0
	Min, Max	24, 52	24, 52	24, 52	23, 55	21, 55	23, 55	21, 55
Age Group								
18 ≤ Age < 35	n (%)	8 (34.8)	8 (33.3)	8 (33.3)	8 (38.1)	11 (45.8)	4 (33.3)	11 (45.8)
35 ≤ Age < 50	n (%)	12 (52.2)	13 (54.2)	13 (54.2)	11 (52.4)	11 (45.8)	6 (50.0)	11 (45.8)
50 ≤ Age < 55	n (%)	3 (13.0)	3 (12.5)	3 (12.5)	1 (4.8)	1 (4.2)	1 (8.3)	1 (4.2)
Age ≥ 55	n (%)	0	0	0	1 (4.8)	1 (4.2)	1 (8.3)	1 (4.2)
Sex								
Male	n (%)	21 (91.3)	22 (91.7)	22 (91.7)	16 (76.2)	18 (75.0)	10 (83.3)	18 (75.0)
Female	n (%)	2 (8.7)	2 (8.3)	2 (8.3)	5 (23.8)	6 (25.0)	2 (16.7)	6 (25.0)
Ethnicity								
Hispanic or Latino	n (%)	4 (17.4)	5 (20.8)	5 (20.8)	5 (23.8)	6 (25.0)	4 (33.3)	6 (25.0)
Not Hispanic or Latino	n (%)	19 (82.6)	19 (79.2)	19 (79.2)	16 (76.2)	18 (75.0)	8 (66.7)	18 (75.0)
Race								
White	n (%)	9 (39.1)	10 (41.7)	10 (41.7)	7 (33.3)	8 (33.3)	5 (41.7)	8 (33.3)
Black or African American	n (%)	11 (47.8)	11 (45.8)	11 (45.8)	10 (47.6)	12 (50.0)	5 (41.7)	12 (50.0)
Native Hawaiian or Other Pacific	n (%)	0	0	0	0	0	0	0
Asian	n (%)	0	0	0	2 (9.5)	2 (8.3)	1 (8.3)	2 (8.3)
American Indian or Alaskan Native	n (%)	0	0	0	0	0	0	0
Multiple	n (%)	3 (13.0)	3 (12.5)	3 (12.5)	2 (9.5)	2 (8.3)	1 (8.3)	2 (8.3)
Other	n (%)	0	0	0	0	0	0	0
Height (cm) at Baseline	n	23	24	24	21	24	12	24
	Mean (SD)	175.39 (7.893)	175.46 (7.726)	175.46 (7.726)	171.64 (11.108)	171.45 (10.558)	170.40 (9.020)	171.45 (10.558)
	Median	174.00	175.50	175.50	172.70	171.45	171.45	171.45
	Min, Max	159.5, 191.5	159.5, 191.5	159.5, 191.5	149.9, 190.5	149.9, 190.5	157.5, 182.9	149.9, 190.5
Weight (kg) at Baseline	n	23	24	24	21	24	12	24
	Mean (SD)	80.83 (10.514)	81.11 (10.373)	81.11 (10.373)	76.59 (13.457)	76.58 (13.101)	75.45 (10.077)	76.58 (13.101)
	Median	81.50	82.00	82.00	73.90	75.95	73.25	75.95
	Min, Max	63.5, 100.4	63.5, 100.4	63.5, 100.4	54.4, 99.3	54.4, 99.3	57.2, 88.9	54.4, 99.3
BMI (kg/m^2) at Baseline [1]	n	23	24	24	21	24	12	24
	Mean (SD)	26.28 (2.532)	26.35 (2.498)	26.35 (2.498)	25.82 (2.430)	25.88 (2.414)	25.93 (2.249)	25.88 (2.414)
	Median	25.90	26.30	26.30	25.10	25.45	25.45	25.45
	Min, Max	22.3, 30.4	22.3, 30.4	22.3, 30.4	21.3, 29.3	21.3, 29.3	21.6, 29.3	21.3, 29.3

8.2.3. Adequacy of the safety database:

The Applicant submitted the safety assessments associated with their pharmacodynamic trial and critical bridging trial.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

All data and documents in this application were electronically submitted following the guidance

for electronic submission. The documents were organized in electronic Common Technical Document (eCTD) format. The overall quality of the submission was adequate. The organization and the ability to navigate the NDA were acceptable.

8.3.2. Categorization of Adverse Events

Adverse events were coded by system organ class and preferred term based on the Medical Dictionary for Regulatory Affairs (MedDRA) coding dictionary version 21.0 and summarized by system organ class (SOC) and preferred term within SOC.[45] The definitions and categorizations provided by the Applicant of treatment-emergent adverse events and serious adverse events are acceptable. The subject narratives of the AEs that led to discontinuations or SAEs were reviewed.

8.3.3. Routine Clinical Tests

None of the routine clinical testing (including complete blood cell counts, complete metabolic testing, and urinalysis) conducted for NAL 1004 or NAL 1005 met or exceeded the clinically notable range.[45] None of the urine or serum pregnancy tests conducted on the female subjects enrolled in NL 1004 or NAL 1005 were positive at screening or participation. One subject enrolled in NAL 1005 tested positive for alcohol at the time of Period 2 check-in and was discontinued from participation.

8.4. Safety Results

8.4.1. Deaths

There were no deaths recorded among the subjects of studies NAL 1002 Part 1 or Part 2, NAL 1003, NAL 1004, and NAL 1005.[45]

8.4.2. Serious Adverse Events

See Section 8.4.4.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

See Section 8.4.4.

8.4.4. Significant Adverse Events

Study NAL1004.
Two subjects discontinued from the study due to an AE(s)[45]:

- Subject (b) (6): discontinued from the study due to symptomatic sinus bradycardia and symptomatic hypotension in Period 1 (fentanyl and NARCAN 4 mg IN)

- Subject (b) (6): withdrew from the study at the end of Period 3 due to 8 AEs experienced in Period 2 (fentanyl and NAI 1.5 mg IM)

Two subjects had study drug interruption due to an AE(s):

- Subject (b) (6): fentanyl infusion was stopped early post-administration of NARCAN 4 mg IN due to an AE (headache)
- Subject (b) (6): fentanyl infusion was stopped early post-administration of Nalmefene hydrochloride Autoinjector 1.5 mg IM due to an AE (emesis) during NAL 1004 Period 1. This same subject has a second AE, pain at the site of NAI administration. The pain later resolved

Two subjects had AEs related to local tolerability

- Subject (b) (6): This subject had a second AE, pain at the site of NAI administration, which resolved without intervention.
- Subject (b) (6): Subject reported mild soreness at the site of NAI injection shortly after administration. The pain was rated mild and resolved less than an hour later.

Study NAL1005.

- Subject (b) (6) exhibited a 0.3 cm diameter area of erythema at the REVEX IM site during their 24 h post dose assessment. However, this observation was not considered an AE because it did not meet the criteria set forth in the 4-point grading scale.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Adverse events were categorized as mild to moderate in severity and resolved by the end of subject participation. The most common TEAEs recorded among subjects in the safety population after receiving ZURNAI, listed by system organ class and stratified by study, is shown in Table 23 (below). These are all small studies, but the higher prevalence of AEs recorded for the pooled safety population (63.6%) might cause one to pause initially. We had asked the Applicant to stratify the AEs from their safety population by study and it is clear the high prevalence of AEs in NAL 1004 (91.3%) biased the results of the pooled safety population. NAL 1004 the pharmacodynamic study demonstrating the time of onset of ZURNAI's ability to reverse the FIRD model of opioid overdose. NAL 1005 was a simple, single-exposure pharmacokinetic bridge between ZURNAI and REVEX (LD). The types and frequencies of AEs related to ZURNAI documented in NAL 1005 is similar in type, frequency, and severity, to the AEs documented for 1.0 mg REVEX IM (LD) and the 1.0 mg REVEX IV substudy (Table 24, below). The distribution of AEs documented in Table 23 is similar to what is documented in the accepted REVEX label (Table 25 below).[6]

Table 17. Relative Frequencies of Most Common Adverse Events that Occurred in Greater than 5% of Subjects in NAL 1004 and NAL 1005 [Source: Adapted from Table 10, page 30, Summary of Clinical Safety][45]

System Organ Class Preferred Term	Nalmefene Auto-Injector 1.5 mg IM		
	Pooled NAL1004 and NAL1005 N=44 n (%)	Study NAL1004 N=23 n (%)	Study NAL1005 N=21 n (%)
Any AE	28 (63.6)	21 (91.3)	7 (33.3)
Cardiac disorders			
Palpitations	4 (9.1)	4 (17.4)	0
Ear and labyrinth disorders			
Tinnitus	4 (9.1)	4 (17.4)	0
Ear discomfort	3 (6.8)	3 (13.0)	0
Gastrointestinal disorders			
Nausea	8 (18.2)	6 (26.1)	2 (9.5)
Vomiting	5 (11.4)	3 (13.0)	2 (9.5)
General disorders and administration site conditions			
Feeling hot	11 (25.0)	11 (47.8)	0
Chills	6 (13.6)	6 (26.1)	0
Feeling abnormal	3 (6.8)	3 (13.0)	0
Nervous system disorders			
Dizziness	7 (15.9)	4 (17.4)	3 (14.3)
Headache	8 (18.2)	5 (21.7)	3 (14.3)
Allodynia	5 (11.4)	5 (21.7)	0
Burning sensation	3 (6.8)	3 (13.0)	0
Psychiatric disorders			
Irritability	3 (6.8)	3 (13.0)	0
Vascular disorders			
Hot flush	3 (6.8)	3 (13.0)	0

The most common TEAEs recorded among the subjects in NAL 1005 who received 1 mg REVEX IV, 1 mg REVEX IM, or ZURNAI are listed in Table 24 (below).

Table 18. Relative Frequencies of Common Adverse Events that Occurred in Greater than 5% of Subjects in Study NAL 1005 (Including IV substudy)[Source: Table 14, page 34, Summary of Clinical Safety][45]

System Organ Class Preferred Term	Nalmefene Auto-Injector 1.5 mg IM	Nalmefene HCl 1.0 mg IM	Nalmefene HCl 1.0 mg IV
	N=21 n (%)	N=24 n (%)	N=12 n (%)
Any AE	7 (33.3)	9 (37.5)	4 (33.3)
Gastrointestinal disorders			
Nausea	2 (9.5)	2 (8.3)	0
Vomiting	2 (9.5)	1 (4.2)	0
General disorders and administration site conditions			
Fatigue	2 (9.5)	3 (12.5)	0
Nervous system disorders			
Dizziness	3 (14.3)	3 (12.5)	2 (16.7)
Headache	3 (14.3)	1 (4.2)	0
Somnolence	1 (4.8)	2 (8.3)	2 (16.7)
Psychiatric disorders			
Euphoric mood	0	0	2 (16.7)
Vascular disorders			
Hot flush	0	2 (8.3)	0
Hypertension	0	0	1 (8.3)

Table 19. Relative Frequencies of Common Adverse Reactions (to REVEX) with an Incidence Greater than 1%. [Source: Accepted label for REVEX][6]

Relative Frequencies of Common Adverse Reactions With an Incidence Greater than 1%
(all patients, all clinical settings)

Adverse Event	Nalmefene N=1127	Naloxone N=369	Placebo N=77
Nausea	18%	18%	6%
Vomiting	9%	7%	4%
Tachycardia	5%	8%	-
Hypertension	5%	7%	-
Postoperative pain	4%	4%	N/A
Fever	3%	4%	-
Dizziness	3%	4%	1%
Headache	1%	1%	4%
Chills	1%	1%	-
Hypotension	1%	1%	-
Vasodilatation	1%	1%	-

8.4.6. Laboratory Findings

No changes in clinical laboratory chemistry results were observed related to ZURNAI

administration. No laboratory values that met or exceeded the clinically notable range values were documented.[45]

8.4.7. Vital Signs

Vital signs were taken on all participants at screening, check-in, and through participation in NAL 1004 and NAL 1005. With one exception, none of the subjects had clinically relevant abnormalities with their vital signs. One subject, (b) (6), had symptomatic bradycardia and hypotension resulting in atropine administration while undergoing the FIRD portion of NAL 1005.

8.4.8. Electrocardiograms (ECGs)

Electrocardiograms were taken at screening, check-in, and end-of-study for both NAL 1004 and NAL 1005. No abnormal ECG was considered significant.

8.4.9. QT

Electrocardiograms were taken at screening, check-in, and end-of-study for both NAL 1004 and NAL 1005. No abnormal ECG was considered significant.

8.4.10. Immunogenicity

Not applicable.

8.5. Analysis of Submission-Specific Safety Issues

Not applicable.

8.5.1. Evaluation of Safety of ZURNAI in Patients with Opioid Dependence

The safety of ZURNAI in healthy individuals is supported by the pharmacokinetic data (C_{max} and AUC) submitted by the Applicant that links ZURNAI to the agency's previous finding of safety of REVEX. The safety of ZURNAI when administered in persons who are physically dependent on opioids is less clear. The patient population at highest risk of opioid overdose and would therefore derive the greatest benefit from opioid reversal products are those who abuse opioids. The prevalence of opioid dependence is expected to be high in these individuals, so the potential risk for the development of withdrawal is a concern when evaluating new opioid reversal products.

Nalmefene hydrochloride can precipitate acute opioid withdrawal depending on the dose administered and the recipient's opioid use history. The symptoms of opioid withdrawal (see Section 1.4) are uncomfortable, but in of themselves not believed to necessitate hospitalization. The fear of withdrawal is an ongoing stressor on the lives of those who use

drugs and a common barrier to seeking opioid use disorder treatment (see Section 1.4).[38, 39] Complications arising from opioid withdrawal include dehydration, refractory vomiting, electrolyte disturbances, and shock, all of which can require hospitalization. The risk of withdrawal requiring hospitalization increases with the severity and duration of symptoms, and the duration of action nalmefene hydrochloride is four times that of naloxone hydrochloride (eight and two hours, respectively). This difference in duration of action prompted the ACMT/AACT statement against nalmefene hydrochloride replacing naloxone hydrochloride.[52] The increased duration of action may be of theoretical benefit in decreasing the risk of relapse (i.e., "renarcotization") in those patients who have been exposed to long-acting opioids, though incidence of relapse is not clear.[46]

There is limited clinical trial data which provides insight into the relative efficacy and safety of REVEX, ZURNAI, and naloxone hydrochloride. The Kaplan study was a double-blind, randomized, multicenter, controlled trial of nalmefene hydrochloride and naloxone hydrochloride in emergency department patients with suspected opioid overdose.[26] Subjects were emergency department patients with suspected opioid overdose (n=176) and randomized to one of three intravenous treatment groups; nalmefene hydrochloride 1 mg, nalmefene hydrochloride 2 mg, and naloxone hydrochloride 2mg. Note that 2 mg of naloxone hydrochloride IV is in the range of approved starting doses to treat presumed opioid overdose.[53] Efficacy, safety, and withdrawal outcomes were assessed. Of the 176 subjects evaluated, seventy-seven were later determined through toxicology testing to be opioid-positive. The Opioid Withdrawal Scale (OWS) score was reported at baseline, 5 minutes, 20 minutes, and 240 minutes after study drug administration (Table 26). The OWS ranges from 0-13 with a patient receiving a point for each opioid withdrawal sign and/or symptom that is demonstrated, with higher scores indicating a more severe withdrawal syndrome. Notably, in the opioid-positive patients, the assessment of opioid withdrawal did not demonstrate any between-group differences in the 0 to 20- or 0 to 240-minute changes. No subjects discontinued the study due to adverse events and the incidence of adverse events with nalmefene hydrochloride increased as the dose increased from 1 mg to 2 mg intravenously.

While the Kaplan study is small, patients in the three arms experienced a similar frequency, types, and severity of AEs, including withdrawal. The Applicant developed ZURNAI to imitate the PK of 1.0 mg REVEX IV (see section 6. Review of Relevant Individual Trials Used to Support Efficacy). Extrapolating the Kaplan evidence to the current application, ZURNAI would be expected to precipitate withdrawal in opioid dependent persons at a rate comparable to existing approved naloxone hydrochloride products. Well-controlled trials in the future may provide further insight.

Table 20. Response to Nalmefene Hydrochloride Among Patients Enrolled in Double-Blind, Randomized Study of Nalmefene Hydrochloride and Naloxone Hydrochloride in Emergency Department Patients With Suspected Narcotic Overdose [Source: Table 1, Kaplan, et al, 1999][12]

		Time			
Variable	**Treatment Group**	**Baseline (T=0)**	**5 Minutes**	**20 Minutes**	**240 Minutes**
No. per group[†]	1-mg nalmefene	63	63	63	58
	2-mg nalmefene	55	55	55	47
	2-mg naloxone	58	57	57	54
RR[‡] (breaths/minute)	1-mg nalmefene	12.6±7.9	18.5±7.0	19.3±6.9	16.6±5.0
	2-mg nalmefene	13.8±7.4	17.9±6.7	17.7±6.3	16.8±7.1
	2-mg naloxone	14.8±8.1	19.3±6.3	19.5±6.2	17.0±3.8
NAS score[§]	1-mg nalmefene	13.8±4.0		8.9±4.8	7.2±4.2
	2-mg nalmefene	14.1±4.1		9.7±5.1	8.6±4.9
	2-mg naloxone	14.1±4.1		9.8±4.7	7.2±4.0
OWS score	1-mg nalmefene	.8±1.4	1.6±2.5	1.0±2.2	.3±.9
	2-mg nalmefene	.5±1.0	1.1±1.9	1.3±2.3	.3±.8
	2-mg naloxone	.8±1.6	1.7±1.9	1.2±1.5	.1±.5

Data presented as mean±SD.
[*]No between-group differences found in changes between 0 to 20 minutes and 0 to 240 minutes ($P>.30$, all comparisons). No time-treatment interactions ($P>.28$, all overall interaction comparisons).
[†]Occasional missing data because of patients' premature withdrawal from study or incomplete case report forms.
[‡]$P\leq.000$, 0 to 20-minute changes (effect of time on all groups).
[§]$P\leq.000$, 0 to 20-minute and 0 to 240-minute changes (effect of time on all groups).

8.6. Safety Analyses by Demographic Subgroups

Not applicable.

8.7. Specific Safety Studies/Clinical Trials

There were no specific additional safety studies or clinical trials completed by the Applicant.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

The carcinogenic potential of nalmefene hydrochloride has not been evaluated. Nalmefene hydrochloride did not have mutagenic activity in the Ames test with five bacterial strains or the mouse lymphoma assay. Clastogenic activity was not observed in the mouse micronucleus test or in the cytogenic bone marrow assay in rats. However, nalmefene hydrochloride did exhibit a weak but significant clastogenic activity in the human lymphocyte metaphase assay in the absence but not in the presence of exogenous metabolic activation.

8.8.2. Human Reproduction and Pregnancy

Reproduction studies have been performed in rats (up to 1200 mg/m /day) and rabbits (up to 2400 mg/m /day) by oral administration of nalmefene hydrochloride and in rabbits by intravenous administration up to 96 mg/m /day (114 times the human dose). There was no evidence of impaired fertility or harm to the fetus.[5] There are, however, no adequate and

well-controlled studies in pregnant women (see Section 12. Post marketing Requirements and Commitments). Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.8.3. Pediatrics and Assessment of Effects on Growth

Safety and effectiveness of the LD, REVEX (nalmefene hydrochloride injection; NDA 020459), was not established in pediatric patients when it was approved in 1995. REVEX was removed from the market for business reasons in 2008.[7] As a new route of administration (IM/SC), the Pediatric Research Equity Act (PREA) was triggered, and pediatric use information was required.

The Applicant provided simulation data showing that the PK of nalmefene hydrochloride could be extrapolated down to 12 years of age. The Division advised Applicant that efficacy cannot be extrapolated for subjects under 12 years of age. Additional PK, safety, and efficacy data would be needed to support an indication in < 12 years old. Moreover, nonclinical PK and repeat dose toxicity studies will need to be completed prior to initiation of clinical studies in < 12 years old.

However, the Division advised the Applicant that it would be acceptable to extrapolate the adult pharmacokinetic (PK) data to the 12 to < 18-year-old pediatric population as no differences in PK are expected between these two populations. Furthermore, as it would be unethical to conduct clinical studies in healthy pediatric volunteers due to their deriving no direct benefit from participation, the Division advised that an "at risk" population be identified for which clinical studies could be completed in the < 12-year-old population. The Division and PeRC agreed with the Applicant to defer the clinical assessments of PK, safety, and efficacy of nalmefene hydrochloride in patients < 12 years of age (all age groups down to birth) because the drug will be ready for approval in patients > 12 years of age prior to the completion of pediatric studies.

As discussed in the Benefit-Risk Integrated Assessment, ZURNAI will be approved down to the age of 12 years. Clinical studies down to birth will be required as a post-marketing requirement (in addition to prerequisite nonclinical studies). Given the public health imperative to make more opioid-antagonists available, we are approving this product even though the full pediatric age range is not currently covered.

There is an injection formulation of nalmefene hydrochloride available (generic of REVEX) which is unlikely to be confused with ZURNAI because ZURNAI will be the only nalmefene hydrochloride-containing community-use product and it will be the only community-use autoinjector available in the US.

On July 3rd, 2024, the FDA's Pediatric Review Committee (PeRC) agreed to the Applicant's agreed initial pediatric study plan (iPSP) submitted as a part of this NDA: "Conduct a Pediatric Pharmacokinetic, Pharmacodynamic and Safety Study in Children From Birth to Less Than 12

Years of Age from an at-risk population"

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Nalmefene hydrochloride is an opioid antagonist with no agonist activity.[5] It has no demonstrated abuse potential, is not addictive, and is not a controlled substance.

Intravenous doses of up to 24 mg of nalmefene hydrochloride, administered to healthy volunteers in the absence of opioid agonists, produced no serious adverse reactions, severe signs or symptoms, or clinically significant laboratory abnormalities. As with all opioid antagonists, use in patients physically dependent on opioids can result in precipitated withdrawal reactions that may result in symptoms that require medical attention. Treatment of such cases should be symptomatic and supportive. Administration of substantial amounts of opioids to patients receiving opioid antagonists in an attempt to overcome a full blockade has resulted in adverse respiratory and circulatory reactions.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

An oral formulation of nalmefene hydrochloride dihydrate, SELINCRO, was approved in 2013 and marketed in the European Union for treatment of alcohol use disorder (AUD) for patients with no active physical withdrawal symptoms and not in need of immediate detoxification.[47] The maximum dose is 18 mg (one tablet) per day. Patients may take this dose on days when they think there is a risk they may drink alcohol. There are case reports of patients who did not disclose their opioid use (and likely dependence) before taking SELINCRO and subsequently suffering from prolonged withdrawal requiring hospitalization.[48, 49] SELINCRO and ZURNAI have induce very different exposures through their different PK profiles (SELINCRO: T_{max} 90 minutes vs. ZURNAI: T_{max} 13 minutes), the C_{max} and AUC of SELINCRO is higher than that of ZURNAI.

(b) (4) that utilizes the same (b) (4) autoinjector described in the current submission. An analysis of FAERS reports related to the (b) (4) autoinjector was conducted by the Office of Pharmacovigilance and Epidemiology (see Section 4.8).

8.9.2. Expectations on Safety in the Postmarket Setting

Nalmefene hydrochloride has a generally favorable risk/benefit profile. Nalmefene hydrochloride has been administered safely at high doses to patients who are not opioid dependent.

Nalmefene hydrochloride can cause opioid withdrawal in those who are dependent on opioids in the US [12, 30, 32] and confirmed more recently with the European experience with nalmefene hydrochloride for alcohol use disorder (SELINCRO, Lundbeck, Switzerland).[48, 50] Opioid withdrawal is characterized by the following signs and symptoms: body aches, diarrhea, tachycardia, fever, runny nose, sneezing, piloerection, sweating, yawning, nausea or vomiting, nervousness, restlessness or irritability, shivering or trembling, abdominal cramps, weakness, and increased blood pressure. The severity and duration of the withdrawal syndrome are known to be related to the dose of the reversal agent administered and to the degree and type of opioid dependence experienced by the patient. Withdrawal symptoms often appear within minutes of administration and subside after the duration of action of the reversal agent has passed (if left untreated). Prolonged and untreated withdrawal is associated with dehydration, renal failure, shock, and electrolyte abnormalities. In neonates, opioid withdrawal may be life-threatening.

Additionally, the development of noncardiogenic pulmonary edema has been reported in patients suffering from opioid overdose who have been revived with nalmefene hydrochloride.[17] Noncardiogenic pulmonary edema is a life-threatening condition where fluid enters the alveolar space and disrupts the gas exchange. Patients with noncardiogenic pulmonary edema often present to emergency departments with a normal mental status and vital signs but a new supplemental oxygen requirement. A subset of these patients then quickly decompensate, developing worsening hypoxia and delirium (air hunger), and require mechanical ventilation. These patients can be difficult to maintain on mechanical ventilation, often requiring high positive end-expiratory pressures and fraction of inspired oxygen, leading to severely elevated airway pressures. The exact pathophysiologic mechanism is not known, but the proposed mechanisms include catecholamine surge, shock lung, and a direct effect by the active drug. There is little data on the frequency or severity of this specific complication in patients receiving REVEX, likely due to REVEX being on the market for only a limited time. The exact incidence of nalmefene hydrochloride-precipitated noncardiogenic pulmonary edema is likely to become clearer as more nalmefene hydrochloride-related products come onto the market. However, naloxone hydrochloride has a similar chemical structure and belongs to the same drug class as REVEX, and therefore may serve as a guide: approximately 1%-2% of patients suffering from opioid overdose develop noncardiogenic pulmonary edema after being revived with naloxone hydrochloride and the risk of developing noncardiogenic pulmonary edema increases with increasing dose. [51-54]

8.10. Integrated Assessment of Safety

The Applicant has submitted safety data from their pharmacokinetic study, their pharmacodynamic study, the results of a computer model extrapolating the effects of their product from adults to those down to 12 years of age, and a review of the literature in support of the safety of ZURNAI. This data was reviewed from February 2024 to July 2024.

The safety for this product is based on the agency's prior findings for REVEX (nalmefene hydrochloride) solution for injection. The PK data showed the systemic exposure level of ZURNAI (1.5 mg nalmefene hydrochloride in 0.5 ml for injection IM/SC) is higher than the reference product, 1.0 mg REVEX (nalmefene hydrochloride, NDA 16636) administered IM/SC. Within the limits of cross-study comparisons, the PK of ZURNAI seems to approximate those of 1.0 mg REVEX administered IV. This is assisted, in part, by the addition of 0.94% MgCl2, (b) (4)
The Applicant also submitted data from the literature to support the safety of the systemic exposure observed with ZURNAI, including several studies to support the safety of higher doses of nalmefene hydrochloride than observed in the current submission.

We reviewed the NDAs of other recent opioid reversal products while preparing this review, both those containing nalmefene hydrochloride (OPVEE [NDA 217470], REVEX [NDA 20459]) and those relying upon naloxone hydrochloride (NARCAN [NDA 208411], KLOXXADO [NDA 212045], REVIVE [NDA 217722], REZENOPY [NDA 215487], and (b) (4) . Allowing for differences in the dose of the active substance, the incidence, types, and severity of AEs documented in those applications were similar those seen in the current application. Consistent with the current application, a minority of subjects in those applications experienced symptoms including, but not limited to, nausea, vomiting, headache, dizziness, and flushing, all of which were recorded as mild and short-lived. Based on the bridging study and the literature review included in the submission, we believe the proposed product would be safe at reversing an opioid overdose in healthy individuals.

The safety of safety of ZURNAI in persons who are physically dependent on opioids is less clear. Limited clinical trial data [12] from emergency department patients suffering from presumed opioid overdose suggests there is similar efficacy and safety between 1.0 mg REVEX IV, 2.0 mg REVEX IV, or 2 mg naloxone hydrochloride IV when used for their approved indication. Extrapolating this evidence to the current application, ZURNAI would be expected to precipitate withdrawal in opioid dependent persons at a rate comparable to existing approved naloxone hydrochloride products. Well controlled trials in the future may provide further insight.

The post-marketing experience of nalmefene hydrochloride is limited, making it difficult to gauge the likelihood of severe complications like noncardiogenic pulmonary edema. Extrapolating from the naloxone hydrochloride experience, we expect the incidence of noncardiogenic pulmonary edema to low and related to the amount of drug administered.

Additionally, OPVEE nasal spray (2.7 mg of nalmefene hydrochloride) has higher pharmacokinetic parameters than ZURNAI and OPVEE was found to be safe and effective in 2023.[11]

In aggregate, these potential safety concerns are outweighed by several factors: the benefit of

reversing a life-threatening opioid overdose, ensuring that a diverse array of reversal drug products with multiple routes of administration is available to the public, and the general population health benefit of increasing access to additional opioid overdose products.

9. Advisory Committee Meeting and Other External Consultations

This product was not presented at an Advisory Meeting. An Advisory Meeting has not been scheduled for this product. There were no product-related issues that required presentation or discussion at an advisory committee meeting.

Please see Section 1.4 Patient Experience Data for a summary of engagement with patient stakeholders relevant to this product.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The Applicant has modelled their label off of two previously-approved products: EVZIO (NDA 205787, NDA 209862)[14] for aspects of the current application related to autoinjectors, and OPVEE (NDA 217480)[11] for content related to nalmefene hydrochloride. DPMH, OPQ, and Clinical requested the following significant revisions:

> Note to Applicant (Section 2, OPQ): For parenteral products: include statement: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
>
> Note to Applicant (Section 3, OPQ): As currently presented, information about the package type (i.e., single dose) or the appropriate information to facilitate identification of the dosage form is not included.
>
> A description of identifying characteristics is required by 21 CFR 201.57(c)(4)(ii) and can be used to help mitigate the risk of administering deteriorated or contaminated drug for this product.
>
> Section 8.4 was heavily revised for clarity by DPMH.
>
> Note to Applicant (Section 11, OPQ): Include a Sterility statement

Note to Applicant (Section 12.2, Clinical): Revise the Figure to "Percentage of recovery of respiratory drive after fentanyl infusion in MV (mean SD) in adult healthy volunteers with ZURNAI (b) (4)."

Note to Applicant (Section 12.2, Clinical): You may describe the PK of IV nalmefene hydrochloride in Table 3 and Figures 3a and 3b below.

Note to Applicant (Section 12.2, Clinical): Please add a column to Table 3 to describe IV nalmefene hydrochloride PK from study NAL 1005.

10.2. Nonprescription Drug Labeling

This is a prescription product.

11. Risk Evaluation and Mitigation Strategies (REMS)

A Risk Evaluation and Management Strategy will not be needed for this product. The active substance has a wide safety margin in patients who are not dependent on opioids.

12. Postmarketing Requirements and Commitments

As mentioned in this review (Sections 2.1 and 8.8.3), there is a lack of efficacy and safety data for nalmefene hydrochloride in patients younger than 12 years of age. OPVEE (NDA 217470) was approved with the following PMRs, focused on addressing these gaps in knowledge. These PMRs are still outstanding at the time of this review and so the current application should be approved under the same constraints. The following will be included as PMRs under PREA in the action letter.

4665-1 Conduct a clinical pharmacokinetic, pharmacodynamic, and safety study of ZURNAI in pediatric patients aged birth to less than 12 years of age.

The timetable you submitted on August 1, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	07/2025
Final Protocol Submission:	12/2025
Study Completion:	10/2028
Final Report Submission:	04/2029

4665-2 Conduct a juvenile animal study in rats to support the initiation of clinical studies in pediatric patients from 3 years to less than 12 years of age. This study will evaluate the effect of the drug on growth and development, specifically reproductive performance/sexual maturation and central nervous system histopathology and long-term behavioral effects.

The timetable you submitted on August 1, 2024, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	01/2024 (Submitted)
Study Completion:	03/2025
Final Report Submission:	09/2025

4665-3 Conduct a juvenile animal study in rats to support the initiation of clinical studies in pediatric patients from birth to less than 3 years of age. This study will evaluate the effect of the drug on development, specifically neuroapoptosis and central nervous system histopathology.

The timetable you submitted on August 1, 2024, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	01/2024 (Submitted)
Study Completion:	03/2025
Final Report Submission:	09/2025

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.

13. Appendices

13.1. References

1. Pharmaceuticals, P., *ZURNAI nalmefene hydrochloride autoinjector (NDA 218590)*, in *Draft Label Text Clean - Word Version*. 2024.
2. Pharmaceuticals, P., *ZURNAI nalmefene hydrochloride autoinjector (NDA 218590)*, in *2.5 Clinical Overview*. 2024.
(b) (4)
4. Pharmaceuticals, P., *ZURNAI nalmefene hydrochloride autoinjector (NDA 218590)*, in *5.3.5.4 Other Study Reports: Human Factors Study*. 2023.

5. Healthcare, B., *REVEX namefene hydrochloride solution for injection (NDA 20459)*, in *Approved Label*.
6. Pharmaceuticals, P., *REVEX nalmefene hydrochloride solution for injection (ANDA 212955)*, in *Approved Label*.
7. Food and Drug Administration, *Determination That REVEX (Nalmefene Hydrochloride Injection), 0.1 Milligram Base/Milliliter and 1.0 Milligram Base/Milliliter, Was Not Withdrawn From Sale for Reasons of Safety or Effectiveness*.
8. Administration, F.a.D. *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations*. 2023 [cited 2023 8/11/2023].
9. *Wide-Ranging ONline Data for Epidemiologic Research (WONDER)*. 2023, Centers for Disease Control and Prevention:
10. Chengdu Shuode Pharmaceutical Co., L., *REVEX namefene hydrochloride solution for injection (ANDA 216007)*, in *Approved Label*.
11. Inc., I., *OPVEE nalmefene hydrochloride spray for intranasal administration approved label (NDA 217470)*.
12. Justin L Kaplan, J.A.M., Joseph J Calabro, Susan L Gin-Shaw, James D Spiller, William L Spivey, Gary M Gaddis, Ning Zhao, Fred P Harchelroad, Jr, *Double-Blind, Randomized Study of Nalmefene and Naloxone in Emergency Department Patients With Suspected Narcotic Overdose.* Annals of Emergency Medicine, 1999. 34(1): p. 42-50.
13. Spencer, M.R., A.M. Miniño, and M. Warner, *Drug overdose deaths in the United States, 2001–2021.* NCHS data brief, 2022. 457: p. 1-8.
14. HF Acquisition Co LLC, D.H., *EVZIO (NDA 209862) naloxone hydrochloride for IM/SC injection approved label, .*
15. *FDA Approves First Over-the-Counter Naloxone Nasal Spray*.
16. *FDA Approves Second Over-the-Counter Naloxone Nasal Spray Product*.
17. Charles A. Henderson, J.E.R., *Acute Pulmonary Edema in a Young Male After Intravenous Nalmefene.* Anesthesia & Analgesia, 1997. 84(1): p. 218-219.
18. *The Voice of the Patient: Opioid Use Disorder*. 2018, Patient-Focused Drug Development Initiative, Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration (FDA):
19. *Understanding Fatal Overdoses to Inform Product Development and Public Health Interventions to Manage Overdose: PUBLIC MEETING SUMMARY*.
20. Rege, S.V., et al., *Epidemiology of pediatric buprenorphine and methadone exposures reported to the poison centers.* Annals of epidemiology, 2020. 42: p. 50-57. e2.
22. Dezman, Z.D.W., et al., *Evidence of fentanyl use is common and frequently missed in a cross-sectional study of emergency department patients in Baltimore, Maryland.* Clinical Toxicology, 2020. 58(1): p. 59-61.
23. Health, M.D.o. *Unintentional Drug- and Alcohol-Related Intoxication Deaths in Maryland, 2020*. 2020 [cited 2023 8/11/2023].
24. Woolf, S.H. and H. Schoomaker, *Life expectancy and mortality rates in the United States, 1959-2017.* Jama, 2019. 322(20): p. 1996-2016.

25. Dezman, Z.S., Bradford; Billing, Amy; Massey, Ebonie; Artigiani, E. Erin; Factor, Julie; Wish, Eric D, *Notes from the Field: High Prevalence of Fentanyl Detected by the Maryland Emergency Department Drug Surveillance System — Baltimore, Maryland, 2019.* Morbidity and Mortality Weekly Report, 2020. 69(23): p. 724-726.
26. Roberts, A., J. Korona-Bailey, and S. Mukhopadhyay, *Notes from the Field: Nitazene-Related Deaths—Tennessee, 2019–2021.* Morbidity and Mortality Weekly Report, 2022. 71(37): p. 1196.
27. Johnson, J., et al., *Increasing presence of xylazine in heroin and/or fentanyl deaths, Philadelphia, Pennsylvania, 2010–2019.* Injury prevention, 2021. 27(4): p. 395-398.
28. LaRue, L., et al., *Rate of fentanyl positivity among urine drug test results positive for cocaine or methamphetamine.* JAMA Network Open, 2019. 2(4): p. e192851-e192851.
29. Glass, P.S., Rajiv M. Jhaveri, et al, *Comparison of Potency and Duration of Action of Nalmefene and Naloxone.* Anesthesiology, 1991. 76(3).
30. William Barsan, D.S., Daniel Danzl, Louis Ling, Robert Bartlett, Ralph Buncher, Candace Bryan, *Duration of Antagonistic Effects of Nalmefene and Naloxone in Opiate-Induced Sedation for Emergency Department Procedures.* American Journal of Emergency Medicine, 1989. 7(2): p. 155-161.
31. Glass, P.S., Rajiv M. Jhaveri, and L. Richard Smith, *Comparison of potency and duration of action of nalmefene and naloxone.* Anesthesia & Analgesia, 1994. 78(3): p. 536-541.
32. Davis, E.A., J. Menegazzi, and A. Sucov, *Safety and Effectiveness of Nalmefene vs. Naloxore in Opioid and Mixed Drug Overdose in the Prehospital Care Setting.* Prehospital and Disaster Medicine, 1994. 9(S2): p. S60-S60.
33. Srivastava, A.B., J.J. Mariani, and F.R. Levin, *New directions in the treatment of opioid withdrawal.* The Lancet, 2020. 395(10241): p. 1938-1948.
34. *Naloxone Access and Utilization for Suspected Opioid Overdoses, Revised February 2023, June 2016, Originally approved October 2015, A joint policy statement of the American College of Emergency Physicians (ACEP), the National Association of EMS Physicians (NAEMSP), and the American College of Medical Toxicology (ACMT)*.
35. Razaghizad, A., et al., *The effect of overdose education and naloxone distribution: an umbrella review of systematic reviews.* American journal of public health, 2021. 111(8): p. e1-e12.
36. Moustaqim-Barrette, A., et al., *Adverse events related to bystander naloxone administration in cases of suspected opioid overdose in British Columbia: An observational study.* PLoS One, 2021. 16(10): p. e0259126.
37. Hudak, M.L., et al., *Neonatal drug withdrawal.* Pediatrics, 2012. 129(2): p. e540-e560.
38. Weiss, R.D., et al., *Reasons for opioid use among patients with dependence on prescription opioids: the role of chronic pain.* Journal of substance abuse treatment, 2014. 47(2): p. 140-145.
39. Pergolizzi Jr, J.V., R.B. Raffa, and M.H. Rosenblatt, *Opioid withdrawal symptoms, a consequence of chronic opioid use and opioid use disorder: Current understanding and*

approaches to management. Journal of clinical pharmacy and therapeutics, 2020. 45(5): p. 892-903.
40. *NDA 16636 injection naloxone hydrochloride*. 1969, Food and Drug Administration.
41. *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, Product Details for NDA 209862*. [cited 2024 6/19/2024].
42. Kaleo, *RAPID OPIOID COUNTERMEASURE SYSTEM naloxone hydrochloride autoinjector (NDA 215457) Approved Label*.
43. Pharmaceuticals, P., *ZURNAI nalmefene hydrochloride autoinjector (NDA 218590)*, in *2.7.3 Summary of Clinical Efficacy*. 2024.
44. McConnell, A., *Exercise physiology and training principles*, in *Respiratory muscle training: theory and practice*.
45. Pharmaceuticals, P., *ZURNAI nalmefene hydrochloride autoinjector (NDA 218590)*, in *2.7.4 Summarry of Clinical Safety*. 2024.
46. Wegman, M., *Analysis Of Naloxone Usage Safety And Efficacy In The Emergency Department And Prehospital Environment During The COVID-19 Pandemic*. 2023, American College of Emergency Physicians.

48. Donnerstag, N., et al., *Severe opioid withdrawal syndrome after a single dose of nalmefene.* European Journal of Clinical Pharmacology, 2015. 71(8): p. 1025-1026.
49. Franchitto, N., et al., *Management of precipitated opiate withdrawal syndrome induced by nalmefene mistakenly prescribed in opiate-dependent patients: a review for clinicians.* Expert Opinion on Drug Metabolism & Toxicology, 2017. 13(6): p. 669-677.
50. Franchitto, N., et al., *Management of precipitated opiate withdrawal syndrome induced by nalmefene mistakenly prescribed in opiate-dependent patients: a review for clinicians.* Expert Opinion on Drug Metabolism & Toxicology, 2017. 13(6): p. 669-677.
51. Farkas, A., et al., *Pulmonary Complications of Opioid Overdose Treated With Naloxone.* Annals of Emergency Medicine, 2020. 75(1): p. 39-48.
52. Sporer, K.A. and E. Dorn, *Heroin-related noncardiogenic pulmonary edema: a case series.* Chest, 2001. 120(5): p. 1628-1632.
53. Ng, B., *Noncardiogenic pulmonary edema associated with ultrapotent opioid overdoses.* BC MediCal Journal, 2019.
54. Al-Azzawi, M., et al., *Naloxone-Induced Acute Pulmonary Edema is Dose-Dependent: A Case Series.* Am J Case Rep, 2021. 22: p. e929412.

13.2. Financial Disclosure

The Applicant has completed the Financial Disclosure form and their investigators (Table 27) did not list any significant conflicts of interest.

Table 21 Covered Clinical Studies: NAL 1002, NAL 1003, NAL 1004, NAL 1005

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 31		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 31		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): Zero		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Zero Significant payments of other sorts: Zero Proprietary interest in the product tested held by investigator: Zero Significant equity interest held by investigator in Study: Zero Sponsor of covered study: 0 Zero		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 31		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

13.3. Inclusion Criteria for NAL 1002 Parts 1 and 2

Copied with relight revisions for formatting from NAL 1002 Clinical Study Report, pages 34-37 [2]:

Inclusion Criteria
Subjects must have met the following criteria to be included in NAL 1002 Part 1 or Part 2:

1. Provided written informed consent.
2. Males and females aged 18 to 55 years of age inclusive, at the time of signing the

Qualification or Treatment (whichever was first) ICF.

3. Body weight ranging from 50 to 100 kg (110 to 220 lb) and a body mass index (BMI) ranging from 18 to 30 kg/m2, inclusive.
4. Healthy and free of significant abnormal findings as determined by medical history, physical examination, clinical laboratory values, vital signs, and electrocardiogram (ECG).
5. Males and females:
    - A male subject with a heterosexual partner who was with a woman of childbearing potential (WOCBP) must either have been vasectomized or agreed to use condoms during the trial and for 30 days following the treatment phase.
    - A female subject was eligible to participate if she was not pregnant, not breastfeeding, and at least one of the following conditions applied:
        - Not a WOCBP. Females who were postmenopausal must have been postmenopausal ≥1 year and must have had elevated serum follicle stimulating hormone (FSH).
        - WOCBPs must have agreed to use a reliable method of contraception with a failure rate of less than 1% per year when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], sexual abstinence or vasectomized partner during the trial and for 30 days following the treatment phase. A female was considered to be of childbearing potential unless she had a hysterectomy, had undergone tubal ligation or was at least one year postmenopausal with elevated serum FSH.
6. Willing to be compliant with the study, capable of subjective evaluation, if applicable, able to read and understand questionnaires, if applicable.
7. Willing to eat the food supplied during the study.
8. Willing to refrain from strenuous exercise during the entire study. Subjects could not begin a new exercise program nor participate in any unusually strenuous physical exertion.

<u>The following additional inclusion criteria applied to the healthy recreational opioid user subjects enrolled in NAL 1002 Part 2</u>

9. Moderately experienced opioid users must have met the following criteria:
    - had used opioids for non-therapeutic purposes (i.e., for psychoactive effects) on at least 10 occasions in the past year,
    - had used opioids at least 3 times in the 12 weeks prior to screening.
10. Must have reported taking a dose of opioid equivalent to 30 mg oxycodone immediate release (IR) or higher on at least one occasion in the past year.

Exclusion Criteria

The following excluded potential subjects from NAL 1002 Part 1 or Part 2:

1. Females who were pregnant (positive beta human chorionic gonadotropin test) or lactating.
2. Any significant illness during the 30 days preceding the initial dose in the study.
3. Use of any medication including thyroid hormonal therapy (hormonal contraception and hormonal replacement therapy in the form of estrogen with or without progestin was allowed), vitamins, herbal and/or mineral supplements during the 7 days preceding the administration of study drug.
4. History or any current conditions that might have interfered with drug absorption, distribution, metabolism, or excretion (ADME).
5. Positive results of hepatitis B surface antigen (HBsAg), anti-hepatitis C virus antibody (anti-HCV).
6. Positive naloxone HCl challenge test.
7. Abnormalities on physical examination, vital signs, ECG, or clinical laboratory values, unless those abnormalities were judged clinically insignificant by the investigator.
8. Refusal to abstain from caffeine or xanthine containing beverages entirely during confinement.
9. Refusal to abstain from consumption of alcoholic beverages 48 hours prior to initial study drug administration (Day 1) and through the end of study (EOS) visit.
10. Blood or blood products donated within 60 days prior to study drug administration or through the EOS visit, except as required by the protocol. The total volume of blood within any 60-day period during this study could not have exceed 550 mL.
11. Plasma donated within 7 days prior to entry into the study or through the EOS visit, except as required by the protocol.
12. Difficulty with venous access or unsuitable for or unwilling to undergo catheter insertion.
13. A subject who, in the opinion of the investigator or designee, was considered unsuitable or unlikely to comply with the study protocol for any other reason.

<u>Part 1</u>
<u>The following would exclude any participant from being enrolled in NAL 1002 Part 1:</u>

14. Current or recent (within 5 years) history of drug or alcohol abuse.
15. Known allergy or hypersensitivity to nalmefene hydrochloride or any of the excipients or other drug product components of nalmefene hydrochloride.
16. Known allergy or hypersensitivity to naloxone.
17. Participation in a clinical drug study during the 30 days preceding the initial dose in this study.
18. Any personal or family history of prolonged QT interval or disorders of cardiac rhythm.
19. Positive urine cotinine results or frequent (>1 × per week) smoking or use of nicotine

products within 45 days of study drug administration.

20. Positive results of urine drug screen or alcohol screen.

Part 2

The following would exclude any participant from being enrolled in NAL 1002 Part 2:

21. Any history of increased intracranial pressure, brain tumor, seizures, or head trauma with sequelae.
22. History of any clinically significant pulmonary condition (e.g., asthma) within the last 2 years requiring admission to the hospital.
23. History of obstructive sleep apnea or previous diagnosis of obstructive sleep apnea based on polysomnography.
24. Pulse oximetry <95% on screening or check-in.
25. Subjects who smoked more than one-half (½) pack of cigarettes per day.
26. Participation in a clinical drug study during the 30 days preceding the initial dose in this study.
27. Participation in a Treatment phase of this study (NAL1002) during the 7 days preceding the initial dose in a new iteration/cohort.
28. Use of prescription drugs that are potential enzyme inducers during the 14 days or 5 half-lives (whichever is longer) before the start of study treatment until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.
29. Use of aspirin, aspirin-containing, or nonsteroidal anti-inflammatory drugs within the 72 hours prior to each drug administration.
30. Subjects taking the following medications
    a. CYP3A4 inhibitors or inducers.
    b. Benzodiazepines or other CNS depressants.
    c. Serotonergic drugs – SSRIs, SNRIs, TCAs, triptans, 5-HT3 receptor antagonists, MAOI inhibitors, and drugs that affect the serotonergic neurotransmitter system (mirtazapine, trazodone, tramadol).
31. Any personal or family history of prolonged QT interval or disorders of cardiac rhythm.
32. Abnormal cardiac conditions that included any of the following:
    a. QTcF interval >450 msec at screening
    b. QTcF interval >480 msec at check-in
33. A resting heart rate on vital signs outside the range of 45 to 100 bpm at screening.
34. History or presence of hypotension judged to be clinically significant based on investigator or designee judgment.
35. Evidence of clinically significant hepatic or renal impairment including alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >1.5 × the upper limit of normal (ULN) or serum total bilirubin >10% above ULN.
36. History of severe allergic reaction (including anaphylaxis) to any food, medication, or

bee sting, or previous status asthmaticus.

37. History of allergy or hypersensitivity to fentanyl, remifentanil, naloxone, nalmefene, naltrexone or related drugs (e.g., other opioids or opioid antagonists), or any of the drug excipients or other drug product components, as well as an allergy or hypersensitivity to ondansetron.
38. Positive results of urine drug screen or alcohol screen, except as noted in exclusion criterion #40. Positive results could have been repeated and/or subjects rescheduled at the Investigator's discretion.

The following additional exclusion criteria applied to the healthy recreational opioid user subjects enrolled in NAL 1002 Part 2

39. Self-reported substance use disorder history (in the past 2 years) or subjects who had ever been in a drug rehabilitation program (other than treatment for smoking cessation or on a case-by-case basis; e.g., as a requirement for reduced incarceration or in lieu of incarceration for the use of marijuana only) or current substance use disorder (within the last 12 months; except for caffeine), as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).
40. On a case-by-case basis, at the discretion of the investigator, positive tetrahydrocannabinol (THC) could have been acceptable for subjects examined (full or brief physical examination) and interviewed by a licensed physician to verify that they were not under the influence of cannabinoids.

Part 2 Naloxone Challenge Criteria (If positive, would exclude persons who were being screened for participation in NAL 1002 Part 2)

Clinical assessment of withdrawal signs and symptoms were based on the Objective Opioid Withdrawal Scale (OOWS) administered during the naloxone challenge test. Subjects were excluded from further participation in the study if their OOWS score was ≥3.

13.4. Inclusion and Exclusion Criteria for NAL 1004

A volunteer must meet all the following [inclusion] criteria:

9.3.1 Inclusion Criteria[2]

1. Capable of providing written informed consent.
2. Participant must be 18 to 55 years of age inclusive, at the time of signing the Part 1 or Part 2 (whichever is first) informed consent.
3. Body weight ranging from 50 to 100 kg (110-220 lbs) and body mass index (BMI) within the range 18-30 kg/m2 (inclusive).
4. Healthy and free of significant abnormal findings as determined by medical history, physical examination, clinical laboratory values, vital signs, and ECG.
5. Males and females:
    a. A male participant with a heterosexual partner who is a woman of childbearing potential must either be vasectomized or agree to use condoms during the trial and for 30 days following the treatment phase.
    b. A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:
    c. Not a woman of childbearing potential (WOCBP). Females who are postmenopausal must have been postmenopausal ≥ 1 year and have elevated serum FSH. Female participants of childbearing potential must agree to use a reliable method of contraception with a failure rate of less than 1 % per year when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], sexual abstinence or vasectomized partner during the trial and for 30 days following the treatment phase. A female is considered to be of childbearing potential unless she has had a hysterectomy, has undergone tubal ligation or is at least one year post-menopausal with elevated serum FSH.
6. Subjects willing to be compliant with the protocol, are capable of subjective evaluation, if applicable, are able to read and understand questionnaires, if applicable.
7. Willing to eat the food supplied during the study.
8. Willing to refrain from strenuous exercise through the end of study visit. Subjects will not begin a new exercise program nor participate in any unusually strenuous physical exertion.
9. Moderately experienced opioid users who meet the following criteria: 1) have used opioids for nontherapeutic purposes (i.e., for psychoactive effects) on at least 10 occasions in the past year and 2) have used opioids at least 3 times in the 12 weeks prior to screening.
    a. Must report having taken a dose of opioid equivalent to 30 mg oxycodone IR or higher on at least one occasion in the past year.

9.3.2 Exclusion Criteria

10. Females who are pregnant (positive beta human chorionic gonadotropin test) or lactating.
11. Any significant illness during the 30 days preceding the initial dose in this study.
12. History or any current conditions that might interfere with drug absorption, distribution, metabolism, or excretion.
13. Positive results of HBsAg, anti-HCV.
14. Positive naloxone HCl challenge test.
15. Abnormalities on physical examination, vital signs, ECG, or clinical laboratory values, unless those abnormalities were judged clinically insignificant by the investigator.
16. Refusal to abstain from caffeine or xanthine containing beverages entirely during confinement.
17. Refusal to abstain from consumption of alcoholic beverages 48 hours prior to initial study drug administration (Day 1) and through the end-of-study visit.
18. Blood or blood products donated within 60 days prior to study drug administration or through the end-of-study (EOS) visit, except as required by this protocol. The total volume of blood within any 60-day period during this study may not exceed 550 mL.
19. Plasma donated within 7 days prior to entry into the study or through the EOS visit, except as required by this protocol.
20. Difficulty with venous access or unsuitable for or unwilling to undergo catheter insertion.
21. Any history of increased intracranial pressure, brain tumor, seizures or head trauma with sequelae.
22. History of any clinically significant pulmonary condition (e.g., asthma) within the last 2 years requiring admission to the hospital.
23. History of obstructive sleep apnea or previous diagnosis of obstructive sleep apnea based on polysomnography.
24. Pulse oximetry <95% on screening or check-in.
25. Subjects who smoke more than one-half (½) pack of cigarettes per day.
26. Participation in a clinical drug study during the 30 days preceding the initial dose in this study.
27. Use of any medication including thyroid hormonal therapy (hormonal contraception and hormonal replacement therapy in the form of estrogen with or without progestin is allowed), vitamins, herbal and/or mineral supplements during the 7 days preceding the administration of study drug. Use of aspirin, aspirin-containing, or nonsteroidal anti-inflammatory drugs within the 72 hours prior to each drug administration.
28. Any personal or family history of prolonged QT interval or disorders of cardiac rhythm.
29. Abnormal cardiac conditions including any of the following:
    a. a. QTcF interval >450 msec at screening
    b. b. QTcF interval >480 msec at check-in
30. A resting heart rate on vital signs outside the range of 45 to 100 bpm at screening.

31. History or presence of hypotension, judged to be clinically significant based on investigator or designee judgment.
32. Evidence of clinically significant hepatic or renal impairment including alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 1.5 × the upper limit of normal (ULN) or serum total bilirubin > 10% above ULN.
33. History of severe allergic reaction (including anaphylaxis) to any food, medication, or bee sting, or previous status asthmaticus.
34. History of allergy or hypersensitivity to fentanyl, naloxone, nalmefene, or related drugs (e.g., other opioids or opioid antagonists), or any of the drug excipients or other drug product components.
35. Positive results of urine drug screen or alcohol screen, except as noted in exclusion 28. Positive results may be repeated and/or subjects rescheduled at the Investigator's discretion.
36. Self-reported substance use disorder history (in the past 2 years) or subjects who have ever been in a drug rehabilitation program (other than treatment for smoking cessation or on a case-by-case basis; e.g., as a requirement for reduced incarceration or in lieu of incarceration for the use of marijuana only) or current substance use disorder (within the last 12 months; except for caffeine), as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).
37. On a case-by-case basis, at the discretion of the investigator, positive tetrahydrocannabinol (THC) may be acceptable for subjects examined (full or brief physical examination) and interviewed by a licensed physician to verify that they are not under the influence of cannabinoids.
38. A subject who, in the opinion of the investigator or designee, is considered unsuitable or unlikely to comply with the study protocol for any other reason.

13.5. Inclusion and Exclusion Criteria for NAL 1005

Inclusion Criteria

1. Capable of providing written informed consent.
2. Participant must be 18 to 55 years of age inclusive, at the time of signing the informed consent.
3. Body weight ranging from 50 to 100 kg (110-220 lbs) and body mass index (BMI) within the range 18 to 30 kg/m2 (inclusive).
4. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring.
5. Males and females:
    a. A male participant with a heterosexual partner who is a woman of childbearing potential (WOCBP) must either be vasectomized or agree to use condoms during the trial and for 30 days following the treatment phase.

   b. A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:
      i. Not a woman of childbearing potential. Females who are postmenopausal must have been postmenopausal ≥ 1 year and have elevated serum FSH.
      ii. Female participants of childbearing potential must agree to use a reliable method of contraception with a failure rate of less than 1% per year when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intra uterine devices (IUDs), sexual abstinence or vasectomized partner during the trial and for 30 days following the treatment phase. A female is considered to be of childbearing potential unless she has had a hysterectomy, has undergone tubal ligation or is at least one year post-menopausal with elevated serum FSH (≥ 40 mIU/mL at screening).
6. Subjects willing to be compliant with the protocol, are able to read, understand and answer verbal questions.
7. Willing to eat the food supplied during the study.
8. Willing to refrain from strenuous exercise through the end of study visit. Subjects will not begin a new exercise program nor participate in any unusually strenuous physical exertion.

Exclusion Criteria

1. Females who are pregnant (positive beta human chorionic gonadotropin test) or lactating.
2. Current or recent (within 5 years) history of drug or alcohol abuse.
3. History or any current conditions that might interfere with drug absorption, distribution, metabolism or excretion.
4. Known allergy or hypersensitivity to nalmefene hydrochloride or any of the excipients or other drug product components of nalmefene hydrochloride.
5. Participation in a clinical drug study during the 30 days preceding the initial dose in this study.
6. Any significant illness during the 30 days preceding the initial dose in this study.
7. Use of any medication including thyroid hormonal therapy (hormonal contraception and hormonal replacement therapy in the form of estrogen with or without progestin is allowed), vitamins, herbal and/or mineral supplements during the 7 days preceding the initial dose.
8. Refusal to abstain from consuming xanthine containing products (e.g., tea, coffee, cola), caffeine, grapefruit, or grapefruit juice within 48 hr prior to initial study drug administration (Day 1) and any time through the end of study visit.
9. Any personal or family history of prolonged QT interval or disorders of cardiac rhythm

10. Abnormalities on physical examination, vital signs, ECG, or clinical laboratory values, unless those abnormalities were judged clinically insignificant by the investigator.
11. Refusal to abstain from consumption of alcoholic beverages 48 hours prior to initial study drug administration (Day 1) and through the end of study visit.
12. Positive urine cotinine results or use of nicotine products within 45 days of study drug administration.
13. Blood or blood products donated within 30 days prior to study drug administration or through the end of study visit, except as required by this protocol.
14. Plasma donated within 14 days prior to study drug administration or through the end of study visit, except as required by this protocol.
15. Positive results of urine drug screen or alcohol screen.
16. Positive results of HBsAg, anti-HCV.
17. Positive naloxone HCl challenge test.
18. Presence of Gilbert's Syndrome, or any known hepatobiliary abnormalities.
19. The investigator believes the subject to be unsuitable for reason(s) not specifically stated in the exclusion criteria.

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/

ZACHARY D DEZMAN
08/07/2024 01:11:14 PM
Clinical Review for NDA 218590

RIGOBERTO A ROCA
08/07/2024 02:19:10 PM