CLINICAL REVIEW

Application Type	505 (b)(2)
Application Number(s)	NDA 215487
Priority or Standard	Standard
Submit Date(s)	3/24/2023
Received Date(s)	3/24/2023
PDUFA Goal Date	January 24, 2024
Division/Office	Anesthesia, Addiction Medicine and Pain Medicine/Office of Neuroscience
Reviewer Name(s)	Zachary Dezman
Review Completion Date	
Established/Proper Name	Naloxone hydrochloride
(Proposed) Trade Name	REZENOPY
Applicant	Summit Biosciences
Dosage Form(s)	Nasal spray
Dosing Regimen(s)	10 mg intranasal, two doses per box
Indication(s)/Population(s)	For the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. Intended for immediate administration as emergency therapy in settings where opioids may be present. The product is not a substitute for emergency medical care.
Recommendation on Regulatory Action	Approval with Postmarketing Required Study

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Glossary

ACEP	American College of Emergency Physicians
AE	Adverse event
BAA	Broad Agency-wide announcement
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CMC	Chemistry, manufacturing, and controls
DMPP	Division of Medical Policy Programs
ECG	Electrocardiogram
eCTD	Electronic common technical document
FDA	Food and Drug Administration
GCP	Good clinical practice
IM	Intramuscular
IN	Intranasal
IND	Investigational New Drug Application
iPSP	initial Pediatric Study Plan
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New drug application
OPDP	Office of Prescription Drug Promotion
PK	Pharmacokinetics
PMR	Post marketing requirement
PPP	Prevention Point Pittsburgh
PREA	Pediatric Research Equity Act
PSUR	Periodic Safety Update report
REMS	Risk evaluation and mitigation strategy
SAE	Serious adverse event
SC	Subcutaneous
TEAE	Treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

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

Summit Bioscience's REZENOPY 10 mg naloxone hydrochloride nasal spray is a single-use, drug-device combination product intended for emergency treatment of patients with apparent opioid overdose in community settings. The Applicant proposes to market the commercially available nasal spray device from (b) (4) pre-loaded with one strength of the drug (10 mg). Two devices will be sold per box. Each device will deliver (b) (4) µl in a single intranasal spray and is intended for use in patients of all ages, both adults and children. Note that the applicant cautions the user in administering their product to neonates and infants.

The Applicant plans to rely on the previous findings of efficacy and safety for the reference product, Narcan (NDA 016636), which is approved for known or suspected opioid overdose. This approval includes pregnant women and ages down to neonates. One pharmacokinetic (PK) study was submitted to provide a scientific bridge between the proposed product and the reference product.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The applicant has provided a study that details the pharmacokinetics, pharmacodynamics, and safety of their product in healthy volunteers. They did not submit a clinical trial demonstrating efficacy, instead relying on previous FDA findings on naloxone hydrochloride (NDA 016636).

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.[1] 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 (CNS) 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. Naloxone is known to be an effective treatment for suspected opioid overdose if an adequate dose is administered in time. There are currently six FDA-approved naloxone-device products spanning an array of doses (3mg-10mg), routes of administration (IN, IM/SC), and patient populations (community use and military).

REZENOPY is a drug-device combination product designed to deliver 10 mg of naloxone in 0.1 mL in a single-use pre-filled nasal spray device from (b) (4). The device is meant to be placed within the nares of the patient suffering from overdose and the dose is administered by depressing the plunger to create an intranasal spray for the treatment of opioid overdose. Summit Biosciences [Applicant] submitted this New Drug Application (NDA) proposing to use the 505(b)(2) regulatory pathway. The indication sought for REZENOPY is emergency treatment for known or suspected opioid overdose in the community setting by untrained personnel, essentially identical to that of other naloxone-containing products. The carton/container contains two nasal spray devices, with the second spray serving as a second dose if needed.

The Applicant states that REZENOPY was developed in response to reports indicating that multiple doses of naloxone have been required in resuscitations, presumably due to the increasing incidence of high-potency opioids in overdoses. However, the Applicant did not provide efficacy data to demonstrate that the proposed dose of 10 mg naloxone IN is effective for reversing high-potency opioid overdose. Reports provided to the FDA using nation-wide data sources show 92.9% of opioid overdoses receive one or two doses of naloxone, with very few receiving 8 mg of naloxone or more.[2] Applicants have chosen to support efficacy by relying on the Agency's prior findings of efficacy and safety for approved naloxone products.

To create a scientific bridge to rely on the previous safety and efficacy findings for the original Narcan (NDA 16636), the Applicant conducted a comparative bioavailability study (Study 11875901). The PK data provided in the application established the scientific bridge between the proposed product REZENOPY and reference drug Narcan injection (both 2mg IV and 0.4 mg SC), thus supporting the efficacy of the proposed product REZENOPY for the proposed indication.

The Applicant has previously submitted a literature review and the safety data from Study 11875901 to support the safety of REZENOPY (naloxone injection, 10 mg / (b) (4) mL). According to the prescribing information of Narcan Injection, up to 2 mg of Narcan may be administered intravenously initially and may be repeated at two-minute intervals up to a total dose of 10 mg. After 10mg, the label suggests the provider consider alternative causes for the patient's presentation, but does not prohibit additional doses. The Applicant has provided literature to support the safety of 10 mg and higher of naloxone injection in non-opioid dependent patients. The main risks of naloxone are severe precipitated opioid withdrawal and associated cardiovascular risks in opioid-dependent patient population. Some of the common symptoms of opioid withdrawal include agitation, anxiety, muscle aches, rhinorrhea, diaphoresis, diarrhea, vomiting, and pruritis. In neonates, withdrawal may be life-threatening. Abrupt postoperative reversal of opioids has been shown to lead to adverse cardiovascular events such as hypotension, hypertension, ventricular tachycardia, ventricular fibrillation, and pulmonary edema. Cardiac arrhythmias, cardiac arrest, and death have been reported in postoperative reversal of opioid depression and have primarily occurred in patients with pre-existing cardiovascular disorders. Acute precipitated opioid withdrawal has been reported in individuals exposed to other high-dose naloxone products and the Applicant was instructed to, but did not, provide safety data in persons with opioid dependence in their application. Acknowledging the weaknesses of cross-study comparisons, we expect REZENOPY to provide similar serum levels of naloxone in patients and so we expect REZENOPY to precipitate withdrawal in opioid-dependent persons. We recommend issuing a PMR to evaluate the rate of precipitated withdrawal in opioid-dependent patients exposed to REZENOPY.

The Agency feels that the importance of approval of more community-use naloxone products outweighs these potential concerns. Given the perceived need for this product, it is recommended that REZENOPY be approved with the PMRs outlined in the Postmarking Recommendations section. These PMRs were developed to evaluate to evaluate whether there is an increased risk compared to typically-dosed products (e.g., 4 mg naloxone nasal spray), and, if so, whether this risk is outweighed by increased benefit..

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.[3] • Around 80% of these drug overdose deaths involved an opioid.[3] • From 2001 to 2021, almost 630,000 people have died from a drug overdose.[3] • On average, 230 Americans die every day from opioid overdoses.[3]	Opioid overdose and death continue to be a public health crisis and a leading cause of death in the US. While naloxone is the treatment of choice to reverse the acute opioid intoxication of a patient, patients require emergency department evaluation afterwards, and receiving naloxone is not a permanent solution for opioid abuse, misuse, and addiction.
Current Treatment Options	• There are several currently approved and available community-use naloxone products.[4] • Narcan Nasal Spray (NNS) and Revive, both 4 mg IN (intranasal) are considered safe for non-prescription use.[5, 6] • Zimhi 5 mg IM and Kloxxado 8 mg IN are currently marketed as prescription products • Evzio (both 0.4 mg and 2 mg intramuscular [IM]) were discontinued. • Some harm reduction organizations distribute unapproved kits comprising parenteral naloxone packaged with a syringe and nasal atomizer. • Anecdotally, some overdoses have required multiple administrations of standard doses of naloxone. However, 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), co-ingestions without mu-opioid receptor activity (e.g., xylazine), or the injection solution administered with a	There are FDA-approved treatment options for opioid overdose. There may be a role for products with a higher dose. There has been increasing concern in the community regarding overdoses with highly potent and synthetic opioids.[7] This high-dose naloxone product may be more effective at reversing certain opioid overdoses, though, that is theoretical at this time. The Applicant has not investigated whether the proposed product offers any advantages compared to approved products and is not seeking an indication for high-potency opioid overdose reversal.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	nasal atomizer as part of a kit. The latter provides a lower concentration, higher volume dose that results in a lower systemic exposure.	
Benefit	• The efficacy of this product for community use is supported by a scientific bridge between the proposed product and the reference products naloxone hydrochloride Injection 0.4 mg/mL (ANDA 070256) and naloxone hydrochloride injection 2 mg IV to NDA 016636 through pharmacokinetic (PK) study 11875901. • The pharmacokinetic data demonstrated that a single dose of 8 mg naloxone IN spray for the proposed product, REZENOPY, results in the same or greater systemic naloxone concentration compared to the 0.4mg naloxone IM product. This includes earlier time points that are most relevant to the immediate treatment of opioid overdose (e.g., 2.5, 5 min post-dose). • The efficacy of this product in the entire pediatric age range is supported by literature review. • 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 naloxone products for community use.	The Applicant provided literature and PK data to support the effectiveness of REZENOPY for the proposed indication intended for community use. The target patient population will include adult and entire pediatric population. 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	• The safety profile of naloxone is well known. • There is literature to support the safety of naloxone doses similar to the proposed dose for this product in adults and in the entire pediatric age range • Recurrent respiratory and central nervous system depression if	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. A postmarketing study may

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	duration of action of certain opioids, such as extended-release opioids, exceeds duration of action of naloxone • Naloxone 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 drugs, but they may be less accepting and less likely to use high-dose products that frequently precipitate withdrawal. • An association between noncardiogenic pulmonary edema and higher naloxone doses has been reported.[8] • Proposed product labeling includes language about the serious risks of precipitating acute opioid withdrawal in the neonate to mitigate the risk of precipitated withdrawal in this population. There are no comparative safety data between this product and other naloxone products to inform prescribing decisions when choosing product for opioid reversal	provide information about the frequency, severity, and outcomes in patients with opioid dependence who are treated with REZENOPY. (b) (4). Approval of this product would provide an additional approved naloxone product.

1.4. Patient Experience Data

A FDA Reagan-Udall meeting was held on March 8th and 9th of 2023 regarding the current management of opioid overdose.[7] 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 naloxone-containing products by persons who use drugs if the only available products are likely to push them into opioid withdrawal.

As a solution, patient advocates requested there be a wide array of naloxone 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.).

Patient Experience Data Relevant to this Application (check all that apply)

☐	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	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
		☐	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,[9] 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 (Spencer 2022).[3] 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.[10] It is also sold as a powder either mixed with, or passed off as, heroin.[11] The potency and uneven quality of street preparations of illicit fentanyl led to rapid increases in fatal and non-fatal opioid overdoses,[12] leading to the largest drop in US life expectancy before the COVID pandemic.[13] Today much of the illicit opioids sold contain fentanyl or are mostly fentanyl and nearly all opioid fatal and nonfatal opioid overdoses involve fentanyl.[14] Fentanyl is increasingly being mixed with stimulants like cocaine and methamphetamine or sedating agents like xylazine and nitazines.[15-17]

Naloxone (NDA 16636) antagonizes opioid effects by competing for the mu, kappa, and sigma opiate receptor sites in the central nervous system. Naloxone has been shown to effectively and rapidly reverse opioid overdose symptoms if given shortly (<2-3 minutes) after the development of symptoms.[18] Co-prescribing naloxone when prescribing opioids is considered a best practice,[19] and increased access to naloxone has been shown to prevent opioid

overdose deaths.[20] Note that the duration of action of naloxone is about 90 minutes, shorter than many opioids, so all patients should be transported to the nearest available emergency department for evaluation after getting naloxone.

It's not clear whether high-dose naloxone (i.e., greater than 4mg via nasal administration) is required in the current era of fentanyl and analogs. A recent report used a nationwide database of medical records to describe the amount of naloxone administered by prehospital providers for presumed opioid overdose[2]. Most patients received only one 2mg dose of intravenous naloxone or 4mg of intranasal naloxone spray. While naloxone infusion 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 midraisis. The risk of a patient with OUD developing opioid withdrawal after receiving naloxone is dose-dependent.[21] 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,[22] and the development of withdrawal is one of the largest barriers to decreasing substance use among people who use drugs.[23, 24]

In a FDA Reagan-Udall meeting held on March 8th and 9th of 2023 regarding the current management of opioid overdose, patient advocates and addiction medicine specialists stated that opioid overdose reversal products will be largely used by persons who use drugs and that community should have a voice in the development of these products.[7] They had seen the current trend of increasing doses in naloxone products and felt these devices, while potentially life-saving, would also be more and more likely to cause withdrawal in opioid-dependent persons. Consistent with the literature, these advocates stated that developing opioid withdrawal is one of the greatest fears among those who are opioid dependent. A market containing only high-dose naloxone products could potentially act as a barrier to naloxone use in the community the drug was intended to save. Advocates and persons with lived experience at the Reagan-Udall meeting requested for a broad range of naloxone products to be made available.

Lastly, high-dose naloxone is also associated with increased risk of pulmonary complications.[8] Noncardiogenic pulmonary edema is an uncommon but life-threatening complication in patients who receive naloxone after an opioid overdose.[25] A labeled condition, pulmonary edema is estimated to occur in 2% of patients, though it is not certain as many overdoses treated in the community do not seek hospital or emergency department care.[26] It is not certain whether noncardiogenic pulmonary edema is due to the catecholamine rush associated with the resolution of the overdose, if it is dependent on the dose of naloxone given, or if it is a severe complication of the opioid overdose syndrome.

2.2. Analysis of Current Treatment Options

Multiple drug products containing the active ingredient naloxone are available and marketed in the United Sates. Naloxone is an effective treatment for suspected opioid overdose if an adequate dose is administered in time. Currently there is no convincing evidence that the available treatment options are insufficient in successfully reversing opioid overdoses in the community. However, as more potent and faster onset opioids have been implicated in a growing proportion of opioid overdose deaths, multiple administrations of naloxone to achieve reversal of an opioid and higher dose/target plasma level of Naloxone may be needed than are available to reverse opioid overdose before hypoxia results in irreversible injury. It is possible that in those who are physically dependent on opioids, naloxone will produce opioid withdrawal symptoms, which may appear within minutes of administration. The severity and duration of the withdrawal syndrome is related to the dose of naloxone received and to the degree and type of opioid dependence.

Narcan (Naloxone hydrochloride; NDA 16636) 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. When naloxone hydrochloride is administered by intravenous injection (IV), the onset of action is generally apparent within 2 minutes; the onset of action is slightly less rapid when it is administered by subcutaneous injection (SC) or intramuscular injection (IM).

Injectable formulations of naloxone have been FDA-approved for the treatment of opioid overdose since 1971 (Table 1, below). The product labels recommend initial doses of 0.4mg to 2mg naloxone by the IM or IV route of administration, followed by repeat doses up to a total dose of 10mg. Nalmefene (Revex) injectable was approved by FDA in 1995 (NDA 020459). It was indicated for complete or partial reversal of opioid drug effects and management of known or suspected opioid overdose and it was available as a sterile solution for IV, IM and SC administration. Nalmefene 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. Nalmefene was discontinued in 2014 not for safety or efficacy reasons. Generic versions of Nalmefene are

currently available in the community.

Table 1: 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 Naloxone				
Narcan (generics 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.
Evzio (NDA 205787)	2014	Autoinjector 0.4 mg IM/SC		Not currently marketed
Narcan Nasal Spray (NDA 208411)	2015	4mg nasal spray	Onset of action is apparent within two minutes	Non-prescription as of 3/2023, to be marketed fall-winter of 2023
EVZIO (NDA 209862)	2016	Autoinjector 2mg IM/ SC		Not currently marketed
Kloxxado/hikma (NDA 212045)	2021	8mg nasal spray	Onset of action is apparent within two minutes	
Zimhi (NDA 212854)	2021	5mg prefilled syringe IM/SC		
Kaleo (NDA 215457)	2022	10mg autoinjector		Designed for military and mass casualty events, not for civilian use
RiVive Nasal Spray (NDA 217722)	2023	3mg nasal spray	Onset of action is apparent within two minutes	Non-prescription as of 7/2023, to be marketed fall-winter of 2023
Other Related Treatments				
Nalmefene hydrochloride (NDA 20459)	1995	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	Discontinued in 2014 not for safety or efficacy reasons. Safety and efficacy in pediatric patients has not been established.
Opvee Nalmefene hydrochloride (NDA 217470)	2023	2.7 mg nasal spray		Not yet marketed, approved for non-prescription as of 7/2023

2.3. Current Trends in Naloxone Administration

There are several recent reports of out-of-hospital naloxone use are relevant to this NDA. The FDA posted two Broad Agency-wide Announcements (BAA) to explore how naloxone is administered in various healthcare settings. BAA #171 was conducted by the American College of Emergency Physicians (ACEP) and utilized a national database of records of emergency medical transports to determine how much naloxone was being given for presumed opioid overdoses in the prehospital setting by paramedics and emergency medical technicians.[2] BAA #167 was conducted by investigators working with Prevention Point Pittsburgh (PPP), a non-profit harm reduction organization with several locations in the Pittsburgh area.[27] Lastly, there is a conference presentation from the New York State Department of Health detailing the performance of 4mg vs 8mg nasal spray for the prehospital treatment of opioid overdose.[28]

The data source used in BAA#171 was the National Emergency Medical Services Information System (NEMSIS) database, a collection of standardized medical records from prehospital care provided in 48 states and represents about 87% of emergency dispatches in the United States.[2] A subset of NEMSIS records are further linked to hospital records through ESO, a large out-of-hospital electronic medical record system that is compliant with the NEMSIS database standards. Both the ambulance agency and the hospital must have ESO-compliant databases to extract the full medication administration records, so only 17% of the NEMSIS encounters are linked to the ESO administration records. The version of the public dataset released in 2019 contained 8,340,148 EMS encounters. The encounters occurred in the South (58%), Midwest (22%), West (16%), and Northeast (5%). The research window for this investigation covered 2017-2021 (inclusive). Based on the United States Census urbanicity categorizations, most encounters occurred in urbanized areas (76%) or urban clusters (18%). Eligible EMS encounters were as identified using standard RxNorm codes (7242, 197117, 203192, 1191230, 343216, 93418, 1179311, 353392, 1191213, 727348, 1010598) in the NEMSIS database or values of “naloxone” or “narcan” were entered in the ESO treatment name database. Encounters were excluded if the call was later cancelled by the patient or if there was no patient contact, if the patient was transported somewhere other than an emergency department (e.g., an interfacility transfer). Approximately 8.1 million encounters met the inclusion/exclusion criteria. Naloxone administrations were grouped by dose and route of administration and displayed in Figure 1.

Table 2. ESO Naloxone administration stratified by route and dosing frequency [2]

Route	Percent
Enteral	0
Intramuscular	7.7
Intranasal	43.6
Inhaled	1
Intraosseous	5.2
Intravenous	42.3
Missing	0.2
Number of Doses (n)	**Percent**
1	68.2
2	24.7
3	5.2
≥4	1.7

Table 3. ESO repeated naloxone dose frequencies by route of first dose [2]

	IM	IN	IO	IV
1 dose	88.2%	80.6%	87.7%	82.7%
2 doses	10.7%	16.9%	10.3%	13.8%
3 doses	1.0%	2.0%	1.5%	2.3%

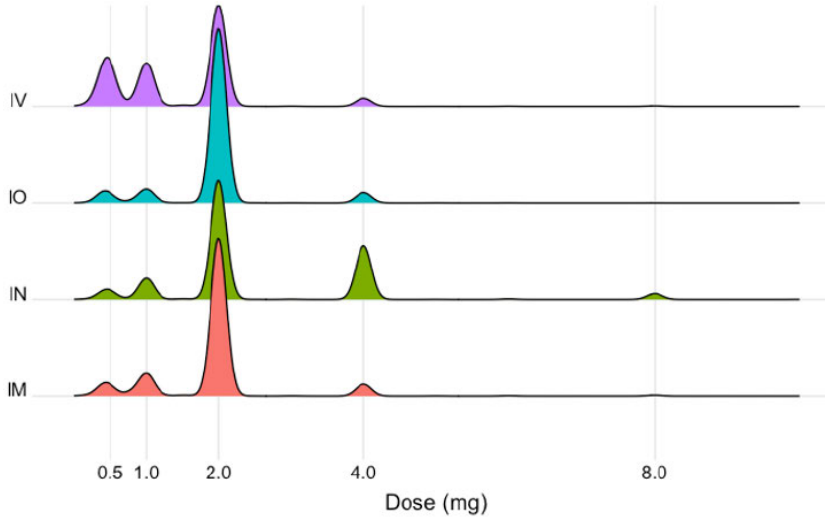


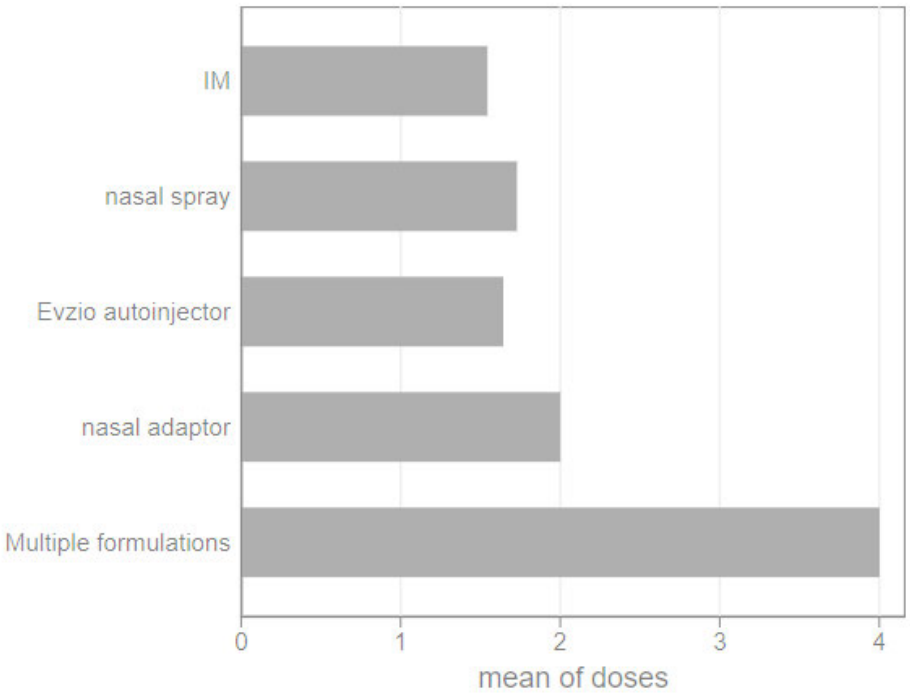
Figure 1. ESO naloxone dose distribution by route [2]

Prevention Point Pittsburgh has been training residents how to use take-home naloxone kits and products for 17 years.[27] Whenever someone returned to PPP for another dose of naloxone, the staff would conduct a brief, usually on paper, survey on how the previous dose of naloxone was used. BAA #167 translated these surveys into an electronic format and summarized the resulting trends of naloxone use by clients at PPP. This report is important to the current application as it focuses on the population of persons who use drugs, the population this NDA is meant to impact. Furthermore, 34.4% (n=899) of PPP participants never called 911, providing insight into a population separate from those patients reported in BAA 171#.

Table 4. Naloxone products distributed and used by Prevention Point Pittsburgh clients [27]

Type of naloxone administered	Frequency	Percent
Intramuscular	1,367	85.97
Nasal spray	207	13.02
Evzio autoinjector	14	0.88
Nasal adaptor	1	0.06
Multiple formulations	1	0.06

Figure 2. Frequency of repeated naloxone dose by Prevention Point Pittsburgh clients, stratified by route [27]



The New York Department of Health collaborated with Albany Medical Center and New York State Police to determine the performance of two different naloxone nasal spray products.[28] Eight out of eleven area officers were given 4mg products, as per usual care prior in New York State. The remaining three police officers were equipped with 8mg nasal spray products. Patients who received naloxone by the officers in the prehospital care environment were followed through their transport by EMS to Albany Medical Center emergency department. The study was conducted from March 2022 to August 2023, totaling 354 administrations (101 eight milligram [28.5%] vs 253 four milligram [71.5%]). There were no difference in the mean number of doses given between groups (1.58 doses of eight milligram products vs 1.67 doses of four milligram products), the percent transported to hospital (81.0% vs 73.4%, respectively), and percent who survived (99.0% vs 99.2%, respectively). There was a significantly larger percent of patients who developed withdrawal symptoms when receiving the 8mg product compared to the 4mg product (37.6% vs 19.4%, relative risk ratio of 2.51, 95% CI: 1.51 to 4.18).

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Naloxone HCL was first approved in 1971 (Narcan, NDA 016636), for intravenous, intramuscular, and subcutaneous administration for treatment of opioid overdose symptoms for use in adults and pediatric patients. The current labeling of Narcan recommends an initial dose of 0.4 mg to 2 mg, followed by repeat doses up to 10 mg in the setting of suspected opioid overdose. Narcan has been discontinued from marketing, however the Agency determined that it was not withdrawn from sale for reasons of safety or effectiveness (74 FR 22751) and there are generic naloxone products available. The first product approved to address the risk of opioid overdose in a community setting was Evzio (Naloxone HCL injection), approved on April 3, 2014. Evzio (NDA 205787) in an autoinjector that delivers 0.4 mg of naloxone in 0.4 mL to the subcutaneous or intramuscular space. A higher dose version, Evzio 2 mg (NDA 209862) was approved on October 19, 2016. Narcan nasal spray (NDA 208411) was approved on November 18, 2015 and consists of a single dose device of 4mg dose naloxone in 0.1 ml. Narcan nasal spray 2 mg strength was approved on January 24, 2017, but manufacturer has not marketed the 2 mg product. A 4mg Narcan nasal spray version was approved for non-prescription use March 2023. ZIMHI, a syringe pre-filled with 5mg of naloxone hydrochloride for IM/SC injection, was approved in 2021 (NDA 212854). Kloxxado, later bought by hikma pharmaceuticals, developed a 8mg nasal spray that was approved in 2021 (NDA 212045). Another drug-device product using naloxone and the (b) (4) delivery device, RiVive 3mg nasal spray (NDA 217722), was approved as a direct-to-nonprescription product in July 2023.

3.2. Summary of Presubmission/Submission Regulatory Activity

A Type B PIND Meeting (PIND 141634) was held on Feb 7, 2019 to discuss the clinical development plan. The relevant FDA comments are summarized as below: The Sponsor had not provided sufficient clinical data to support that naloxone exposures higher than those achieved with the approved naloxone products for community use are necessary to provide improved efficacy or faster onset of action over the already approved products, nor why their proposed dose would be adequate. Additionally, they had not provided evidence that there is currently an unmet medical need for higher doses of naloxone.

The Sponsor was reminded that their product would trigger PREA and the Sponsor was encouraged to address the requirements under PREA by providing a justification (e.g., from literature, published clinical practice guidelines, approved Narcan labeling) for why the proposed product, containing a fixed high dose of naloxone, is acceptable for all pediatric age ranges to support the safety and efficacy of the proposed dose in pediatric patients and the pediatric labeling for the proposed products. The Sponsor asked for clarification on whether juvenile animal toxicity studies will be required. The Agency stated that the Sponsor must provide justification as to why juvenile animal toxicity studies are not required in their initial Pediatric Study Plan (iPSP).

The Sponsor was advised that they would need nonclinical support for local toxicity and that that should be done in two species. The Sponsor reported that they plan to conduct one pivotal bioavailability PK study to support their NDA. The Sponsor was given advice regarding the importance of measuring the onset of action of their product and that since rapid onset of action is critical for reversal of opioid overdose, your proposed product must demonstrate comparable or higher exposure to the comparator in the comparative bioavailability study during the early absorption phase (e.g. first 2 to 5 minutes).

This is the first review cycle for REZENOPY, a NDA under section 505(b)(2) of the Food, Drug, and Cosmetic Act. REZENOPY is a drug and device combination of naloxone hydrochloride and the (b) (4) nasal spray delivery device. The drug component of this application relies upon the agency's previous findings of safety and efficacy of Adapt Pharma's Narcan (NDA 16636).

The Sponsor applied for Fast Track Designation in 2019. The FDA understood opioid overdose is a serious public health problem, but there are multiple approved products that are effective in reversing opioid overdose. [T]he Sponsor did not provide data to show that the currently approved products fail to reverse overdose in specific situations and what dose would be required to potentially reverse higher-dose opioids and more potent opioids. The Sponsor did not submit data to support that their product can address an unmet medical need, providing only data from one bridging study in healthy adults. Fast Track Designation was denied.

As a part of IND Type C meeting held on September 2020, The sponsor asked "*Does the Division agree that there is no issue regarding safety margins for systemic exposure with Summit's IN*

product?" The FDA response was: "*You should provide adequate safety information to support use of your product in the opioid-dependent population. We are concerned that higher doses of naloxone may precipitate severe and life-threatening adverse events in this population.*" Other naloxone-containing products have not had a requirement for safety data in opioid-dependent persons. But this requirement is consistent with the sentiments voiced by addiction medicine specialists and patient advocates during the Reagan-Udall meeting held in March 2023 regarding the management of opioid overdose.[7]

With the submission of this application Summit requested Priority Review. As stated earlier, there are a number of approved products on market, two of which are suitable for non-prescription use. The Applicant does not provide data to show significant improvements in safety or efficacy in treatment or compared to existing products; in their bridging study, they compared their product to single-dose naloxone 0.4 mg IV and 0.4mg IM. They did not compare REZENOPY to Narcan 4mg nasal spray. The sponsor argues for the need for high-dose products to treat high-potency opioids like fentanyl, but did not compare REZENOPY to existing approved high-dose products (e.g., Kloxxado 8mg IN). The sponsor did not demonstrate that REZENOPY was a significant improvement over the existing products by the following measures: Increased effectiveness in treatment, prevention, or diagnosis of condition; Elimination or reduction of a treatment-limiting drug reaction; Documented enhancement of patient compliance that will lead to improved outcomes; Evidence of safety and effectiveness in a new subpopulation. Priority review was denied.

3.3. Foreign Regulatory Actions and Marketing History

There is no foreign regulatory marketing development for naloxone nasal spray.

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

4.1. Office of Scientific Investigations (OSI)

An Office of Scientific Investigation declined to conduct an inspection for this application because of the inspection history of the study site.

4.2. Product Quality

The facility passed a pre-approval inspection conducted from 9/11/2023 to 9/14/2023.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

There are no novel excipients in this application, and the leachables and extractables are at or below limits. The purity of the drug substance is acceptable. A novel (b) (4) is above specification. The Applicant submitted the results of a DEREK analysis, showing it is less likely that (b) (4) is mutagenic, but this analysis was felt to be insufficient. The 28-day high-exposure rat study submitted by the applicant used (b) (4)% solution of (b) (4) which is not comparable to the (b) (4)% concentration of (b) (4) seen in REZENOPY. Nonclinical will request a PMR to further characterize what hazards, if any, (b) (4) poses to patients.

4.5. Clinical Pharmacology

The Applicant submitted a single comparative bioavailability study submitted in support of their product. The following summary of the clinical pharmacology assessment is taken from Dr. Wei Qiu's review.

(1) A single spray of the proposed Naloxone HCl nasal spray 10 mg in one nostril (i.e., 10 mg IN dose) exhibited a median (min, max) Tmax of 0.75 hour (0.25, 1.03 hour). The median (min, max) Tmax for 0.4 mg IM injection was 0.50 hour (0.17, 2.00 hour).

(2) A 10 mg IN dose of the proposed Naloxone HCl nasal spray 10 mg showed higher naloxone plasma concentrations than 0.4 mg IM injection at all post-dose timepoints including early absorption phase. The mean partial AUC values, AUC0-2.5min, AUC0-5min, and AUC0-10min, during the early absorption phase for a 10 mg IN dose were 4.4-fold, 4.1-fold, and 5.2-fold greater than those for a 0.4 mg IM injection. A 10 mg IN dose showed 12-fold greater Cmax, 9.9-fold greater AUC0-t and 9.8-fold greater AUC0-inf values than a 0.4 mg IM injection. Because the approved initial dose of Narcan injection (NDA 016636) is from 0.4 mg to 2 mg in adults via IV, IM or SC administration, the Applicant's proposed reliance on effectiveness findings of Narcan injection (NDA 016636) is warranted.

(3) A 10 mg IN dose of the proposed Naloxone HCl nasal spray 10 mg showed 49% lower Cmax, but 58% and 60% greater AUC0-t and AUC0-inf values, respectively, than a 2 mg intravenous (IV) injection. The mean absolute bioavailability of naloxone based on AUC0-inf for IN dosing was 34% relative to IV dosing.

4.6. Devices and Companion Diagnostic Issues

The Center for Devices and Radiologic Health (CDRH) has no significant issues. This product submission utilizes the (b) (4) device, which has been used in multiple prior approved products.

4.7. Consumer Study Reviews

No consumer study reviews were requested for this application.

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 application.

5.2. Review Strategy

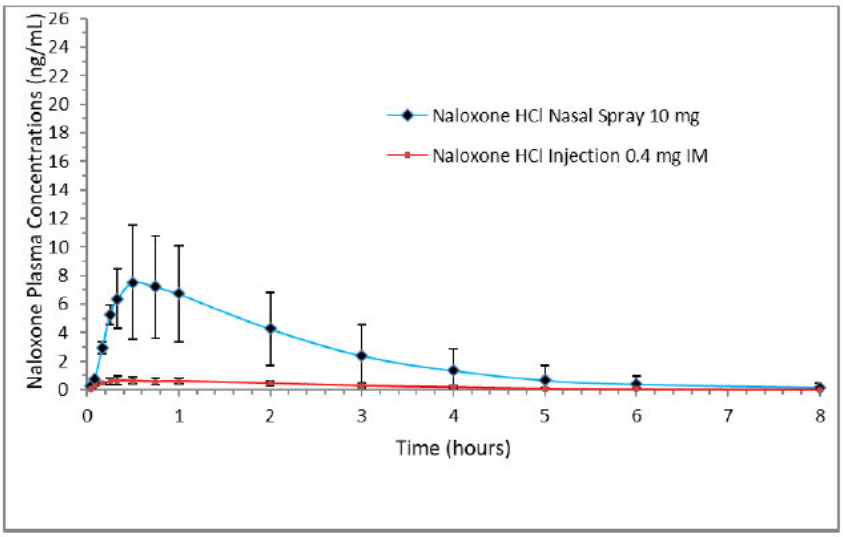
No clinical efficacy trials were conducted in support of this application. This application relies on PK data and previous agency findings of the efficacy of naloxone. The safety of the submitted product was assessed based on the safety evaluations completed as a part of the PK study.

6. Review of Relevant Individual Trials Used to Support Efficacy

No clinical efficacy trials were conducted in support of this application. This application relies on PK data and previous agency findings of the efficacy of naloxone (NDA 16636).

Trial 11875901 linked the current product's performance to two previously approved products: 0.4 mg naloxone IM/SC and 2.0 mg IV. Trial 11875901 was an open-Label, single-dose, randomized, three-treatment, three-period, two-sequence crossover (Treatments A and B), fixed-period (Treatment C) study (Fasted). The study would further demonstrate the safety and tolerability of the product, including testing to evaluate nasal irritation and impact on olfactory ability. The general design of Trial 11875901 is typical of pharmacokinetic bridging studies submitted in support of other FDA-approved products. The trial was conducted at a single site, the Novum Pharmaceutical Research Services (Las Vegas, NV, Phone: 702-435-3739).
The bridging Trial 11875901 showed the systemic exposure level of Summit 10mg Nasal Spray is higher than the reference product, Narcan (naloxone hydrochloride, NDA 16636), supporting the efficacy of the product.

The results of bridging Study 11875901 are shown in Figures 3 and 4 (below). REZENOPY provides serum exposures of naloxone greater than, or comparable to, those exposures caused by the reference treatments, 0.4 mg IM and 2 mg IV naloxone hydrochloride.



The systemic plasma exposure of naloxone from a single 10 mg IN administration of Naloxone Hydrochloride NS (Treatment A) was higher than that from a single 0.4 mg IM injection of Naloxone Hydrochloride Injection, USP (Treatment B) dose at all early time points. The LSGM values of all early partial AUCs ($AUC_{0\text{-}xmin}$, x = 2.5, 5, 10, 15 and 30) and C_{max} were > 4.1-fold larger for IN compared to IM administration, with LSGM A/B ratios of 1249% for C_{max} (n = 29) and ranging from 409-920% for partial AUCs (n = 9-29); the IN total systemic exposures, as characterized by $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$, were nearly 10-fold higher, with LSGM A/B ratios of 992% and 977% (n = 29), respectively (Table 3).

Figure 3. Mean Plasma Concentration ± Standard Deviation of Naloxone over Time for Naloxone Hydrochloride Nasal Spray, 10 mg, and Naloxone Hydrochloride Injection, 0.4 mg IM [Source: Summit Biosciences, NDA 215487, Clinical Overview, Figure 1, page 20] [29]

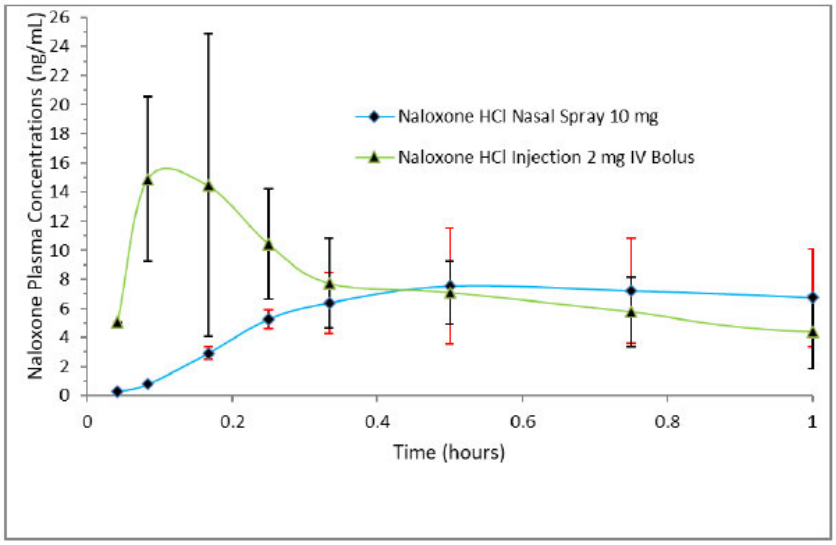


Figure 4. Mean Plasma Concentration ± Standard Deviation of Naloxone over Time for Naloxone Hydrochloride Nasal Spray, 10 mg, and Naloxone Hydrochloride Injection 2 mg IV bolus. [Source: Summit Biosciences, NDA 215487, Clinical Overview, Figure 2, page 22] [29]

7. Integrated Review of Effectiveness

See Section 6.

8. Review of Safety

8.1. Safety Review Approach

The Applicant utilized the 505(b)(2) pathway, relying on the Agency's previous efficacy and safety findings for naloxone product, Narcan (NDA 016636). They have bridged to our findings by of safety and efficacy of NDA 016636 by supplying a literature review and a performing a bioavailability study (Trial 11875901). The local safety findings from Trial 11875901 were reviewed to support the application and were considered necessary to approval.

The applicant was required to support the safety and efficacy of Narcan nasal spray in Pediatrics. The Applicant provided a review of available information, including the published literature, clinical published guidelines, and the approved injectable labeling for Narcan. Because REZENOPY nasal spray represents a change in dosing regimen, the Applicant is required to conduct a pediatric assessment under the Pediatric Research Equity Act (PREA). The pediatric assessment was required to have address the following issues (see list below). The application was reviewed by the Pediatric Review Committee (PeRC) and a agreed iPSP was issued.

- The safety and effectiveness of the proposed dose of naloxone for all pediatric age ranges, including neonates.
- Why the absorption of the drug through the nasal mucosa will be different in pediatric patients, including neonates, compared to adults.
- Justification for the proposed dose volume in all pediatric patients, including neonates.
- A device that can appropriately deliver the correct volume to all pediatric patients, including neonates.
- The nasal actuator tip is appropriately sized for and can appropriately deliver the correct volume to all pediatric patients, including neonates.

(b) (4) Project # 2134 is a human factors study that was conducted in support of this product. It is mentioned here for completeness but is not included in the review of safety.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

A total of 30 patients were exposed to the REZENOPY nasal spray formulation containing 10 mg naloxone HCL within the single bridging Trial 11875901 (Tables 5 and 6, below).

Table 5. Listing of Clinical Trials Relevant to this NDA

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population
Controlled Studies to Support Safety						
11875901	Open label, singe-dose, randomized, crossover study	IV,IM/SC,IN	Serum naloxone concentration, tolerability	Single dose	30	Healthy volunteers
Studies to Support Human Factors Assessment						
(b) (4) #2134	Cohort	NA	Validate that the intended user populations can successfully use the nasal spray product and associated materials.	Single session	45 (15 adults, 15 first-responders, 15 under 18 years of age [5 were 12 and younger])	Healthy volunteers

Table 6: Safety Population, Size, and Denominators

Safety Database for the Study Drug[1] Individuals exposed to any treatment in this development program for the indication under review N=30 (N is the sum of all available numbers from the columns below)			
Clinical Trial Groups	REZENOPY 10 mg naloxone HCL IN	Naloxone HCL 0.4 mg IM/SC	Naloxone HCL 2mg IV
Healthy volunteers	30	30	26

[1] *Study drug* means the drug being considered for approval.
[2] to be used in product's labeling
[3] If placebo arm patients switch to study drug in open label extension, then the sample n should count those patients only once; do not count twice patients who go into extension from randomized study drug arm
[4] Include n in this row only if patients exposed to the study drug for indication(s) other than that in the marketing application have been included in the safety database under review.

8.2.2. Relevant characteristics of the safety population:

Thirty subjects were included in the pharmacokinetics study. The safety population consisted of randomly-selected healthy adults. None of the subjects had a history of opioid dependence.

8.2.3. Adequacy of the safety database:

Thirty subjects were included in the pharmacokinetics study. The safety population consisted of

randomized healthy adult population. The bridging study was an open-Label, single-dose, randomized, three-treatment, three-period, two-sequence crossover (Treatments A and B), fixed-period (Treatment C) study (Fasted). As the applicant is utilizing the 505(b)(2) pathway and relying on the Agency's previous findings of Narcan, the exposure to 30 subjects to the proposed 10 mg nasal naloxone from on pharmacokinetic study is adequate for the purposes of this safety evaluation.

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. The definitions and categorizations provided by the Applicant of treatment-emergent adverse events and serious adverse events are acceptable.

8.3.3. Routine Clinical Tests

Blood sampling for pharmacokinetic analysis were collected for Study 11875901. Additional clinical laboratory assessments were collected at screening and final study visits. These consisted of hematology, chemistry, urinalysis, and drug testing. Hematology, chemistry, and urinalysis values were within 20% of the normal range or considered not clinically significant. Drug testing consisted of urine metabolites of cannabis, cocaine, and opiates. A breathalyzer was used to test blood alcohol levels. Pregnancy testing was performed at screening, baseline and final study visits. All pregnancy tests were negative.

Reviewer comment: The clinical laboratory testing from both studies were acceptable and provided some information to support the safety of using 8 mg Naloxone nasal spray. The nasal irritation assessment tool and monitoring are adequate to evaluate the potential for local toxicity.

8.4. Safety Results

8.4.1. Deaths

There were no deaths recorded among the subjects of Study 11875901.

8.4.2. Serious Adverse Events

There were no serious adverse events recorded among the subjects of Study 11875901.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

There were no dropouts or discontinuations due to AEs or SAEs.

Thirty subjects were enrolled in Periods I and II (Crossover trial of Naloxone Hydrochloride NS, 10 mg [Treatment A] vs Naloxone Hydrochloride Injection 0.4 mg IM [Treatment B]) of Study 11875901. Twenty-four subjects met enrollment criteria for Period III (Naloxone Hydrochloride Injection 2 mg IV bolus). One subject's intravenous catheter connection leaked during dosing and they did not receive a full dose of the study drug. That subject completed the safety evaluations and did not experience any AEs.

8.4.4. Significant Adverse Events

There were no significant adverse events recorded for Study 11875901.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

A summary of the adverse events that occurred during bridging Study 11875901 is summarized in Table 7 below. Nine of the 30 subjects reported ten total AEs across Study 11875901. Six AEs reported during or just after administration of Naloxone Hydrochloride NS, 10 mg. One was reported after administration of Naloxone Hydrochloride Injection 0.4 mg IM. Three occurred after Naloxone Hydrochloride Injection was given as a 2 mg IV bolus. All AEs were categorized as "mild" in severity. Nine had "recovered/resolved" by study completion. One AE was considered "recovering/resolving" by study completion. No subjects were discontinued due to AEs.

Dysgeusia (medication aftertaste) was both the most frequently reported AE in the study and the most commonly reported AE for the study drug (Naloxone Hydrochloride NS, 10 mg), and was reported among four subjects. Dysgeusia was not reported among any subjects after receiving the comparator drugs (Naloxone Hydrochloride Injection 0.4 mg IM or Naloxone Hydrochloride Injection 2 mg IV bolus).

Table 7. Summary of Adverse Events by Body System and MedDRA Term (Study 11875901) [Source: Summit Biosciences, NDA 215487, Clinical Overview, Table 6, page 31] [29]

Body System	MedDRA Term	10 mg IN (N = 30) # of Events	10 mg IN (N = 30) # of Subjects	0.4 mg IM (N = 30) # of Events	0.4 mg IM (N = 30) # of Subjects	2 mg IV (N = 24) # of Events	2 mg IV (N = 24) # of Subjects
Subjects with at least one AE	Total	6	6 (20.0%)	1	1 (3.3%)	3	3 (12.5%)
Gastrointestinal disorders	Abdominal pain upper	1	1 (3.3%)	0	0 (0.0%)	0	0 (0.0%)
General disorders and administration site conditions	Application site bruise	0	0 (0.0%)	0	0 (0.0%)	1	1 (4.2%)
Infections and infestations	Nasopharyngitis	1	1 (3.3%)	0	0 (0.0%)	0	0 (0.0%)
Nervous system disorders	Dysgeusia	4	4 (13.3%)	0	0 (0.0%)	0	0 (0.0%)
Nervous system disorders	Headache	0	0 (0.0%)	1	1 (3.3%)	1	1 (4.2%)
Nervous system disorders	Paraesthesia	0	0 (0.0%)	0	0 (0.0%)	1	1 (4.2%)

% = (Number of subjects reporting AE / number of subjects dosed with study treatment) × 100

Reviewer's Note: The frequency of dysgeusia was similar to that reported in other studies of similar products.

Subjects underwent a functional smell test, the University of Pennsylvania Smell Identification Test Assessment (UPSIT, components listed in Table 8) at time of check-in for both period I and II, as well as at the Period II follow-up visit. The UPSIT consists of four booklets, each containing ten with scratch-and-sniff panels. Subjects are asked to identify the smell using a multiple-choice format. Normosmia (i.e., a normal sense of smell) is rated as 34-40 in men and 35-40 in women (Table). The UPSIT scores of the subjects are described in Table 9. The subset of individuals with worsening UPSIT scores during the Study 11875901 are detailed in Table 10.

Table 8. University of Pennsylvania Smell Identification Test Total Score Strata [Source: Summit Biosciences, NDA 215487, Clinical Overview, page 34] [29]

Test Score	Olfactory Diagnosis
00 – 05	Probable Malingering
06 – 18	Total Anosmia
19 – 25	Severe Microsmia
26 – 29	Moderate Microsmia (Males)
26 - 30	Moderate Microsmia (Females)
30 – 33	Mild Microsmia (Males)
31 - 34	Mild Microsmia (Females)
34 – 40	Normosmia (Males)
35 - 40	Normosmia (Females)

Table 9. Descriptive Statistics for University of Pennsylvania Smell Identification Test Total Score for Naloxone Hydrochloride NS, 10 mg (Treatment A)(Study 11875901) [Source: Summit Biosciences, NDA 215487, Clinical Overview, Table 7, page 34] [29]

Evaluation	Time point	N	Arithmetic Mean ± SD (% CV)	Minimum, Maximum (Median)
UPSIT Total Score	*Subjects Receiving Naloxone Hydrochloride NS 10 mg in Period I*			
	Period I Check-In	15*	31.20 ± 4.28 (13.72)	24, 37 (32)
	Period II Check-In#	15*	32.07 ± 3.63 (11.33)	25, 37 (33)
	Subjects Receiving Naloxone Hydrochloride NS 10 mg in Period II			
	Period II Check-In	15†	32.20 ± 6.65 (20.64)	15, 39 (34)
	Period II Follow-Up	15†	30.87 ± 5.10 (16.51)	22, 38 (30)

*Subjects received Naloxone HCl NS, 10 mg (Treatment A) in Period I.
†Subjects received Naloxone HCl NS, 10 mg (Treatment A) in Period II.
#Note that Period II Check-In is also the Period I Follow-Up

Table 10. Descriptive Summary of University of Pennsylvania Smell Identification Test Assessment Naloxone Hydrochloride 10 mg (Treatment A)(Study 11875901) [Source: Summit Biosciences, NDA 215487, Clinical Overview, Table 8, page 35] [29]

Subject Number	UPSIT Total Score		
	Period I Check-In	Period II Check-In	Period II Follow-Up
(b) (6)	Mild Hyposmia/ Microsmia (32)	Normosmia (34)	Moderate Hyposmia /Microsmia (29)
	Normosmia (34)	Normosmia (35)	Mild Hyposmia/ Microsmia (30)
	Mild Hyposmia/ Microsmia (30)	Mild Hyposmia/ Microsmia (31)	Severe Hyposmia/ Microsmia (25)
	Normosmia (34)	Mild Hyposmia/ Microsmia (30)	Mild Hyposmia/ Microsmia (31)
	Moderate Hyposmia/ Microsmia (30)	Mild Hyposmia/ Microsmia (32)	Moderate Hyposmia/ Microsmia (28)

[†] Subject received Naloxone Hydrochloride NS in Period I
* Subject received Naloxone Hydrochloride NS in Period I

Subjects underwent nasal mucosa examinations prior to dosing, and again at 5 minutes, 30 minutes, and 4 hours after intranasal administration of REZENOPY. Examinations were scored, using a 0 to 4 scale (no findings to severe pathology), for the following characteristics: irritation, erythema, crusting, edema, and discharge. One subject had scores of two for nasal irritation (moderate mucosal erosion) and erythema (moderate redness) at the Period II follow-up, but not at intervening evaluations. The other subjects did not have any symptoms of nasal irritation (no sign of nasal irritation or mucosal erosion) at any period or follow up, though some had a maximum score of one for nasal erythema (slight redness).

Reviewer Comment: The findings of mild nasal erythema in a minority of subjects without nasal irritation, is consistent with findings from the bridging studies completed for NDAs 217722 and 212045. These findings do not raise new or additional safety concerns.

8.4.6. Laboratory Findings

Not applicable

8.4.7. Vital Signs

No clinically significant changes in vital sign or ECG measurements were noted during the study.

8.4.8. Electrocardiograms (ECGs)

A 12-lead ECG was done at each study check-in period. No clinically significant changes in ECG measurements were noted during the study.

8.4.9. QT

A 12-lead ECG was done at each study check-in period. No clinically significant changes in ECG measurements were noted during the study.

8.4.10. Immunogenicity

Not applicable.

8.5. Analysis of Submission-Specific Safety Issues

8.6. Safety Analyses by Demographic Subgroups

Not applicable.

8.7. Specific Safety Studies/Clinical Trials

No additional safety studies or updates were submitted for review.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Long-term animal studies to evaluate the carcinogenic potential of naloxone have not been completed.

8.8.2. Human Reproduction and Pregnancy

All pregnancy tests conducted as a part of Study 11875901 were negative.

8.8.3. Pediatrics and Assessment of Effects on Growth

The safety and effectiveness of naloxone has already been established in pediatric patients of all ages for the emergency treatment of known or suspected opioid overdose. Use of naloxone in this population has already been supported by adult bioequivalence studies as well as evidence of safety and effectiveness in pediatrics in clinical practice. Division of Pediatric and Maternal Health (DPMH) was consulted to assist in the review of the submitted pediatric information, label, and approval recommendations including the Pregnancy and Lactation Labeling Rule (PLLR) language. The application is compliant with PREA and has an approved iPSP. Both Divisions agreed that this product is appropriate for pediatric use for all ages including down to birth.

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

There is no clinical experience with naloxone HCL regarding overdose in humans. Naloxone does not have any known abuse potential. It is not a psychoactive substance and does not produce physical dependence. It does precipitates withdrawal in morphine-dependent subjects. There is no available data regarding withdrawal from naloxone HCL and rebound in humans.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

REZENOPY is not approved in the U.S. market or in any foreign market; therefore, no postmarketing experience is available for REZENOPY specifically. However, other IN naloxone products are approved in the U.S. market. The analyses of postmarketing safety data for these other IN naloxone products are presented in Section 8.10.

8.9.2. Expectations on Safety in the Postmarket Setting

Naloxone has been used for many years and has a relatively favorable risk/benefit profile. In particular, naloxone has been administered safely at high doses to patients who are not opioid dependent.

Use of naloxone may precipitate opioid withdrawal in patients who are opioid dependent. 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 naloxone and to the degree and type of opioid dependence. Withdrawal symptoms often appear within minutes of administration and subside in about 2 hours. Prolonged and untreated withdrawal is associated with dehydration, renal failure, shock, and electrolyte abnormalities. In neonates, opioid withdrawal may be life-threatening.

The proposed dose of naloxone in the Rezenopy product is 10 mg (delivered at a concentration of 100 mg per mL at a volume of administration of (b) (4) mL), so we expect there will be a higher risk for precipitation of opioid withdrawal symptoms in opioid-dependent patients compared to naloxone products that produce lower exposures.

Additionally, approximately 1%-2% of patients suffering from opioid overdose develop noncardiogenic pulmonary edema after being revived with naloxone.[8] 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 have 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 very 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 naloxone. It is known that the risk of developing noncardiogenic pulmonary edema increases as the dose of naloxone received increases.[8]

It is recommended that the Applicant be asked to perform a post-marketing study to evaluate this risk.

8.10. Integrated Assessment of Safety

The Applicant has submitted a literature review and safety data from a PK study to support the safety of REZENOPY (naloxone nasal spray, 10 mg / (b) (4) mL). The Applicant also submitted adequate data to characterize the reaction of the nasal mucosa exposed to the product. This data was reviewed from June to October 2023.

The safety for this high-dose naloxone product is based primarily on the agency's prior findings for Narcan (naloxone hydrochloride) solution for injection. The PK data showed the systemic exposure level of REZENOPY (naloxone nasal spray, 10 mg / (b) (4) mL) is higher than the reference product, Narcan (naloxone hydrochloride, NDA 16636). The Applicant submitted literature review to support the safety of the systemic exposure observed with REZENOPY (naloxone nasal spray, 10 mg / (b) (4) mL). The Applicant has described several studies to support higher doses of naloxone in the submission.

An example of an article that the Applicant specifically cited is from Springborg, which describes naloxone infusions at doses of 3.25 mg/kg, or 227.5 mg for a 70 kg male, to assess the development of hyperalgesia in a standardized cutaneous injury model. Twenty-two (57.9%) subjects receiving naloxone reported mild AEs like tiredness, nausea, vomiting, dizziness, headache, itching, and restlessness compared to four subjects following placebo (10.5%, $p < 0.001$). One subject experienced moderate AEs, including anxiety, nausea, and dizziness. One subject experienced anxiety, dizziness, unilateral paresthesia of the arm and leg, and perioral numbness during the naloxone infusion. Symptoms for both subjects resolved after the naloxone infusion was stopped and both subjects agreed to further participation.

The finding of dysgeusia did not raise significant or new safety concerns. A minority of subjects experienced nasal erythema as a part of the key bridging study 11875901. This did not raise safety concerns as these were consistent with findings from the bridging studies completed for other, similar products.

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 an individual not physically dependent on opioids.

The safety of REZENOPY when administered in persons who are physically dependent on opioids is less clear. Depending on the dose administered and the person's opioid use history, naloxone may precipitate an acute withdrawal syndrome. The symptoms of spontaneous opioid withdrawal (which include nausea, vomiting, diarrhea, diaphoresis, chills, mydriasis, piloerection, and yawning, similar to the discontinuation of opioid in a dependent individual) are uncomfortable, but in of themselves not generally believed to necessitate hospitalization. However, when withdrawal is precipitated abruptly by the administration of an opioid antagonist to an opioid-dependent patient, the resulting withdrawal syndrome can be severe enough to require hospitalization. Complications arising from precipitated withdrawal include dehydration, refractory vomiting, electrolyte disturbances, and shock. In a recent non-randomized trial comparing eight milligram to four milligram naloxone nasal sprays of out-of-hospital opioid overdose found that there was no difference between the number of administrations per patient, but those patients who received the eight milligrams naloxone product of naloxone were 2.5 times more likely to suffer from precipitated withdrawal.[28] Similarly, a study of patients suffering from opioid overdose found that increasing doses of naloxone were associated with non-cardiogenic pulmonary edema.[8] Lastly, the applicant justifies their product development on the basis that illicit fentanyl is so potent it requires high doses of naloxone to reverse. However, this report cites several recent reports, all developed within the current era of illicit fentanyl, that demonstrate the large majority of opioid overdoses in the prehospital environment are reversed with 1-2 administrations of 4mg of naloxone nasal spray.[2, 27, 28]

In aggregate, these potential safety concerns are outweighed by the benefit of reversing a life-threatening opioid overdose and increasing access to additional naloxone products. The concerns regarding precipitated withdrawal in higher dose naloxone products can be addressed through post-marketing requirements.

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

Division of Medical Policy Programs (DMPP) and Office of Prescription Drug Promotion (OPDP) were consulted to review the proposed carton and container labeling. Their consults were based on the draft labeling submitted by the sponsor to the electronic document room on March 24, 2023. revised by the Review Division throughout the review cycle and received by DMPP and OPDP on October 5, 2023. The labelling for REZENOPY is based on a similar product, KLOXXADO (NDA 212045). Additionally, DMPP's and OPDP's review referenced labels for the approved NARCAN (naloxone hydrochloride) nasal spray (dated March 27, 2023) and the approved KLOXXADO (naloxone hydrochloride) nasal spray (dated April 29, 2021).

The Patient Package Insert, the Instructions for Use, and the Quick Start Guide were revised. Most changes were made to enhance legibility or increase consistency across sections, and were generally minor.

Language was added to note that comparing different naloxone products on the basis of nominal dose might be misleading. This was included because the 10 mg nominal dose in REZENOPY produces naloxone exposures lower than the 8 mg nominal dose of KLOXXADO, presenting an opportunity for misleading conclusions.

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. The sponsor will provide data on the safety of the product (i.e., rate of precipitated withdrawal and non-cardiogenic pulmonary edema) in patients who are opioid-dependent via a post-marketing requirement.

12. Postmarketing Requirements and Commitments

As mentioned in the pre-NDA meeting for REZENOPY, the high naloxone dose contained in REZENOPY could precipitate withdrawal in opioid-dependent users of REZENOPY. Based on cross-study comparison of naloxone exposure between REZENOPY and a similar product, KLOXXADO 8mg Nasal spray (NDA 212045), both products provide a similar level of naloxone exposure. We examined post-marketing reports for KLOXXADO 8mg nasal spray and found multiple cases of precipitated withdrawal since it was approved. This further strengthens our suspicions that REZENOPY to would precipitate withdrawal in opioid-dependent persons. We recommend that Summit Biosciences be required to perform a postmarketing study on the incidence of precipitated withdrawal, including noncardiogeneic pulmonary edema among users of their product, stratified by presence or absence of opioid-dependence.

For completeness, there is no concern at this time for abuse or withdrawal from naloxone, and there are no concerns about off-label use that would require a REMS or similar post-marketing surveillance.

13. Appendices

13.1. References

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13.2. Financial Disclosure

The Applicant has completed the Financial Disclosure form as detailed below (Table 3) (Statement 1 of FDA Form 3454). All of the investigators listed below participated in Study Protocol 11875901 (Table 11).

Table 11. List of Investigators with No Reportable Financial Disclosure [29]

Name
(b) (6)

Covered Clinical Study (Name and/or Number): 11875901

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)

Total number of investigators identified: 8		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 8		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
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: NA Significant payments of other sorts: NA Proprietary interest in the product tested held by investigator: NA Significant equity interest held by investigator in S Sponsor of covered study: NA		
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) NA		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Compliance with Good Clinical Practices

Applicant stated that all studies were conducted in accordance with Guidelines for Good Clinical Practice and the Declaration of Helsinki and in compliance with the United States Food and Drug Administration regulations for informed consent and protection of patient rights as described in 21 Code of Federal Regulations Parts 50, 56, and 312. performed in compliance with Good Clinical Practices (GCP), including the archiving of essential documents, the International Conference on Harmonization (ICH) Guidelines, and is consistent with the ethical principles of the Declaration of Helsinki. The Applicant also states that the studies were approved by Institutional Review Boards/Independent Ethics Committees and that all studies underwent regular monitoring by the Applicant or an appointed Contract Research

Organization (b) (4)

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
01/24/2024 04:11:23 PM
Primary clinical review for Summit, Rezenopy product, NDA 215487

CELIA J WINCHELL
01/24/2024 04:14:48 PM