CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215487Orig1s000

SUMMARY REVIEW

Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Cross-Discipline Team Leader and Division Summary Review

Date	April 19, 2024
From	Celia Winchell, MD (Cross Discipline Team Leader) Rigoberto Roca, MD (Division Director)
Subject	Summary and Cross-Discipline Team Leader Review
NDA Number	NDA 215487
Applicant	Summit Biosciences
Date of Submission	March 24, 2023
PDUFA Goal Date	January 24, 2024
Proprietary Name	REZENOPY
Established or Proper Name	Naloxone hydrochloride
Dosage Form(s)	Nasal spray, 10 mg/dose, two blister-packed single-spray devices per carton
Indication	1. Indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression in adult and pediatric patients. 2. Intended for immediate administration as emergency therapy in settings where opioids may be present. not a substitute for emergency medical care.
Recommendation on Regulatory Action	*Approval*

Material Reviewed/Consulted OND Action Package, including:	
DAAP Clinical Review	Zachary Dezman, M.D.
OSE / OMEPRM / DMEPA 1	Murewa Oguntimein, PhD; Jason Flint, MBA (Human Factors) Damon Birkemeier, PharmD; Valerie A. Vaughan, PharmD (Labeling)
OPDP	L. Sheneé Toombs, PharmD; Sam Skariah, PharmD, RAC
DPT-N	Carlic K. Huynh, PhD; Newton H. Woo, PhD; Daniel Mellon, PhD
OPQ Review	Katharine Duncan, PhD; Donna Christner, PhD; Renishkumar Delvadia, PhD; Valerie Amspacher, PharmD; Julia Pinto, PhD; Vicky He; Shu-Wei Yang, PhD; Renee A Marcasisin, PhD; Elizabeth Bearr, PhD
Clinical Pharmacology Review	Wei Qiu, PhD, Yun Xu, PhD
CDRH/OPEQ/OHT3/DHT3C	Dunya Karimi; Courtney Evans, CAPT Alan Stevens

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

1. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Overdose is a major problem in the United States, being the cause of more than 100,000 unintentional deaths in 2021. 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 (b) (4) 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, similar to that of other naloxone-containing products approved for community use.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. 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 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 exposed in utero, withdrawal upon abrupt discontinuation of exposure at birth 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-induced respiratory 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 anticipate REZENOPY to provide similar serum levels of naloxone in patients and so we expect REZENOPY to precipitate withdrawal in opioid-dependent persons.

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, the clinical review team has recommended that REZENOPY be approved with a clinical PMRs to address these questions.

After additional internal discussions, it was agreed that, although it is important to obtain this information, it was also noted that a PMR may not be the only way to obtain this information. The Division will continue to explore other options, including researching emerging data streams. Therefore, at this time, the application will be approved without the clinical PMRs, while additional internal discussions continue

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. • Around 80% of these drug overdose deaths involved an opioid. • From 2001 to 2021, almost 630,000 people have died from a drug overdose. • On average, 230 Americans die every day from opioid overdoses.	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. • Narcan Nasal Spray (NNS) and Revive, both 4 mg IN (intranasal) are approved for non-prescription use. • 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 formerly distributed unapproved kits comprising parenteral naloxone packaged with a syringe and nasal atomizer. • Anecdotally, some overdoses have required multiple administrations 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 nasal atomizer as part of a kit. The latter provides a lower concentration, higher volume dose that results in a lower systemic exposure.	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. 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.
Benefit	• The efficacy of this product for community use is supported by a scientific bridge between the proposed product and Narcan (naloxone hydrochloride injection 0.4 mg/ml) 2 mg IM (NDA 016636) through pharmacokinetic (PK) study 11875901 comparing REZENOPY to an approved generic version of Narcan (ANDA	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

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	070256). • 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.	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 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. • 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	The Applicant, like those marketing similar high-dose naloxone products, 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. Approval of this product would provide an additional approved naloxone product, while internal discussions continue as to the best way to obtain this information.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	comparative safety data between this product and other naloxone products to inform prescribing decisions when choosing product for opioid reversal	

2. Background

2.1 Product Information

This is the first review cycle for REZENOPY, a new drug application (NDA) under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. REZENOPY is a naloxone hydrochloride nasal spray delivering 10 mg/ (b) (4) ml, and the application relies upon the agency's previous findings of safety and efficacy of NARCAN injectable product (NDA 16636). NARCAN was approved in 1971; the NDA has since been withdrawn (not for reasons of safety or efficacy) and an approved generic, ANDA 070256, was used as the comparator in bioavailability studies.

The proposed device is supplied by (b) (4) (DMF# (b) (4)) nasal spray device, which has been used in multiple commercial drug products approved by FDA, including other naloxone nasal sprays.

Container Closure/Device Constituent	 Product Carton Individual Nasal Device in Blister Pack (sealed and opened) (b) (4) Intranasal Device
Intended Users	Lay users (adults and adolescents' users), first responders
Intended Use Environment	Public, domestic, and emergency environments

Source: Human Factors Review

REZENOPY is intended for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. It is designed to be suitable for use in non-healthcare settings by laypersons to rescue patients experiencing the

life-threatening effects of an accidental or intentional opioid overdose while awaiting emergency medical attention. The Applicant conducted the clinical development program under IND 141634.

The Applicant submitted a request for fast-track designation in 2019. The FDA recognizes opioid overdose to be a serious public health problem, but there are multiple approved products that are effective in reversing opioid overdose. Summit 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.

The Applicant also requested Priority Review with the submission of this NDA, indicating there is a need for high-dose products to treat high-potency opioids like fentanyl, but did not provide any data to support the position that their product offers a significant improvement over the existing products. Priority review was denied.

The Applicant is also relying on published literature to support the safety of the proposed dose[1].

2.2 Therapeutic Context: Opioid Overdose and Naloxone

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, 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. 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. It is also sold as a powder either mixed with, or passed off as, heroin. The potency and uneven characteristics of street preparations of illicit fentanyl led to rapid increases in fatal and non-fatal opioid overdoses, leading to the largest drop in US life expectancy before the COVID pandemic. Today much of the illicit opioids sold contain fentanyl or are mostly fentanyl and nearly all opioid fatal and nonfatal opioid overdoses

[1] Springborg AD, Jensen EK, Kreilgaard M, Petersen MA, Papathanasiou T, Lund TM, Taylor BK, Werner MU. High-dose naloxone: Effects by late administration on pain and hyperalgesia following a human heat injury model. A randomized, double-blind, placebo-controlled, crossover trial with an enriched enrollment design. PLoS One. 2020 Nov 12;15(11):e0242169. doi: 10.1371/journal.pone.0242169

involve fentanyl. Fentanyl is increasingly being mixed with stimulants like cocaine and methamphetamine or sedating agents like xylazine and nitazines.

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 to 3 minutes) after the development of symptoms. Co-prescribing naloxone when prescribing opioids is considered a best practice, and increased access to naloxone may prevent opioid overdose deaths.

As potent synthetic opioids (e.g., fentanyl) entered the illicit drug supply, some stakeholders called for the development of higher-dose products to address a perceived inadequacy of customary doses of naloxone. However, in the last several years, as naloxone devices specifically developed for administration by lay bystanders became available (e.g., Narcan 4 mg nasal spray, initially by prescription and then over-the-counter), data began to accumulate suggesting that the conventional doses of naloxone were adequate. Dr. Dezman's clinical review provides specific examples from recent data on trends in naloxone administration.

Conversely, patient advocates and harm reduction groups expressed concern over the risk of precipitated withdrawal associated with the use of high-dose naloxone in opioid-dependent individuals. The Reagan-Udall Foundation for the FDA convened a meeting in March 2023 to discuss priorities in drug development to address opioid overdose, and presentations at this meeting highlighted the uncertainties. Pharmacokinetic modeling predicts that, in some circumstances, higher doses could increase the proportion of overdose victims who survive. However, the risks of precipitated withdrawal, including life-threatening pulmonary edema, as well as less medically serious, but common complications, would need to be weighed against any incremental benefit.

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. A generic version of nalmefene injection was recently approved,

and subsequently a nalmefene nasal spray was approved.

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 (NDA 212045)	2021	8mg nasal spray	Onset of action is apparent within two minutes	
Zimhi (NDA 212854)	2021	5mg prefilled syringe IM/SC		
Naloxone NAI (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	
Other Related Treatments				
Nalmefene hydrochloride (NDA 20459)	1995	IV:0.5 to 2.0 mg IM/SC: 1 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

3. Product Quality

The drug substance, drug product, process/facilities, and microbiology review teams all recommend approval.

4. Center for Devices and Radiological Health (CDRH)

The CDRH team noted a concern with one specification for the device; however, the specification for the finished drug product is adequate so this concern is addressed.

5. Nonclinical Pharmacology/Toxicology

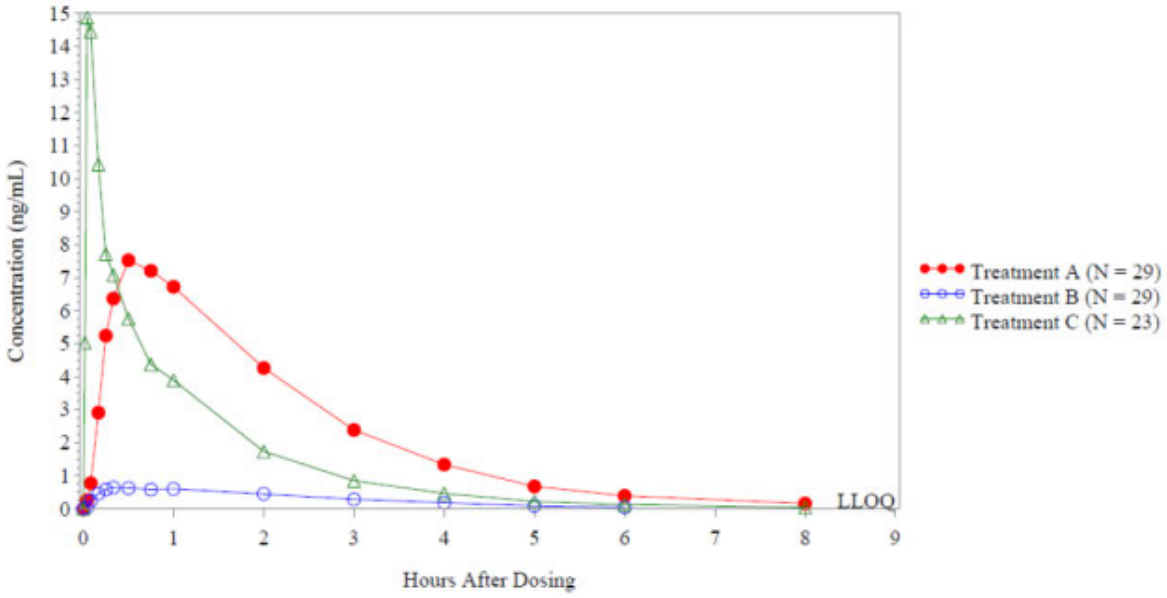
The Applicant submitted two intranasal repeat-dose toxicity studies in rats and dogs that qualified the safety of the higher naloxone concentration and higher maximum daily dose in comparison to the reference product. The drug product did not contain any novel excipients and there are no safety concerns with the container closure system. Drug substance and drug product impurities, elemental impurities, and (b) (4) levels were within respective thresholds with the exception of one drug product degradant, (b) (4) which exceeded ICH Q3B(R2) qualification thresholds. To qualify the safety of the proposed specification of this degradant at (b) (4)%, the Applicant submitted a negative computational toxicology evaluation that assessed the mutagenic potential of the compound and submitted a 28-day intranasal repeat-dose toxicity rat study that evaluated a naloxone formulation that contained different degradants that included (b) (4)% of (b) (4). However, the concentration used in the study was not appropriate to provide non-clinical support for the local safety of this degradant. Nonetheless, the pharmacology/toxicology review team recommended approval given the lack of safety signal in the 28-day study and the fact that the product is for acute use in a life-threatening situation. The team recommended further post-approval characterization of the (b) (4)

6. Clinical Pharmacology

The application contains a comparative bioavailability study, Study 11875901, that compares the proposed product to Hospira Inc's generic naloxone HCl injection 0.4 mg/ml (ANDA 070256) because the referenced drug, Narcan injection (NDA 016636), is no longer marketed. Two comparator arms, 0.4 mg IM and 2 mg IV bolus, were used. Thirty healthy subjects were enrolled in the three-period crossover design. All 30 completed Treatment A (test article) and Treatment B (0.4 mg IM dose) and 23 completed Treatment C (2 mg IV dose).

The results are illustrated in this figure from Dr. Wei Qiu's review:

Figure 1 Mean Plasma Concentration Time Profiles of Naloxone Following a Single Dose of One IN Spray of Naloxone HCl Nasal Spray 10 mg (Treatment A, Test) versus 0.4 mg IM Injection (Treatment B, Reference) and 2 mg IV Injection (Treatment C, Reference) from 0-8 hours (Study 11875901)



Mean concentration values below LLOQ (<0.020) in the terminal phase are not plotted

Treatment A – 1 × 110 µL actuation of Naloxone Hydrochloride Nasal Spray, 10 mg/spray (Summit Biosciences Inc.) – 10 mg total dose
Treatment B – 1 × 1.0 mL IM injection of Naloxone Hydrochloride Injection, 0.4 mg/mL (Hospira, Inc.) – 0.4 mg total dose
Treatment C – 1 × 5.0 mL IV bolus of Naloxone Hydrochloride Injection, 0.4 mg/mL (Hospira, Inc.) – 2.0 mg total dose
Source: Study report 11875901 Figure 11-1

Dr. Qiu noted that:
"Study results showed that a single 10 mg IN dose of the proposed Naloxone HCl nasal spray 10 mg showed higher naloxone plasma concentrations at all post-dose timepoints including early absorption phase, greater Cmax, AUC0-t and AUC0-inf values than a single dose of 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 injection, the Applicant's proposed reliance on effectiveness findings of Narcan injectable (NDA 016636) is warranted. A single 10 mg IN dose of the proposed Naloxone HCl nasal spray 10 mg showed 49% lower Cmax than a single 2 mg IV injection. The AUC0-t and AUC0-inf values for a single 10 mg IN dose were 58% and 60% greater, respectively, than that for a single 2 mg IV injection. The mean absolute bioavailability of naloxone for IN dosing based on AUC0-inf was 34% relative to IV dosing."

Because the AUC of the proposed product is higher than Naloxone 2 mg IV injection, Dr. Qiu compared the exposures associated with a single dose of the proposed product (10 mg IN) to two approved products Kloxxado™ nasal spray 8 mg and Zimhi™ IM/SC injection 5 mg, based on cross-study comparison. A single dose of the proposed product (10 mg IN) appears to have lower Cmax and similar AUC0- inf to Kloxxado™ nasal spray 8 mg, and lower Cmax and AUC0-inf than Zimhi™ IM/SC injection 5 mg, highlighting the potential for user

confusion when comparing nominal doses. The table below from Dr. Qiu's review compares the three products.

Table 4 Cross-study Comparison of Mean (CV%) Naloxone PK Parameters

PK Parameter	NDA 215487 Naloxone HCl Nasal Spray 10 mg (from Study 11875901)	NDA 212045 Kloxxado Nasal Spray 8 mg		NDA 212854 Zimhi 5 mg IM/SC (from Study APC6000-03)**
		Study I*	Study II*	
Cmax (ng/mL)	9.11 (35.45)	12.3 (55.4)	12.8 (37)	17.2 (44)
AUC0-inf (ng.h/mL)	19.52 (24.78)	16.7 (31.9)	19.0 (32.7)	26.6 (21.2)

*Kloxxado package insert; **Zimhi package insert

Language was added to labeling to address this concern.

7. Clinical Microbiology

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

8. Clinical/Statistical-Efficacy

No new clinical efficacy data were included in this submission. The Applicant plans to rely on the agency's prior findings of efficacy from the reference product, Narcan (naloxone hydrochloride, NDA 16636), which is approved for known or suspected opioid overdose, to establish the efficacy of the proposed product. The PK data provided in the application established the scientific bridge between the proposed product and reference drug Narcan injection, thus supporting the efficacy of the proposed product ZIMHI for the proposed indication.

9. Safety

The application rests on the systemic safety of the reference product, literature supporting safety of higher exposures of naloxone, and on the results of the adverse event assessments from the PK bridging study. 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). Subjects underwent a functional smell test, the University of Pennsylvania Smell Identification Test Assessment, and nasal mucosa examinations. The findings were limited to mild erythema/irritation in some participants and did not raise any new concerns.

10. Advisory Committee Meeting

An Advisory Committee (AC) meeting was not held to discuss this product because there were no issues that required presentation or discussion at an advisory committee meeting.

11. Pediatrics

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. Per agreed iPSP, the product is considered appropriate for all ages.

12. Other Relevant Regulatory Issues

Inspections
The Office of Study Integrity and Surveillance (OSIS) declined to conduct an on-site inspection for the clinical and analytical sites based on inspection history.

13. Labeling

Labeling was consistent with similar products and changes made to the Applicant's proposed labeling were minor. One difference from other products is the recommendation that only two doses of the product should be given. This reflects the recommendation in Narcan labeling to consider etiologies other than opioid overdose after giving 10 mg im/iv.

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.

14. Postmarketing Recommendations

Use of naloxone may precipitate opioid withdrawal in patients who are opioid dependent. 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. The proposed dose of naloxone in the Rezenopy product is 10 mg (delivered at a concentration of (b) (4) 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. 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.

Although this risk is likely acceptable in the setting of increased survival rates, growing evidence suggests that there may not be a survival advantage of higher doses vs more typical doses (e.g., 4 mg IN).

After additional internal discussions, it was agreed that, although it is important to obtain this information, it was also noted that a PMR may not be the only way to obtain this information. The Division will continue to explore other options, including researching emerging data streams. Therefore, at this time, the application will be approved without the clinical PMRs, while additional internal discussions continue.

The nonclinical PMRs will be required as per above.

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/s/

RIGOBERTO A ROCA
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