Cross-Discipline Team Leader Review

Date	(electronic stamp)
From	Joshua M. Lloyd, MD
Subject	Cross-Discipline Team Leader Review
NDA	208411
Applicant	Adapt Pharma, Inc.
Date of Submission	July 20, 2015
PDUFA Goal Date	January 20, 2016
Proprietary Name / Established (USAN) names	Narcan nasal spray / Naloxone hydrochloride
Dosage forms / Strength	Intranasal spray / 40 mg/ml
Proposed Indication(s)	1. Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression 2. Intended for immediate administration as emergency therapy in settings where opioids may be present 3. Not a substitute for emergency medical care
Recommended:	Approval

1. Introduction

Adapt Pharma, Inc. ("Applicant"), submitted this new drug application (NDA) for Narcan (naloxone hydrochloride) nasal spray for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. Narcan nasal spray is a single-use, drug-device combination product intended for use in the community. It is designed 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 114,704 in collaboration with the National Institutes for Drug Abuse (NIDA) and proposes to market Narcan nasal spray in one strength (i.e., 40 mg/ml) that delivers 0.1 ml (4 mg) in a single intranasal spray and is for use in patients of all ages, both adult and pediatric. The investigational new drug (IND) application was submitted by Lightlake Therapeutics, Inc. (also referred to as the "Applicant" throughout this review), on July 18, 2014, and the ownership of the IND was transferred to Adapt Pharma, Inc., on December 16, 2014. This IND was granted fast track designation on January 27, 2015, for the proposed indication.

The Applicant submitted bioavailability data to cross-reference their NDA for Narcan[1] (naloxone hydrochloride; NDA 16636), an injectable formulation of naloxone. Narcan was approved April 13, 1971, and is available for subcutaneous, intramuscular, and intravenous use

[1] The Narcan NDA was transferred from Endo Pharmaceuticals, Inc., to the Applicant effective May 26, 2015

for the complete or partial reversal of opioid depression, including respiratory depression, induced by natural and synthetic opioids, including propoxyphene, methadone and certain mixed agonist-antagonist analgesics: nalbuphine, pentazocine, butorphanol, and cyclazocine. Narcan is also indicated for diagnosis of suspected or known acute opioid overdosage. The indication and usage section of the labeling further states that Narcan may be useful as an adjunctive agent to increase blood pressure in the management of septic shock. 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). Therefore, the Applicant used a generic naloxone product manufactured by (b) (4), in the pivotal relative bioavailability study to create a scientific bridge to their NDA for Narcan to establish the safety and efficacy of Narcan nasal spray for the proposed indication. Although the Applicant owns the Narcan NDA, this NDA for Narcan nasal spray is relying on the published literature to support the safety and efficacy of the product in the pediatric population and, therefore, was submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act.

This NDA was accepted for rolling review and was granted priority review status upon submission of the final sections of the application reflecting the importance of this product from the public health perspective, as, currently, there are no approved intranasal naloxone products intended for use in the community.

Both Narcan nasal spray and Narcan contain naloxone, and the proposed population for Narcan nasal spray (i.e., known or suspected opioid overdose) is encompassed by the indicated population for Narcan. However, several important differences exist between Narcan nasal spray and Narcan. Narcan nasal spray represents a change in the route of administration from intravenous (IV), intramuscular (IM), or subcutaneous (SC) injection to intranasal (IN). Therefore, the Applicant evaluated the potential for local toxicity in the relative bioavailability studies. Narcan nasal spray also represents a change in the intended setting. Narcan is generally used in healthcare settings by healthcare professionals, whereas Narcan nasal spray is intended to be used in a community setting by laypersons. The Applicant submitted a human factors evaluation to support use in this different setting. Lastly, the proposed dosing for Narcan nasal spray represents a change in dosing regimen for pediatric patients. Narcan labeling recommends weight-based dosing in pediatric patients, whereas Narcan nasal spray contains a fixed dose of naloxone. This review will explore these issues in greater detail, in addition to confirming that Narcan nasal spray achieves comparable or greater systemic exposures to naloxone as compared to Narcan, particularly in the period immediately after drug administration, as this represents a critical period in which the patient's opioid overdose must be reversed to avoid irreversible injury or death.

2. Background

Accidental or intentional overdose and death associated with the use, misuse, and abuse of illicit and/or prescription opioids is a public health crisis in the United States. Opioid overdose can occur in a patient prescribed an opioid medication or in household contacts of the patient and in people who misuse or abuse opioids. Opioid overdose is characterized by life-threatening respiratory and central nervous system (CNS) depression that, if not immediately

treated, may lead to significant morbidity and mortality due to irreversible hypoxic injury. Naloxone is a nonselective opioid receptor antagonist, with the greatest affinity for the mu-opioid receptor that, if immediately administered, can reverse these life-threatening effects in an opioid overdose and prevent hypoxia-associated injury and death. However, there are limitations to the use of naloxone in this setting. The effects of some opioids, such as buprenorphine, may be difficult to antagonize. Larger doses of antagonist may be necessary than are available and the opioid overdose must be reversed before hypoxia results in irreversible injury. Also, it is important to realize that the duration of antagonists such as naloxone are generally shorter than the duration of action of most opioids. Therefore, even when an antagonist is available, it is not a substitute for seeking emergency medical help.

The US Department of Health and Human Services (HHS) has made addressing this public health crisis a top priority and has outlined a targeted initiative to do so that includes providing training and educational resources, increasing the use of naloxone, and expanding the use of medication-assisted treatment. The availability of an approved intranasal naloxone product intended for use in the community would contribute towards meeting these goals and is of great importance from a public health perspective.

Generic versions of Narcan are currently available; the approved Narcan labeling recommends initial doses of 0.4 mg to 2 mg for known or suspected opioid overdose in adults with repeat doses every two to three minutes up to a total of 10 mg. In children, initial doses of 0.01 mg/kg with repeat doses of 0.1 mg/kg are recommended. Additionally, Evzio, an injectable naloxone product that delivers 0.4 mg of naloxone HCl intramuscularly or subcutaneously intended for use in the community, was approved on April 3, 2014, and is available.

Naloxone has also been increasingly available in the community through a variety of public health programs, which have generally supplied an injectable formulation of naloxone (i.e., either a vial or syringe) along with a needle or mucosal atomizer device (MAD) to provide access to this life-saving medicine. The MAD allows for the injectable formulation to be delivered as an intranasal spray (currently, an off-label route of administration), typically from an injectable solution containing 2 mg of naloxone HCl in 2 ml of solution. The bioavailability of this off-label intranasal route of administration using an MAD may be less than the exposure following approved routes of administration for naloxone, based on reports in the literature, but there are also reports in the literature and from addiction treatment programs that naloxone administered this way has been successful in reversing opioid overdose. Therefore, the minimum effective dose of naloxone is unclear.

Evaluating the efficacy of a new formulation or route of administration of naloxone to establish an effective dose range presents significant logistical and ethical challenges, as already-approved naloxone-containing products are available for treatment of this life-threatening condition, which, if not immediately treated, could result in substantial morbidity and mortality. The Division has determined that it would not be ethical to deliver an experimental naloxone (i.e., through a novel formulation or via a novel route of administration) to an actual patient suffering from opioid overdose and potentially delay life-saving treatment with an already-approved naloxone product in the context of a clinical

efficacy study. Furthermore, intentionally administering enough opioid to actually create a clinically meaningful opioid overdose is not ethical.

Therefore, the Division has outlined a path for the clinical development of novel naloxone products, including those intended to be used in the community, which consists of demonstrating comparable or greater systemic exposure to naloxone with the new naloxone product, particularly in the early critical period after drug administration. This relative bioavailability study would be conducted in healthy volunteers, thus obviating the need to conduct a study in patients suffering from an opioid overdose. The necessary clinical development program was discussed with the Applicant at a Pre-IND meeting held May 24, 2012. It was further discussed that, although the proposed product represents a new route of administration, nonclinical studies to evaluate local toxicity would not be required given the clinical experience with intranasal naloxone, lack of any novel excipients, the acute use of the drug product, and the potentially life-saving indication, provided that the Applicant includes adequate clinical monitoring of local tissues in the relative bioavailability studies. A Pre-NDA meeting was held March 27, 2015.

3. CMC/Device

The Quality Assessment review consisted of the following disciplines: Drug Substance and Drug Product (Venkat Pavuluri, PhD), Process (Christina Capacci-Daniel, PhD and Edwin Jao, PhD), Microbiology (Christina Capacci-Daniel, PhD, and Erika Pfeiler, PhD), Facility (Christina Capacci-Daniel PhD and Grace McNally, PhD), Regulatory Business Process Manager (Steve Kinsley), Application Technical Lead (Julia Pinto, PhD), and CDRH OC Combination Products (Juandria Williams). CDRH was also consulted (Ryan McGowan and Rick Chapman). The information for the naloxone drug substance is referenced in DMF (b) (4) for which (b) (4) is the holder, and the information for the nasal spray device is referenced in DMF (b) (4) for which (b) (4) is the holder. Both DMFs were found to be adequate. The quality review team recommended approval for this NDA. The following is a summary of the quality review.

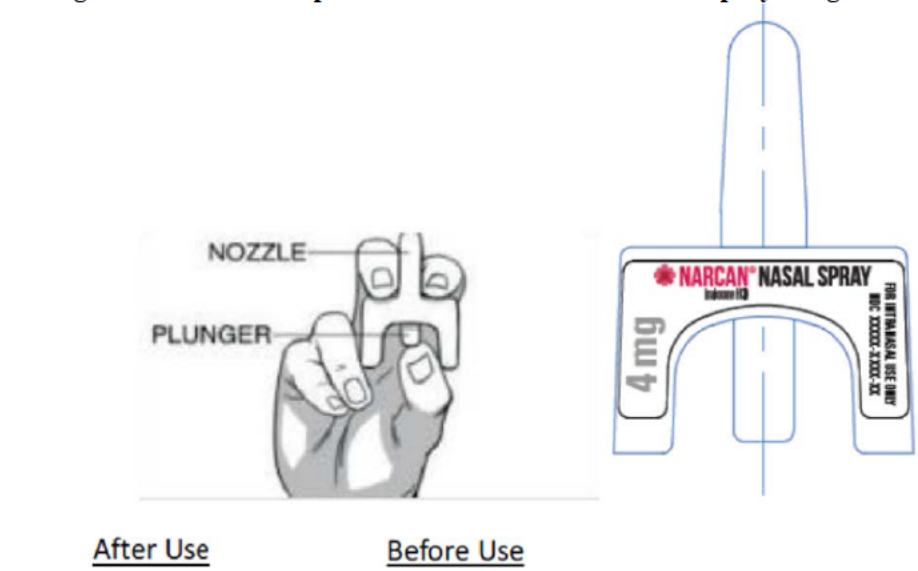
The quality review team noted that:

> The naloxone API is supplied by (b) (4). The drug product is formulated in (b) (4) comprising the following excipients: sodium chloride, (b) (4), and benzalkonium chloride, in a concentration of 40 mg/ml. The container closure system is a glass vial with a (b) (4) stopper, which is then encased within a nasal actuator and container holder. The nasal spray device is by (b) (4) under DMF (b) (4), and has been reviewed by CDRH and OPQ, for use with the naloxone drug product. Each unit dose device, formulated to deliver one dose of naloxone, is placed within a blister package. Two units or blister packages are then stored per carton. Adequate data to assess the device delivery of the drug product and to assure the identity, strength, purity, and quality of the drug product is provided. The drug product is granted an expiry of 24 months, when stored at room

temperature. Further, the Office of Process and Facilities, has made an overall recommendation of adequate for all facilities related to this application.

Dr. Pavuluri noted that "the drug substance specifications include both USP and EP monograph specified tests and acceptance criteria (wherever the methods and acceptance criteria in the two compendia are different)," and found this to be adequate. He further noted that "[t]he drug substance complies with the USP monograph and USP <467> Residual Solvents" and found this to be acceptable. The drug product solution is presented in a 125 µL (0.125 mL) (b) (4) glass vial (fulfills the requirements of USP) closed with a (b) (4) plunger (container closure system), which in turn is mounted into a unit-dose non-pressurized nasal spray device and container holder assembly. When the device is actuated (b) (4) and deliver a 100 µL (0.1 ml) spray of the naloxone intranasal solution. There is no priming required before use and that the device can be used in any orientation.

Figure 1. Schematic Representations of the Narcan Nasal Spray Drug Product



(b) (4)

Dr. Pavuluri found the drug product specifications to be adequate. Dr. Pavuluri noted that "[a]vailable stability data support [the] proposed expiration dating of 24 months from the date of manufacture of the drug product. [The Applicant] also commits to conduct stability studies on [an] additional three validation/commercial batches of the drug product, 40 mg / mL (4 mg / spray) post approval, stored at accelerated and long-term storage conditions and on one batch annually at 25°C/60 % RH as long as the drug product is manufactured ," as is required.

Over the course of labeling negotiations, the Applicant proposed to allow excursions from the storage conditions to 4°C to 40°C. The CMC team held a teleconference with the Applicant on November, 16, 2015, and found the Applicant's proposal acceptable, based on existing preliminary data, provided that the Applicant agree to a postmarketing commitment to test drug product batches on stability through the course of expiry at the excursion conditions of 4°C to 40°C.

Dr. Capacci-Daniel noted that the manufacturing process controls are adequate and that "there are no significant, outstanding manufacturing process risks that prevent approval of this application" and that "there are no significant, outstanding microbiological risks that prevent approval of this application."

Dr. Capacci-Daniel found all of the facilities to be acceptable; however, she recommended post-approval inspections of several of the facilities (drug product and device).

The CDRH design review was conducted by Ryan McGowan, biomedical engineer. This review was conducted to evaluate the information submitted in this NDA that is intended to support the safety and functionality of the of the device constituent parts of the propose drug-device combination product. Mr. McGowan determined that "the device constituent parts of the combination product have been designed appropriately for the product's intended use and essential performance requirements have been verified with a reasonable degree of certainty at a time period shortly after manufacture." However, Mr. McGowan notes that the application contains inadequate information to demonstrate that the manufactured product is able to activate reliably after exposure to a variety of real-world conditions. There is a potential for under-dose or failure-to-dose events leading to undertreated, life-threatening CNS and respiratory depression as a consequence of a device failure under these conditions. Mr. McGowan recommends approval, from the device constituent design perspective, with postmarket requirements / commitments to verify combination product reliability. I concur with Mr. McGowan. Because this product should only be made available in a two-pack configuration, (b) (4) (refer to Section 12 below for additional discussion), of the impressive pharmacokinetic profile of this product, and of the importance of having an approved intranasal product available for use in the community, it is acceptable to approve this product with a postmarketing requirement to evaluate reliability of the product in a variety of conditions.

Mr. McGowan found the device-related product specifications acceptable with the exception of dose content uniformity, which allowed for relatively wide batch release specifications. This specification requires that (b) (4)

(b) (4)

. Given the relatively wide safety margin with naloxone, there is little concern for the upper limits of these release specifications, particularly since Narcan is labeled with dosing recommendations up to a total of 10 mg of naloxone. In general, the greatest concern would be for releasing a batch that might not deliver an adequate dose of naloxone in an immediately life-threatening situation. However, given the pharmacokinetic profile of this product (refer to Section 5 below), which achieves much higher systemic exposures to naloxone than the approved comparator dose of naloxone (i.e., 0.4 mg IM), the lower limit of these specifications are also acceptable. Additionally, Narcan nasal spray should only be made available in a two-pack configuration, (b) (4) (refer to Section 12 below for additional discussion), ensuring that a second dose is available in the event of an inadequate response.

Vicky Borders-Hemphill, PharmD, conducted the Division of Medication Error Prevention and Analysis (DMEPA) summative human factors study review. The human factors study was conducted in 53 participants who were representative of the intended user group, which consists of the general population of individuals 12 years and older and low literacy layusers who were untrained on the use of the device. Dr. Borders-Hemphill notes that "[o]f the 53 participants, 5 participants did not successfully complete one of the two critical tasks of inserting the nozzle into the nostril and pressing the plunger to release the dose in the nose:

- Two of the five participants administered the dose into the mouth of the overdose victim (mannequin). The Applicant's root cause analysis indicated that one of the participants used common sense rather than reading the IFU, and the other participant thought that they only saw one opening on the mannequin, which was the mouth. None of the root causes were attributed to the product design or labeling.
- Two of the five participants did not press the plunger completely to release the dose. The Applicant's root cause analysis showed that these participants were confused by the setting of simulation, and attributed these failures to study artifacts.
- One of the five participants expelled the product into the air prior to inserting it into the nasal opening. The participant indicated that he was trying to test how hard to push the plunger prior to administering to the mannequin.

Dr. Borders-Hemphill concluded that "the human factors validation study report provides sufficient data to conclude that the product can be used safely and effectively by intended users for intended uses and environments" and recommended revised labeling based on this study.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology review was conducted by Newton Woo, PhD, with secondary concurrence by R. Daniel Mellon, PhD. The following is a summary of the nonclinical pharmacology/toxicology review.

The Applicant did not submit any new nonclinical studies to support this NDA and none were required. Dr. Woo concluded that "[t]he Applicant has provided adequate data to support the

safety of the drug substance, drug product, and drug product formulation." There are no novel excipients in Narcan nasal spray. All of the excipients are listed in the FDA Inactive Ingredients Database (IID) and are present at lower levels than contained in several FDA-approved nasal drug products. The Applicant's specifications for the drug substance comply with the requirements of the United States Pharmacopeia (USP) and European Pharmacopoeia (EP) monographs, based on a maximum daily dose of two sprays (8 mg of naloxone hydrochloride). Dr. Woo found the impurity specifications acceptable, including the specification for (b) (4) (not detected). Dr. Woo noted that the drug product specifications for the degradants were acceptable, including for (b) (4) (not detected).

Regarding the container-closure system, the Applicant provided data on extractables; however, the Applicant did not conduct a leachables assessment. The Applicant noted that leachables will be evaluated in long-term stability samples. The nonclinical review team concluded that "the absence of leachables data does not preclude marketing approval for the following reasons: 1) the (b) (4) is used in other FDA-approved aqueous based nasal and injectable drug products; 2) analysis of water extracts did not identify any substances; 3) the Applicant has committed to monitor for leachables during stability; 4) most importantly, this product is indicated for an acute, single-use indication; and 5) the drug product is a potentially life-saving therapy." Dr. Woo recommends approval with a postmarketing commitment (PMC) to complete the leachables assessment in addition to providing comments to the Applicant on the leachables assessment (see Section 13 below). I concur with the conclusions reached by the nonclinical reviewer, including that there are no nonclinical issues that would preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review was conducted by Suresh Naraharisetti, PhD, with secondary concurrence by Yun Xu, PhD. According to the clinical pharmacology team, this NDA is acceptable. The following is a summary of the findings from the clinical pharmacology review.

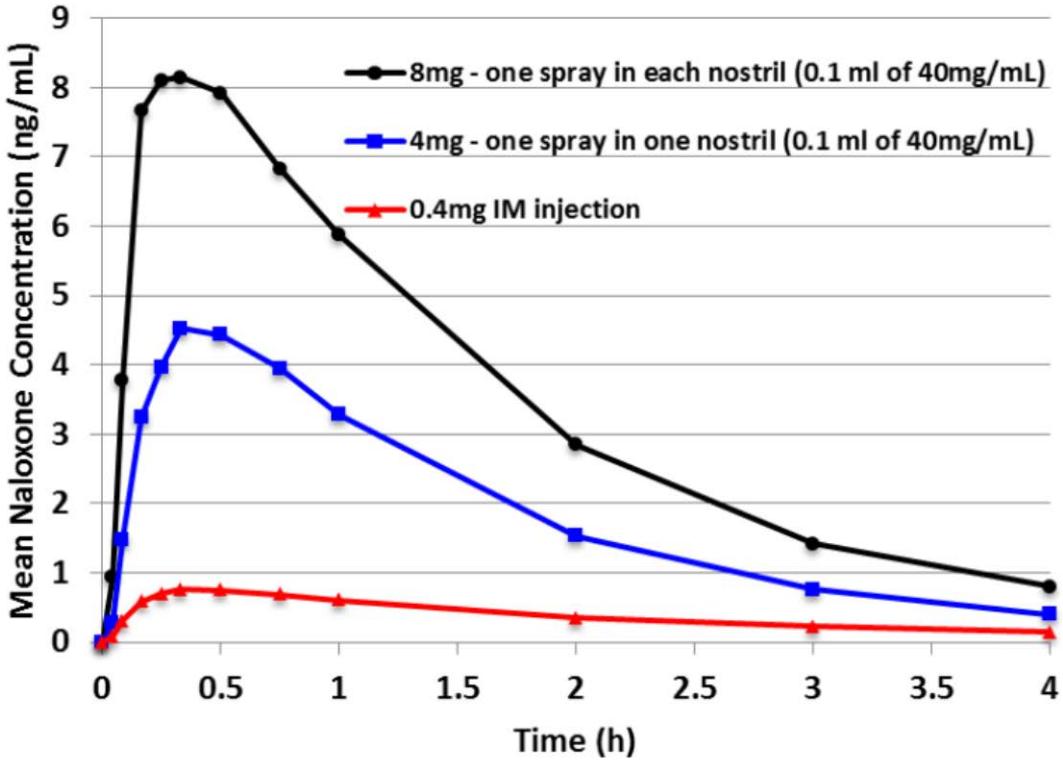
The Applicant conducted study Naloxone-Ph1a-002 (also referred to as study 002, in this review), a pivotal relative bioavailability study, in support of this application to establish a scientific bridge to their NDA for Narcan (NDA 16636) in order to establish the safety and efficacy of Narcan nasal spray.

Study 002 was an open-label, randomized, 5-period, 5-treatment, 5-sequence, crossover study conducted in 30 adult male and female healthy volunteers in an inpatient setting to evaluate the pharmacokinetics of two doses of Narcan nasal spray (i.e., 4 mg [one spray in one nostril] and 8 mg [one spray in each nostril) in comparison to an approved generic version of naloxone given intramuscularly (i.e., 0.4 mg). Two doses of another formulation of intranasal naloxone that are not the to-be-marketed formulation were also evaluated in this study. Subjects were assigned to one of five sequences, with six subjects planned in each sequence. A four-day washout period separated the treatments. Narcan nasal spray was administered using an (b) (4) single-dose device ((b) (4) with the subject in a fully supine position.

The left nostril was used for the 4-mg dose, and one spray was administered into each nostril for the 8-mg dose. Subjects were instructed not to breathe through the nose during administration of Narcan nasal spray and remained fully supine for approximately one hour post-dose. Intramuscular (IM) naloxone was administered as a 1-ml (i.e., 0.4 mg/ml) single injection into the gluteus maximus muscle using a 23-gauge needle.

Both one Narcan nasal spray in one nostril (i.e., 4-mg dose) and one Narcan nasal spray in each nostril (i.e., 8-mg dose) demonstrated much higher systemic exposure to naloxone, in terms of both AUC and Cmax values, in comparison to the reference product. The naloxone plasma concentration-time profiles are shown in Figure 2. Narcan nasal spray exhibited a 5.5 -fold higher Cmax and 4.7 –fold higher AUCt from one spray in one nostril (4 mg total dose) and 11 -fold higher Cmax and 8.9 -fold higher AUCt from one spray in each nostril (8 mg total dose) compared to the reference, a single dose of naloxone 0.4 mg given via IM injection.

Figure 2. Mean Plasma Concentration-Time Profiles of Naloxone from 0 to 4 hours Following Intranasal and Intramuscular Naloxone Administration to Healthy Subjects (N = 30; n=29 for each treatment)



Source: Dr. Naraharisetti's review, pg. 3

Both Narcan nasal spray doses demonstrated higher naloxone concentrations than the reference product at all time points, as described in Table 1.

Table 1. Comparison of Mean Naloxone Concentrations between Intramuscular Naloxone and Two Doses of Narcan Nasal Spray from 2.5 to 60 Minutes Post Dose.

Time post-dose after naloxone drug product administration (minutes)	Mean Concentration (ng/mL) (% CV) N=29			Fold higher naloxone concentration:	Fold higher naloxone concentration:
	Reference IM injection (0.4 mg)	Test One IN spray in one nostril (4mg)	Test One IN spray in each nostril (8mg)	One IN spray (4mg) Vs. IM injection (0.4 mg)	One IN spray in each nostril (8mg) Vs. IM injection (0.4mg)
2.5	0.079 (168)	0.28 (151)	0.93(131)	3.5	11.8
5	0.306 (108)	1.48 (117)	3.78 (105)	4.8	12.3
10	0.578 (55)	3.24 (67)	7.66 (68)	5.6	13.3
15	0.696 (46)	3.97 (56)	8.10 (44)	5.7	11.6
20	0.754 (36)	4.53 (50)	8.14 (31)	6.0	10.8
30	0.749 (25)	4.43 (43)	7.92 (25)	5.9	10.6
45	0.684 (25)	3.95 (41)	6.83 (24)	5.8	10.0
60	0.604 (24)	3.28 (37)	5.87 (23)	5.4	9.7

Source: Dr. Naraharisetti's review, pg. 4

Dr. Naraharisetti noted that "[t]he median naloxone Tmax after IN administration was not significantly different compared to the IM administration." However, the Tmax for the IM route exhibited relatively high variability (i.e., range of 0.08 to 2.05 hours) compared to the IN route. Further, the IN route had slightly longer half-life of 2.1 hours compared to 1.2 hours for IM route.

I concur with the conclusions reached by the clinical pharmacology reviewer. There are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not Applicable

7. Clinical/Statistical- Efficacy

No new clinical efficacy studies were submitted in support of this application. The Applicant is cross-referencing their NDA for Narcan (naloxone hydrochloride, NDA 16636), which is approved for known or suspected opioid overdose, to establish the safety and efficacy of the proposed product.

8. Safety

There were no new safety studies submitted in support of this application. The Applicant is cross-referencing their NDA for Narcan (naloxone hydrochloride; NDA 16636) to establish the safety and efficacy of the proposed product. The relative bioavailability study

demonstrated that the naloxone levels achieved with Narcan nasal spray are approximately five times that of 0.4 mg naloxone given IM. This exposure is likely to fall well within the doses recommended in the approved Narcan labeling, which recommends up to a 2 mg initial dose and repeating the dose every two to three minutes up to a total dose of 10 mg.

Naloxone is generally administered in the setting of opioids, and many of the adverse events described in approved Narcan labeling may be attributable to the reversal of the effects of the opioid. Narcan labeling describes the potential for precipitation of opioid withdrawal in opioid-tolerant patients characterized by 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. In the neonate, opioid withdrawal may also include convulsions, excessive crying, and hyperactive reflexes.

Narcan labeling also notes that, in the postoperative setting, there have been postmarketing reports of hypotension, hypertension, ventricular tachycardia and fibrillation, dyspnea, pulmonary edema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. These have occurred in patients most of whom had pre-existing cardiovascular disorders or received other drugs, which may have similar adverse cardiovascular effects. Excessive doses of naloxone hydrochloride in postoperative patients have resulted in significant reversal of analgesia and have caused agitation.

Because of the higher fixed dose of this product (i.e., 4 mg, which provide roughly 5 times the systemic exposure of a 0.4 mg IM dose), as compared to other naloxone-containing products intended for use in the community (e.g., Evzio), and the concern for precipitating adverse events related to the reversal of the opioid (i.e., in an inpatient postoperative population and in opioid-tolerant neonates), additional warning language is warranted to inform prescribers that:

> In monitored settings, in situations where it is preferable to avoid the abrupt precipitation of opioid withdrawal symptoms, consider use of an alternate naloxone-containing product that can be titrated to effect and, where applicable, dosed according to weight. These situations include the emergency treatment of opioid overdose, as manifested by respiratory and/or central nervous system depression in the immediate, inpatient postoperative period, particularly in patients with pre-existing cardiac disease, and in the postpartum period in neonates with known or suspected exposure to maternal opioid use.

Refer to the discussion under “Section 10 Pediatrics” regarding additionally addressing the potential for inducing neonatal opioid withdrawal.

Narcan labeling recommends dosing with naloxone for suspected opioid overdose with repeat dosing in adults up to 10 mg before questioning the diagnosis of opioid overdose. The risk of administering Narcan nasal spray to a patient who is not opioid-tolerant and whose symptoms are caused by an emergency other than opioid overdose is minimal given this wide safety margin. Because Narcan nasal spray can be administered in a very timely fashion and the

labeling recommends immediately seeking emergency medical attention after the first dose, it is unlikely that administering Narcan nasal spray to a patient suffering another emergency would significantly delay their definitive treatment.

The Applicant conducted two Phase 1 relative bioavailability studies in healthy volunteers, Naloxone-Ph1a-001 (also referred to as study 001, in this review) and Naloxone-Ph1a-002 (also referred to as study 002, in this review), comparing various intranasal (IN) formulations of naloxone to an approved injectable formulation of naloxone given via the intramuscular (IM) route. Because this NDA represents a change in the route of administration from the original Narcan NDA, the development program was required to evaluate the potential for local toxicity with this new route of administration. The Division determined that nonclinical studies to evaluate local toxicity would not be required, provided that the clinical studies included an assessment of nasal irritation (see discussion under Section 2). Both of the relative bioavailability studies collected safety data and included a formal assessment of nasal irritation. Only study 002 evaluated the to-be-marketed drug product.

Study 001

Study 001 was an open-label, randomized, 3-period, 3-treatment, 6-sequence, crossover, inpatient study conducted in 14 healthy adult volunteers to compare the pharmacokinetics of 2 doses of IN naloxone to IM naloxone and to evaluate safety. Subjects received a single 2 mg IN dose (one spray of 0.1 mL of a 10 mg/mL solution in each nostril), a single 4 mg IN dose (2 sprays of 0.1 mL of a 10mg/mL solution in each nostril), and a single 0.4 mg IM dose. The to-be-marketed formulation was not used in these studies, therefore, the results of this study are not emphasized in this review.

Study 002

Title: Phase 1, Pharmacokinetic Evaluation of Intranasal and Intramuscular Naloxone in Healthy Volunteers

Objectives:

- To determine the pharmacokinetics of four IN doses of naloxone compared to a 0.4 mg dose of IM naloxone to identify an appropriate IN dose that could achieve systemic exposure comparable to an approved parenteral dose
- To determine the pharmacokinetics of two different concentrations (20 mg/mL and 40 mg/mL) of IN naloxone.
- To determine the safety of IN naloxone, particularly with respect to nasal irritation (erythema, edema, and erosion).

Duration: 18 days inpatient; single-dose with 4-day washout between doses

Population: Healthy adult volunteers

- Inclusion criteria
  - Males and females 18 to 55 years of age
  - Provide written informed consent

- BMI ranging from 18 to 30 kg/m^2
- Adequate venous access
- No clinically significant concurrent medical conditions determined by medical history, physical examination, clinical laboratory examination, vital signs, and 12-lead ECG
- Agree to use a reliable double-barrier method of birth control from the start of screening until one week after completing the study. Oral contraceptives are prohibited.
- Agree not to ingest alcohol, drinks containing xanthine >500 mg/day (e.g., cola, coffee, tea, etc.), or grapefruit/grapefruit juice or participate in strenuous exercise 72 hours prior to admission through the last blood draw of the study

- Exclusion criteria
  - Any IN conditions including abnormal nasal anatomy, nasal symptoms (i.e., blocked and/or runny nose, nasal polyps, etc.), or having a product sprayed into the nasal cavity prior to drug administration
  - Taking prescribed or over-the-counter medications, dietary supplements, herbal products, vitamins, or recent use of opioid analgesics for pain relief (within 14 days of last use of any of these products)
  - Positive urine drug test for alcohol, opioids, cocaine, amphetamine, methamphetamine, benzodiazepines, THC, barbiturates, or methadone at screening or admission
  - Previous or current opioid, alcohol, or other drug dependence (excluding nicotine and caffeine), based on medical history
  - Subject consumes greater than 20 cigarettes per day on average, in the month prior to screening, or would be unable to abstain from smoking (or use of any nicotine-containing substance) for at least one hour prior to and 2 hours after naloxone dosing.
  - On standard 12-lead ECG, a QTcF interval >440 msec for males and >450 msec for females
  - Significant acute or chronic medical disease
  - A likely need for concomitant treatment medication during the study
  - Donated or received blood or underwent plasma or platelet apheresis within the 60 days prior to Day -1
  - Female who is pregnant, breast feeding, or plans to become pregnant during the study period or within one week after naloxone administration
  - Positive test for HBsAg, HCVAb, or HIVAb at screening
  - Current or recent (within 7 days prior to screening) upper respiratory tract infection

Treatment:

- Naloxone 0.4 mg IM administered into the gluteus maximus muscle
- Naloxone 2 mg IN, one 0.1 mL spray of the 20 mg/ml formulation in one nostril

- Naloxone 4 mg IN, one 0.1 mL spray of the 20 mg/ml formulation in each of two nostrils
- Narcan nasal spray 4 mg (one 4 mg spray in one nostril)
- Narcan nasal spray 8 mg (one 4 mg spray in each of two nostrils)

IN naloxone was delivered using an (b) (4) single-dose device ((b) (4)) with the subject in a fully supine position. The subject remained fully supine for approximately one hour post-dose. Subjects were instructed not to breathe through the nose during administration of the nasal spray into the nose. The 40 mg/ml formulation using the (b) (4) device is the to-be-marketed product (i.e., Narcan nasal spray).

Design: This was an open-label, randomized, single-center, inpatient, 5-period, 5-treatment, 5-sequence, crossover study. Safety assessments included adverse events, physical examination, nasal passage examination, vital signs, laboratory tests (clinical chemistry, hematology, coagulation, urinalysis, and serum pregnancy test [females]), and electrocardiogram (ECG) (Table 2). Nasal irritation was evaluated by a trained observer at the time points listed in Table 2 on the following scale:

- Nasal Irritation Scale
    - 1 - Inflamed mucosa, no bleeding
    - 2 - Minor bleeding which stops within 1 minute
    - 3 - Minor bleeding, taking 1-5 minutes to stop
    - 4 - Substantial bleeding for 4-60 minutes, does not require medical intervention
    - 5 - Ulcerated lesions, bleeding which requires medical intervention

Table 2. Study 002 Time and Events Schedule

N = 30 subjects	Screening	Admission/ Baseline	Period 1	Washout			Period 2	Washout			Period 3	Washout			Period 4	Washout			Period 5	Dis-charge	Follow-Up
Study Day(s)	-21 to -2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	+3 to 5 days
Informed Consent	X																				
Medical History	X	X																			
Demographics	X																				
Eligibility	X	X																			
Physical Examination	X	X																		X	X
Nasal Irritation Scoring	X	X	5X[a]	X			5X[a]	X			5X[a]	X			5X[a]	X			5X[a]	X	X
12-lead ECG	X	X	3X[b]				3X[b]				3X[b]				3X[b]				3X[b]	X	X
Vital Signs	X[c]	X[c]	5X[d]	X			5X[d]	X			5X[d]	X			5X[d]	X			5X[d]	X[c]	X[c]
Height, Weight, BMI	X																				
Clinical Chemistries & Coag[e]	X	X																		X	X
Hematology[f]	X	X																		X	X
Urinalysis[g]	X	X																		X	X
Serum Pregnancy test (females only)	X	X																			X
Drug/Alcohol Screen[h]	X	X																			X
HIV, Hepatitis B and C	X																				
PK Sample			16X				16X				16X				16X				16X		
AEs			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Con. meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomize		X																			
IP Admin[j]			X				X				X				X				X		
Meals[k]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

[a] Nasal passage examination pre-dose, 5 minutes, 30 minutes, 60 minutes, 4 hours, and 24 hours post-dose.
[b] 12-lead ECG approximately 60 minutes pre-dose, and 60 and 480 minutes post-dose.
[c] Sitting blood pressure, heart rate, respiration rate, and temperature.
[d] Sitting (5 minutes) blood pressure, heart rate, respiration rate, pre-dose and approximately 30 (supine position), 60, 120, and 480 minutes post-dose.
[e] Chemistry parameters include: total protein, albumin, blood urea nitrogen, creatinine, alkaline phosphatase, ALT, AST, total bilirubin, glucose, sodium, potassium, chloride, CO_2, total cholesterol, and calcium. Coagulation parameters include PT and aPTT.
[f] CBC with differentials and platelet count will be performed.
[g] Urinalysis includes: pH, specific gravity, blood, ketones, nitrites, glucose, bilirubin, leukocyte esterase, protein.
[h] Urine toxicology screen for alcohol, opioids, cocaine, amphetamine, methamphetamine, benzodiazepines, barbiturates, THC, or methadone.
[i] Pre-dose, 2.5, 5, 10, 15, 20, 30, 45, 60, 120, 180, 240, 300, 360, 480, and 720 minutes post-dose.
[j] Subjects will receive either a 0.4 mg IM dose of naloxone or a 2 mg (20 mg/mL), 4 mg (20 mg/mL), 4 mg (40 mg/mL) or a 8 mg (40 mg/mL) IN dose of naloxone depending upon the crossover randomization schedule.
[k] Subjects will fast from midnight the day before naloxone dosing until one hour after dosing. Water will be provided *ad libitum*.

Source: Applicant, protocol for study 002, pp. 58-9

Study drug redosing and discontinuation criteria:

- Redosing criteria: vital signs had to be within the following limits before study treatment was administered:
  - Systolic blood pressure: 140 mmHg or less and greater than 90 mmHg
  - Diastolic blood pressure: 90 mmHg or less and greater than 55 mmHg
  - Heart rate: 100 beats per minute (bpm) or less and greater than 40 bpm
  - Respiratory rate: 20 respirations per minute (rpm) or less and greater than 8 rpm

- Discontinuation criteria:
  - Systolic blood pressure >180, diastolic blood pressure >110, respiratory rate >24 or <8
  - Significant arrhythmia defined as >6 beats of supraventricular tachycardia or ≥3 beats of ventricular tachycardia (study drug was discontinued for a clinically significant abnormal ECG at any time after clinic admission)
  - QTcF interval >500 msec
  - Reported significant nausea or abdominal pain

- Reported significant chest pain or dyspnea
- Subject confusion, seizures or seizure like behavior, agitation or inability to cooperate
- Subject requests to leave the experiment or is unwilling or unable to cooperate in carrying out the assigned protocol procedures

Primary endpoint: Pharmacokinetic

Secondary endpoints: Adverse events, vital signs (heart rate, sitting blood pressure, and respiratory rate), ECG, clinical laboratory changes, and nasal irritation (erythema, edema, and erosion)

Results

This section will focus on the results of study 002 because this is the only study that employed the to-be-marketed formulation. However, the results from study 001 did not identify any specific safety concerns for those other formulations of IN naloxone (i.e., no deaths, serious adverse events, or discontinuations due to adverse events; limited number of mild adverse events, none of which suggest significant local toxicity with IN naloxone).

Extent of exposure:

In study 002, there were a total of 87 single exposures of Narcan nasal spray to a nostril (Table 3). Thirty unique subjects received Narcan nasal spray, including 28 subjects who received both 4 mg in one nostril and 4 mg in each nostril (8 mg total dose), 1 subject who received 4 mg in one nostril only (subject was discontinued due to an adverse event), and 1 subject who received 4 mg in each nostril (8 mg total dose) but not 4 mg in one nostril (discontinued at the subject's request), as summarized in Table 4. The extent of exposure and nasal irritation monitoring are adequate to evaluate the potential for local toxicity.

Table 3. Overall Extent of Exposure, Studies 001 and 002.

Doses	001[a,b] # of Subjects	002[a,b] # of Subjects	Total # of Exposures
2 mg IN Naloxone (one 0.1 mL spray of 20 mg/mL formulation in one nostril)	-	29	43 (2 mg IN)
2 mg IN Naloxone (one spray of 20 mg/mL formulation in each nostril)	14	-	
4 mg IN Naloxone (two sprays of 20 mg/mL formulation in each nostril)	14	-	72 (4 mg IN)
4 mg IN Naloxone (one 0.1 mL spray of 20 mg/mL formulation in each nostril)	-	29	
4 mg IN Naloxone (one 0.1 mL spray of 40 mg/mL formulation in one nostril)	-	29	
8 mg IN Naloxone (one 0.1 mL spray of 40 mg/mL formulation in each nostril)	-	29	29 (8 mg IN)
0.4 mg IM Naloxone (1 mL of a 0.4 mg/mL commercial formulation)	14	29	43 (0.4 mg IM)

[a] Study number begins with Naloxone-Ph1a
[b] There was a 4-day washout period between doses.

Source: Applicant, summary of clinical safety, pg. 7

Subject disposition:
Subject disposition is summarized in Table 4. Thirty subjects were randomized with 28 subjects receiving all 5 treatments. Two subjects discontinued prior to completing the inpatient treatment period (one discontinuation due to an adverse event and one discontinuation due to the subject's request). Twenty-six subjects completed the follow-up visit.

Table 4. Subject Disposition, Study 002.

	Naloxone Administration Sequence					
	I	**II**	**III**	**IV**	**V**	**Total**
Randomized Participants	6	6	6	6	6	30
Discharged for safety reasons	-	-	1(a)	-	-	1
Withdrew before completing	-	1(b)	-	-	-	1
Completers	6	5	5	6	6	28
Underwent follow- up	6	4	5	5	6	26

a: Participant 2028 received only Narcan nasal spray 4 mg in one nostril
b: Participant 2046 received all treatments except Narcan nasal spray 4 mg in one nostril
Source: Applicant, study 002 clinical study report, pg. 32

Demographics and baseline characteristics:
Subjects ranged in age from 22 to 55 years, and the study population was predominantly male and African American (Table 5).

Table 5. Demographics and Baseline Characteristics, Study 002.

Label	Total (N=30)
Age (years)	
Mean	35.9
Standard Deviation	9.6
Minimum	22.0
Maximum	55.0
Weight (kg)	
Mean	80.1
Standard Deviation	13.4
Minimum	56.0
Maximum	102.0
Height (cm)	
Mean	173.3
Standard Deviation	9.5
Minimum	157.0
Maximum	190.0
BMI (kg/m^2)	
Mean	26.5
Standard Deviation	2.6
Minimum	19.6
Maximum	29.8
Gender	
Female	12 (40.0%)
Male	18 (60.0%)
Race	
Black Or African American	23 (76.7%)
White	7 (23.3%)
Ethnicity	
Hispanic Or Latino	2 (6.7%)
Not Hispanic Or Latino	28 (93.3%)

Source: Applicant, study 002 clinical study report, pg. 32

Safety results:

All thirty subjects received at least one dose of study medication and were included in the safety population. There were no deaths or serious adverse events. One subject discontinued due to an adverse event (AE). This subject was a 26 year-old male with a history of smoking who was discontinued 4 days after receiving Narcan nasal spray 4 mg (one spray in one nostril). The subject had a blood pressure reading that did not meet redosing criteria and was discontinued by the investigator. The subject had the following blood pressure readings: 137/73 mmHg (screening), 144/73 mmHg (baseline), 138/81 mmHg (5 minutes pre-dose),

134/76 mmHg (30 minutes post-dose), 140/72 mmHg (60 minutes post-dose), 144/85 and 147/93 mmHg (120 minutes post-dose), 153/85 and 150/83 mmHg (480 minutes post-dose), and 147/87 and 160/84 mmHg (Day 2). Prior to the next scheduled dosing (Day 5), the subject's blood pressure was 141/80 and 144/86 mmHg. He was subsequently discontinued as he did not meet redosing criteria. This subject appears to have hypertensive issues at baseline, and it is unclear what role the study medication may have played in this case.

There were 27 adverse events (AEs) reported by 17 subjects. All AEs were considered mild in severity except for the one subject who experienced a moderate increase in blood pressure that lead to discontinuation. Table 6 lists all AEs that occurred in study 002. The list of AEs for a particular treatment includes all AEs recorded beginning with the administration of that treatment until the next treatment administration in the sequence. The Narcan nasal spray groups (40 mg/ml formulation) are highlighted in yellow in the table. AEs reported for subjects in the Narcan nasal spray groups included increased blood pressure, musculoskeletal pain, headache, and xeroderma, in addition to AEs indicative of local nasal irritation, including nasal dryness, nasal edema, nasal congestion, and nasal inflammation. The IM naloxone comparator arm reported nausea, dizziness, and headache.

Table 6. All Adverse Events, Treatment Period, Study 002.

MedDRA SOC	MedDRA PT	0.4 mg IM n=29	2 mg IN (one spray of 20 mg/ml) n=29	4 mg IN (two sprays of 20 mg/ml) n=29	4 mg IN (one spray of 40 mg/ml) n=29	8 mg IN (two sprays of 40 mg/ml) n=29
Cardiac and vascular investigations (excluding enzyme tests)	Blood pressure increased	0	0	0	1 (3.4%)	0
Gastrointestinal disorders	Constipation			1 (3.4%)		
	Nausea	1 (3.4%)				
	Toothache		1 (3.4%)			
Musculoskeletal and connective tissue disorders	Muscle spasms			1 (3.4%)		
	Musculoskeletal pain					1 (3.4%)
Nervous system disorders	Dizziness	1 (3.4%)				
	Headache	1 (3.4%)				1 (3.4%)
Respiratory, thoracic, and mediastinal disorders	Nasal dryness				1 (3.4%)	
	Nasal edema		4 (14%)		3 (10%)	1 (3.4%)
	Nasal congestion					1 (3.4%)
	Nasal inflammation		4 (14%)	1 (3.4%)	1 (3.4%)	
	Rhinalgia		1 (3.4%)			
Skin and subcutaneous tissue disorders	Xeroderma				1 (3.4%)	

Source: Reviewer, adapted from Applicant's Table 7, summary of clinical safety, pg. 14

The results of the nasal irritation exam are detailed in Table 7. The majority of subjects were found to have no irritation. Erosion was not observed in any subjects. No subject was scored higher than a "1" on the nasal irritation scale; all findings listed in Table 7 below were scored as a "1" on that scale.

Table 7. Nasal Irritation, Study 002.

Table 12.2.5-1. Nasal Irritation, Study Naloxone-Ph1a-002												
Scheduled Assessment	Treatment											
	2 mg (20 mg/mL, one 0.1 mL spray) N=29			4 mg (20 mg/mL, two 0.1 mL sprays) N=29			4 mg (40 mg/mL, one 0.1 mL spray) N=29			8 mg (40 mg/mL, two 0.1 mL sprays) N=29		
	Erythema	Edema	Erosion	Erythema	Edema	Erosion	Erythema	Edema	Erosion	Erythema	Edema	Erosion
Predose	1 (3.4%)[a]	1 (3.4%)	0	0	0	0	0	1 (3.4%)	0	0	0	0
5 min	0	3 (10.3%)	0	0	0	0	1 (3.4%)	0	0	0	0	0
30 min	0	3 (10.3%)	0	0	0	0	1 (3.4%)	0	0	0	0	0
60 min	0	1 (3.4%)	0	0	0	0	0	0	0	0	1 (3.4%)	0
4 hr	0	2 (6.9%)	0	0	0	0	0	1 (3.4%)	0	0	0	0
24 hr	2 (6.9%)	2 (6.9%)	0	1 (3.4%)	0	0	0	1 (3.4%)	0	0	0	0
Number (%) of Participants Observed with Nasal Irritation Symptoms												
Total	3 (10%)	5 (17%)	0	1 (3.4%)	0	0	1 (3.4%)	3 (10.0%)	0	0	1 (3.4%)	0

a: Number of participants (%)

Source: Applicant, study 002 clinical study report, pg. 68

The adverse event profile demonstrated the potential for Narcan nasal spray to result in mild local irritation. There is no question that this is an acceptable risk given the potentially life-saving benefits of this medication; however, the potential for local irritation will be communicated in labeling.

9. Advisory Committee Meeting

An Advisory Committee Meeting was not held for this application.

10. Pediatrics

Narcan is approved for use in the entire pediatric age range. In contrast to adults, approved labeling recommends weight-based dosing for known or suspected opioid overdose in children. The Narcan package insert contains the following pediatric labeling:

> **Usage in Children**
> Opioid Overdose–Known or Suspected:
> The usual initial dose in children is 0.01 mg/kg body weight given IV. If this dose does not result in the desired degree of clinical improvement, a subsequent dose of 0.1 mg/kg body weight may be administered. If an IV route of administration is not available, naloxone may be administered IM or SC in divided doses. If necessary, naloxone hydrochloride injection can be diluted with sterile water for injection.

Because Narcan nasal spray represents a change in dosing regimen (a fixed 4-mg dose) and route of administration (intranasal) for naloxone, the Applicant is required to conduct a pediatric assessment under the Pediatric Research Equity Act (PREA). Efficacy studies are not feasible in pediatric patients in the same way they are not feasible in adults. However,

unlike in adults, pediatric pharmacokinetic studies in healthy children are not feasible because of limits on the ability to conduct studies in normal, healthy children where the study involves more than minimal risk. Therefore, the Applicant was required to support the safety and efficacy of Narcan nasal spray in pediatrics, based on a review of available information, including the published literature, clinical practice guidelines, and the approved labeling for Narcan. This pediatric assessment was required to have addressed the following issues:

- The safety and effectiveness of the proposed dose of naloxone for all pediatric age ranges, including neonates
- Justification for the proposed dosing volume in all pediatric patients, including neonates
- Justification for why the absorption of drugs through the nasal mucosa will not be different in pediatric patients, including neonates, compared to adults
- A device (e.g., nasal tip) that can appropriately deliver the correct volume to all pediatric patients, including neonates

The Applicant received an agreed pediatric study plan (PSP) on June 22, 2015, which included a plan to submit the required pediatric assessment with the NDA. The Division of Pediatric and Maternal Health (DPMH) was consulted to evaluate the adequacy of the pediatric assessment to support approval in the full pediatric age range and the proposed labeling.

DPMH recommended "approval for the proposed indication for pediatric patients from birth to under age 17 years for emergency treatment of known or suspected opioid overdose until emergency medical services can be provided by trained professionals," provided that "DAAAP is satisfied that IN delivery with the proposed unit dose device will result in absorption of a minimally effective dose in pediatric patients of all ages."

DPMH raised concerns in their review about the safety of the proposed product as it relates to IN drug delivery. Specifically, DPMH requested DAAAP to confirm that the actuator tip may be properly positioned and, based on concerns of differences in nasal morphology, can deliver a minimally effective dose in pediatric patients under five years of age. Further, given the fixed dose, DPMH raised concerns that the 4-mg dose could deliver a dose approximately 100-fold higher than what is recommended in Narcan labeling if the full dose is systemically absorbed. DPMH raised additional concerns for the potential to induce respiratory distress with intranasal instrumentation in the youngest patients because of obligate nasal breathing.

Therefore, DPMH recommended a postmarketing requirement (PMR) and a postmarketing commitment (PMC) to, respectively, capture any treatment failures or serious AEs of airway obstruction, respiratory distress, or respiratory arrest in pediatric patients under one year of age and evaluate the pharmacokinetic profile of this product in patients under five years of age.

This application was discussed at a meeting of the Pediatric Review Committee (PeRC) on November 4, 2015, where the above PMC and PMR were initially discussed.

Narcan nasal spray is intended to address community-based treatment of opioid overdose, and it is vitally important that laypersons, who will be administering the product, do not have to

make complex medical decisions, such as determining a weight-based dose or having to decide between different doses for different age groups. The caregiver must seek definitive medical treatment on the patient's behalf after administering Narcan nasal spray in this treatment setting. Pediatric use of Narcan nasal spray in the **youngest** age ranges must be considered in the context of the different clinical scenarios where naloxone may be used in that population:

- Otherwise healthy children may be accidentally exposed to an opioid that is available in their environment resulting in life-threatening CNS and respiratory depression that requires naloxone.
- A pediatric patient who is taking a prescribed opioid for medical reasons may accidentally overdose on that opioid requiring naloxone. Use of naloxone in this population may result in signs and symptoms of opioid withdrawal if the patient is opioid-dependent, and this possibility would depend on the duration of prior opioid exposure.
- Naloxone may be required for neonates in the delivery room who present with respiratory depression at the time of birth due to maternal exposure to opioid, and these neonates may or may not be opioid-dependent depending on the duration of prior exposure to maternal opioids.
- Opioid-dependent babies born to mothers on medication-assisted treatment or who are illicitly using opioids may be treated with a gradual opioid taper at home in order to prevent life-threatening opioid withdrawal and may be at risk for opioid overdose.

Additional considerations in this treatment setting include that naloxone prescribed for use in the community may ultimately be administered to a person other than the recipient of the prescription because it cannot be known in advance who will overdose on an opioid. It is vitally important for Narcan nasal spray to be available for an accidental opioid ingestion in a child who may not have been the person for whom the prescription was written. Because of the wide safety margin for naloxone, particularly in non-opioid-dependent patients in a non-hospital setting, and that the dose of naloxone delivered from Narcan nasal spray, based on the pharmacokinetic study conducted in adults, is relatively high compared to what is recommended in the approved Narcan labeling for the youngest pediatric patients, there is a reasonable expectation that an effective dose of naloxone will be systemically available to reverse the life-threatening effects of the opioid in the youngest patients. Narcan nasal spray results in a systemic exposure to naloxone that is approximately 5 times that of the 0.4 mg IM dose. Evzio, which delivers a 0.4 mg IM dose, is approved in pediatric patients down to birth. Although the nasal tip may not fit in the nostrils of all pediatric patients, the opening through which the medication is sprayed is small enough to deliver the medication into the nose, if positioned properly.

In situations where a younger child is being considered for a prescription for naloxone to be used in the community to address the risk for accidental exposure or in cases where there is concern for inducing potentially life-threatening withdrawal, alternative products may be more appropriate. Additionally, in supervised medical settings, such as in the delivery room, emergency room, or inpatient unit, a weight-based naloxone dose that is amenable to titration is more appropriate.

The benefits of having this product available for those pediatric patients who may be accidentally exposed to an opioid resulting in life-threatening CNS and respiratory depression far outweighs the risks in this setting. Labeling must clearly describe which pediatric patients may not be the most suitable for this product so that the prescriber can make an informed decision as to which naloxone product to prescribe in these settings. I conclude that Narcan nasal spray should be approved for the full pediatric age range without the proposed PMR and PMC.

The concerns that DPMH raised resulting in their recommendations for a PMR could be addressed through enhanced pharmacovigilance, which should be considered to capture any treatment failures or serious AEs of airway obstruction, respiratory distress, or respiratory arrest in pediatric patients under one year of age. However, the Division has determined that, after extensive internal discussion, the proposed PMC to assess the pharmacokinetics in patients less than five years of age poses significant feasibility and ethical challenges because, in settings where this study could potentially be conducted (i.e., inpatient-type settings), another more appropriate naloxone therapy would be available (i.e., weight-based product), and, therefore, it would not be ethical to use a potentially suboptimal product for that setting in a clinical study. The value of this product in the community for the youngest pediatric patients will be clearly communicated in labeling, and its value does not necessarily fully extend to all community-based clinical scenarios or healthcare settings.

11. Other Relevant Regulatory Issues

There are no unresolved relevant regulatory issues.

Inspections of the clinical and analytical portions of the relative bioavailability study
The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of the analytical portion of the pivotal relative bioavailability study (study 002) and arranged an inspection of the clinical portion of the study with the Office of Regulatory Affairs (ORA). OSIS recommended that "the clinical and analytical data from study Naloxone-Phla-002 be accepted for Agency review." The final classification for both the clinical portion (Vince & Associates Clinical Research) and the analytical portion (b) (4) was VAI (voluntary action indicated).

The OSIS review noted two observations at the clinical site (Vince & Associates Clinical Research) and a Form FDA 483 was issued.

1. Observation: "An investigation was not conducted in accordance with the investigational plan."

    - The first issue involved one subject who developed a respiratory rate of 25 per minute at the 30-minute post-dosing time point. The protocol specified that subjects be discontinued for a respiratory rate of less than 8 or greater than 24 and did not allow for repeat measurements. However, the source document designed by the study site allows for repeated measurements, per the study site's Standard Operating Procedure (SOP). A study sub-investigator was called to assess the

subject. The sub-investigator repeated the vital signs assessment and recorded a respiratory rate of 24 per minute. The finding was considered not clinically significant by the sub-investigator and the subject was allowed to continue in the study. The out-of-range respiratory rate was not documented as an adverse event (AE). The OSIS review noted that "[a]lthough the above observation is not likely to impact the study outcome, the DAAAP medical reviewer should evaluate the impact of this unreported adverse event (AE) on the safety evaluation of the investigational product."

Adverse events are generally recorded by the investigator(s) at the clinical study site, based on a clinical evaluation of a patient or subject. Therefore, it is common that, in the context of clinical studies, not all out-of-range vital signs are coded as adverse events. In this case, I agree that the OSIS finding described above is unlikely to impact the safety evaluation of this drug, particularly since the finding of safety for Narcan nasal spray is primarily resting on the Applicant cross-referencing their NDA for Narcan injection.

- The second issue involved numerous pharmacokinetic samples that were late to the freezer (i.e., LTF; not placed in the (b) (4)°C freezer within (b) (4)). The failure to place serum samples in the freezer within (b) (4) was not documented on the site's protocol deviation log, nor were any LTF-related occurrences reported as protocol deviations.

  To address this issue and to assess the integrity of LTF samples, the analytical site, (b) (4) was requested to evaluate the stability of naloxone over conditions that mimicked the worst-case scenario for the samples at the clinical site. The results of this study were made available to the investigators over the course of this inspection, which demonstrated the stability of the samples. OSIS concluded that this issue "is unlikely to impact the integrity of the naloxone concentration data." The clinical pharmacology review team concurred with OSIS's conclusion.

2. Observation: "Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation."

   - The first issue involved discrepancies between the reported protocol deviations and the source documents. Specifically, the protocol deviations submitted to the Agency do not accurately represent the information from the pharmacokinetic Specimen Processing Log. OSIS determined that there were post-dose discrepancies in the actual sampling times in the pharmacokinetic analysis for three subjects, at one post-dose time point each. OSIS noted that "[t]his observation is unlikely to impact the outcome of the study." However, OSIS requested that the clinical pharmacology reviewer include the actual sampling times in their pharmacokinetic analysis for these three subjects. The clinical pharmacology reviewer noted that two of the deviations were in subjects who received the 20 mg/ml strength, and, therefore, these two deviations can be

disregarded. The third subject had a one minute deviation at the 5-minute post-dose time point. The clinical pharmacology reviewer concluded that "this one minute deviation at [the] 5 minute time point in one subject would not affect the calculated [pharmacokinetic] parameters [or] conclusion for the study," and I concur with that assessment.

- The second issue involved adverse event information not corresponding to applicable source documentation.

  Two subjects reported adverse events related to nasal irritation (i.e., nasal edema and left nostril dryness with occasional bleeding); however, those subjects had corresponding nasal examinations recorded as normal (i.e., "0" on the nasal irritation scoring scale). Physical exam finding do not always correlate with subjective reports.

  Two additional subjects reported adverse events related to nasal irritation and also had corresponding nasal examinations recorded as normal. However, these subjects had their corresponding nasal examination score(s) changed to "1" (inflamed mucosa, no bleeding) at a later time or date, in some cases over a month later.

  For all of these cases, the same sub-investigator was involved (i.e., identified as "LDV"). These findings do not impact the safety evaluation of the investigational product. The finding of safety for Narcan nasal spray is primarily resting on the Applicant cross-referencing their NDA for Narcan injection. We are relying on this study to provide a qualitative assessment of the potential for local nasal irritation, and this study did demonstrate that Narcan nasal spray has the potential to cause mild local irritation. This conclusion is unchanged by these inspectional findings. Further, it is unlikely that the sub-investigator missed a serious finding on nasal examination, and the issue appears to be with the more clinically subtle aspects of the exam (i.e., "0" versus a "1"). However, these findings do raise concerns over the adequacy of the training for the clinical nasal examination.

Financial disclosures

The Applicant certified that the investigator did not have reportable financial disclosures.

505(b)(2) committee

This application was presented at a meeting of the 505(b)(2) committee on October 26, 2015, and it was cleared for action from their perspective. The 505(b)(2) committee recommended that an approval action be coordinated with the Exclusivity Board/Office of Regulatory Policy (ORP), as they may wish to include a memorandum to the record regarding the potential for exclusivity attached to other naloxone-containing products to block the approval of this NDA. A memorandum from ORP is pending at the time of this writing,

12. Labeling

The proprietary name, Narcan nasal spray, was found acceptable following review by the Division of Medication Error Prevention and Analysis (DMEPA). DMEPA and the Office of Prescription Drug Promotion (OPDP) provided recommendations on the proposed labels and labeling. DMEPA noted that their proposed changes do not require an additional human factors validation study. The patient labeling team reviewed the patient package insert, instructions for use, and quick start guide and found them acceptable with their recommended changes. Refer to the individual reviews for more details.

Additionally, the Division of Pediatric and Maternal Health (DPMH) was consulted regarding the proposed labeling (i.e., pregnancy and lactation labeling rule [PLLR]). DPMH provided recommendations for the proposed labeling, based on their review.

Labeling is ongoing at the time of this writing, and specific recommendations have been made in the relevant sections of this review. However, two additional aspects of the proposed labeling warrant further discussion here:

1. The Applicant proposed (b) (4) .
2. Additionally, the Applicant proposes (b) (4)

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

  Approval

- Risk Benefit Assessment

  The Applicant established the safety and efficacy of the naloxone contained in Narcan nasal spray by conducting a relative bioavailability study to bridge to their NDA for Narcan (NDA 16636). This study compared two doses of Narcan nasal spray to an approved generic injectable naloxone product and demonstrated that the systemic exposure to naloxone was much higher than that of an initial approved dose of naloxone for injection (i.e., 0.4 mg IM) at all measured time points. Therefore, the Applicant successfully met the pharmacokinetic standard outlined by the Division, which was required to ensure that Narcan nasal spray will deliver an effective dose of naloxone in a timely fashion. This is particularly important in the early time points where it is critical to provide adequate exposure to naloxone given the grave consequences of under treating an opioid overdose.

  The application supported the change in route of administration by evaluating the potential for local toxicity in the relative bioavailability study, the change in intended treatment setting (i.e., from use in a healthcare setting by health professionals to use in a community setting by laypersons) by conducting a human factors study, and the change in dosing regimen for pediatric patients (i.e., from weight-based dosing to a fixed dose) by providing a pediatric assessment with support from the published literature.

  This product would be the first approved intranasal naloxone product. It is intended for use in the community and will provide an important alternative to other approved naloxone products, which require a needle for drug administration. The risks discussed in this review are far outweighed by the potential benefits of this potentially life-saving medication. Therefore, I recommend approval for adults and the full range of pediatric patients in the proposed indication with the labeling recommendations described throughout this review.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

  None

- Recommendation for other Postmarketing Requirements and Commitments

  Postmarketing Requirements:

  1. Establish reliability requirements for the combination product and complete testing which verifies combination product reliability as described in detail below:

     a. Establish reliability requirements for your combination product. It is recommended that reliability be directly specified as R(t) = x%, where t = time and x% = probability of meeting essential performance requirements. These requirements should be objective and relate to the ability of a

population of devices to meet essential performance requirements after pre-conditioning to elements outlined within c, below. The reliability requirements should be verified with a high degree of statistical confidence.

b. Provide rationale and justification supporting the clinical acceptability of the established reliability requirements.
c. Perform a test to verify the reliability requirements specified above.

Devices assessed within the reliability test should be preconditioned to worst-case reasonably foreseeable conditions. The Agency has conceived the following recommended preconditioning activities, however you should provide rationale supporting the final precondition elements chosen, and the order in which the products are conditioned. Your assessment of the preconditioning parameters should be based on your own failure analyses (e.g., fault tree analysis) in order to assure that the scope of preconditions and their boundary values are adequately correct and complete.

- Shipping
- Aging
- Storage orientation and conditions
- Vibration handling
- Shock handling (e.g., resistance to random impacts, such as being dropped)

Devices assessed within the reliability analysis should be activated under worst-case reasonably foreseeable conditions. The Agency has conceived the following recommended circumstances of activation; however, you should provide rationale supporting the final circumstances of activation chosen.

- Activation orientation
- Environmental temperature

2. Establish procedures for monitoring reports of failure of the combination product to activate or failure of the combination product to deliver the full labeled dose. Provide annual updates to the NDA record, which contain a detailed analysis of reported device failures (including reported malfunctions that did not result in patient harm), full event narratives, and the results of root cause analysis performed for the reported failure.

Postmarketing Commitments:

1. Conduct and submit an adequate leachable safety assessment for your drug product and container closure system. This assessment must include leachable data from long-term stability studies taking into consideration the proposed shelf-life to determine if the specified extractables also leach into the drug product over time, and a toxicological risk assessment justifying the safety of the leachables taking into consideration the maximum daily dose of the identified materials for this drug product.

2. A postmarketing commitment to test drug product batches on stability through the course of expiry at the excursion conditions of 4°C to 40°C. (final language pending at the time of this writing)

- Recommended Comments to Applicant

  Additional Comments for the Leachables Assessment:

  1. The leachable compounds you propose to evaluate in your leachables assessment appear appropriate.
  2. In your leachables assessment, evaluate at least three batches of your drug product over the course of your stability studies at multiple timepoints during the proposed shelf-life of your product.
  3. Submit a toxicological risk assessment for any leachable that exceeds 5 mcg/day. From a genetic toxicology perspective, any leachable that contains a structural alert for mutagenicity must not exceed 120 mcg/day for this acute indication, or be adequately qualified for safety. The risk assessment should be based on the maximum level of each leachable detected in long-term stability samples that include any intended secondary container closure system(s) unless otherwise justified.
     - Published literature to support the safety of a leachable rarely provides adequate detail of the study design and study results to permit a thorough independent evaluation of the data. Summary reviews, (e.g., BIBRA, CIR, HERA), although potentially useful to identify original source material, are not acceptable as the source material is not provided and the conclusions cannot be independently verified. Submission of any published study reports must be accompanied by a detailed comparison to modern toxicology study endpoints and any shortcomings of the study must be discussed and justification must be provided to support your assertion that these data are adequate to support the safety of your container closure system.
     - Safety justifications based on analogous compounds are also not acceptable unless you can provide adequate data to support your conclusions that a risk assessment based on one compound can be logically interpolated to represent an adequate safety evaluation for your leachable. This should include a detailed understanding of the absorption, distribution, metabolism, and elimination of the compounds and an adequate scientific bridge to interpolate a NOAEL for the leachable.

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/s/

JOSHUA M LLOYD
11/18/2015