Medical Officer, Cross-Discipline Team Leader, and Division Director Summary Review

Date	Refer to signature date at the end.
From	Division of Anesthesiology, Addiction Medicine, and Pain Medicine Tanya Brescia-Oddo, MD; Primary Clinical Reviewer Robert Shibuya, MD; Cross Discipline Team Leader Rigoberto Roca, MD; Division Director
NDA	217470
Applicant	Opiant Pharmaceuticals, Inc.
Date of Submission	November 22, 2022
PDUFA Goal Date	May 22, 2023
Proprietary Name	Opvee
Established or Proper Name	Nalmefene hydrochloride
Dosage Form	Nasal Spray; 2.7 mg of nalmefene hydrochloride in 0.1 mL
Applicant Proposed Indication/Population	• Complete or partial reversal of opioid drug effects, including respiratory depression, induced by either natural or synthetic opioids • Emergency treatment of known or suspected opioid overdose
Applicant Proposed Dosing Regimen	Initial Dosing: • One spray delivered by intranasal administration, which delivers 2.7 mg of Opvee Repeat Dosing: • Seek emergency medical assistance as soon as possible after intranasal administration of the first dose. The requirement for repeat doses depends upon the amount, type, and route of administration of the opioid being antagonized • If the patient responds and then relapses back into respiratory depression before emergency assistance arrives, administer an additional dose using a new nasal spray and continue surveillance of the patient • If the desired response is not obtained after 2 to 5 minutes, administer an additional dose using a new nasal spray • If there is still no response and additional doses are available, administer additional doses of nasal spray every 2 to 5 minutes using a new nasal spray with each dose until emergency medical assistance arrives • Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance
Regulatory Action	Approval
Indication/Population	• Emergency treatment of known or suspected overdose, induced by natural or synthetic opioids in adults and pediatric patients aged 12 years and older, as manifested by respiratory and/or central nervous system depression

Review Team

Discipline	Primary / Secondary / Tertiary Assessment
Office of Pharmaceutical Quality (OPQ)	
ATL	Valerie Amspacher, PhD
Drug Substance	Katie Duncan, PhD / Gaetan Ladouceur, PhD
Drug Product	Renish Delvadia, PhD / Julia Pinto, PhD
Process/Facilities	Raeann Wu, PhD / Cassandra Abellard, BSc
Microbiology	Ryan Blower, PhD / Erika Pfeiler, PhD
RBPM	Anika Lalmansingh, PhD, GWCPM
Pharmacology/Toxicology	Min Zhang, PhD / Newton Woo, PhD / R. Daniel Mellon, PhD
Clinical Pharmacology	Srikanth Nallani, PhD / Yun Xu, PhD
DARS	Zhihua Li, PhD / Jeffry Florian, PhD
DPM	Michael Bewernitz, PhD / Atul Bhattaram, PhD
Clinical	Tanya Brescia-Oddo, MD / Robert Shibuya, MD
Biometrics I	Yunfan Deng, PhD / Sue-Jane Wang, PhD
Labeling (ADL)	Lisa Basham, MS
RPM	Sandy Truong, PharmD /Swati Patwardhan, MS, RAC
Office of Surveillance and Epidemiology (OSE)	
DMEPA	Avani Bhalodia, PharmD, BCPS / Damon Birkemeier, PharmD / Valerie Vaughan, PharmD / Murewa Oguntimein, PhD, MHS, CPH, MCHES / Mishale Mistry, PharmD, MPH
DPVI	Jamie Klucken, PharmD, MBA
DPVII	Sarah Kang, PharmD
DRM	Somya Dunn, MD / Carolyn Tieu, PharmD, MPH
DEPI	Natasha Pratt, PhD
RPM	Carol Corbie / Louis Flowers, PharmD, MS, BCPS, CPH / Darrell Jenkins, MS
Consults	
CDRH	Porsche Bennett, MS / Alan Stevens, MS
OSE/DEPI II/Drug Utilization	Yuze Yang, PharmD / Corinne Woods, RPh, MPH / Rajdeep Gill, PharmD
Division of Pediatric and Maternal Health (DPMH)	
Pediatric	Sonaly McClymont, MD / Shamir Tuchman, MD (Acting TL) / Shetarra Walker, MD, MSCR, FAAP
Maternal Health	Christos Mastroyannis, MD / Tamara Johnson, MD, MS
RPM	Michelle Pollack, PA-C
Labeling	
OPDP	L. Shenee Toombs, PharmD, CPH
PLT	Jessica Chung, PharmD, MS / Barbara Fuller, RN, MSN / Sharon Mills, BSN, RN, CCRP

ATL = Application Technical Lead	DPV = Division of Pharmacovigilance
CDRH = Center for Devices and Radiological Health	DRM = Division of Risk Management
DARS = Division of Applied Regulatory Science	OPDP = Office of Prescription Drug Promotion
DEPI = Division of Epidemiology	RBPM = Regulatory Business Project Manager

DPM = Division of Pharmacometrics	RPM = Regulatory Project Manager
DMEPA = Division of Medication Error Prevention and Analysis	PLT = Patient Labeling Team

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Opioid-related overdoses continue to exact a significant societal burden in the United States. While the rise in opioid overdose deaths began in the late 1990s with increased opioid prescribing, the last nine years have seen an emergence of - and increasing fatal and non-fatal overdoses from synthetic opioids, namely, illicit fentanyl analogues used as 'adulterants' in opioid and non-opioid drugs. Adulteration by fentanyl, 100 times more potent than morphine, has resulted in an increase in inadvertent ingestion of synthetic opioids by both opioid-dependent and opioid-naïve individuals. Symptoms of overdose can occur within seconds to minutes as highly lipophilic fentanyl and related analogs rapidly diffuse across the blood-brain barrier into the central nervous system. Moreover, not uncommonly, a mismatch exists whereby the duration of effect of the administered opioid exceeds the duration of effect of naloxone; this mismatch in duration of effect between opioid agonism and antagonism may lead to a recurrence of opioid overdose symptoms known as "renarcotization."

In 2017, the National Institutes of Health (NIH) noted that they "…will now work with private partners to develop stronger, longer-acting formulations of antagonists, including naloxone, to counteract the very-high-potency synthetic opioids that are now claiming thousands of lives each year." In response, the Applicant has developed Opvee (nalmefene) Nasal Spray, a single-use, drug-device combination product, for a proposed indication of complete or partial reversal of opioid drug effects, including respiratory depression, induced by either natural or synthetic opioids in addition to the emergency treatment of known or suspected opioid overdose. The nalmefene moiety has characteristics that may provide an advantage over existing opioid reversal products in the reversal of highly potent fentanyl analogs; namely, a higher affinity for the mu opioid receptor and a longer duration of action than naloxone drug products. Opvee Nasal Spray was developed for community use by non-medically trained laypersons and contains an absorption enhancer to improve intranasal bioavailability for early onset of action.

Opvee Nasal Spray was developed under Investigational New Drug (IND) application 136851. This new drug application (NDA) was assigned number 217470. The Sponsor is using the 505(b)(2) pathway and is relying on the Agency's previous findings of safety and efficacy for the listed drug (LD) REVEX (nalmefene hydrochloride injection; NDA 020459). The Applicant's clinical development program consisted of three clinical studies: one to establish a scientific bridge to the LD, one to inform PK and safety of repeat dosing, and one to demonstrate the onset of action and duration of action on a clinically relevant respiratory endpoint to confirm its appropriateness as an emergency-use opioid antagonist in a community setting. A conventional, prospective, randomized, double-blind, placebo-controlled study in patients with opioid overdose is not feasible for these products that are intended for use in the community. Thus, efficacy was extrapolated from the known pharmacology of the opioid antagonist and clinical pharmacology studies done on the formulation and proposed route of administration. The PK/PD study (Study OOD-001) was conducted to address the observation that REVEX was shown to have a slow onset of action which would compromise effectiveness for this indication. Collectively, these studies support the safety and efficacy of nalmefene for intranasal use in a community setting. Furthermore, population pharmacokinetics and PK/PD modelling was determined by the review team to be suitable to allow for extrapolation of the adult PK data to the 12 to < 18-year-old pediatric population.

A key clinical safety issue considered during the review cycle was that of the potential for Opvee to precipitate a severe and/or prolonged withdrawal in patients physically dependent on opioids. This point was thoroughly assessed through review of the original Revex (LD) review which contained 1) assessments of opioid withdrawal in patients receiving nalmefene or naloxone in a randomized, controlled trial for opioid overdose and 2) narratives of individuals who experienced serious adverse events (SAEs) including death. Furthermore, the Applicant submitted a summary of the literature in which opioid withdrawal was inadvertently precipitated in patients who initiated treatment with Selincro, an oral nalmefene drug product available in the European Union for alcohol use disorder. Altogether, these data allowed for comparisons in Cmax and AUC between different routes of administration as well as repeat-dose pharmacokinetic simulations to provide support for safe use in opioid-dependent individuals.

An important regulatory aspect of this 505(b)(2) NDA was that the listed drug, Revex injection (NDA 020459) was discontinued for business reasons and no ANDA was approved at the time Opiant was ready to conduct their relative bioavailability study, Study PK-001. After considerable discussion between the Agency and the Applicant, the Applicant was permitted to manufacture a nalmefene injectable product to compare the exposure with that of the proposed product in their relative bioavailability study to establish the scientific bridge.

Importantly, as a regulatory and policy issue, the Division considered that currently marketed naloxone products have data to support safety and efficacy in all age groups down to birth. Confusion is therefore avoided over which naloxone products are indicated for use across pediatric age groups. The Division acknowledges that, currently, Opvee lacks data supporting use in patients under 12 years of age – PREA PMRs of nonclinical PK and repeat dose toxicity studies will need to be completed prior to initiation of clinical studies in the age groups of 3 to less than 12 years and birth to less than 3 years.

The Division notes the following as support for approval of Opvee:

1. No other nalmefene nasal spray products are approved or marketed, so there should not be any confusion among the lay public as to whether this can be administered to patients under 12 years of age. As noted above, regarding all nalmefene-containing products, REVEX injection was discontinued from marketing in the US. An abbreviated NDA (ANDA [212955]) for nalmefene injection (2 mg/2 mL) was approved in 2022 and is commercially available. Discussion with the Division of Medication Error Prevention and Analysis (DMEPA) verified that the likelihood of drug product confusion is low between nalmefene injection and Opvee nasal spray, primarily because the distribution channels are separate.
2. Preliminary data show that Opvee may be more effective in reversing certain opioid overdoses (e.g., carfentanil); illicit fentanyl analogues currently account for the majority of opioid overdoses and adolescents have overdosed and died due to inadvertent ingestion of these analogues.

Therefore, given the current need for additional opioid reversal agents, the Division concludes that Opvee should be approved for community use despite the lower limit of use as 12 years of age.

The Applicant has demonstrated the safety and efficacy of Opvee for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression in adults and pediatric patients aged 12 years and older. The benefit:risk is favorable as potential risks are outweighed by the benefits of this life-saving drug. The regulatory action for this application is Approval.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Opioid misuse, abuse, and addiction are prevalent in the United States • Prescribed opioids accounted for most overdose deaths at the beginning of the opioid epidemic; however, synthetic opioids, namely illicit fentanyl analogues, have emerged on the illicit market and may have accounted for approximately 88% of opioid overdose deaths in 2021 • Synthetic opioids are used as "adulterants" in heroin, methamphetamine, cocaine, benzodiazepines, and other drugs which has increased the inadvertent ingestion of synthetic opioids by opioid-naïve individuals (true accidental overdose) • Accidental overdoses are occurring in both opioid-dependent and non-opioid dependent patients including adolescents	• Opioid overdose is a life-threatening condition, and the emergence of high-potency illicit fentanyl analogues has accelerated non-fatal overdoses and overdose-related deaths over the past few years
Current Treatment Options	• NIH leadership asked for the pharmaceutical sector to develop "…stronger, longer-acting formulations of antagonists…" (Volkow, 2017) • Naloxone is the only approved drug product for emergency reversal of opioid toxicity in a community setting • Naloxone is approved and available for community use as Narcan Nasal Spray (NNS) 4 mg IN (intranasal), Kloxxado 8 mg IN, and ZIMHI 5 mg IM/SC injector • Nalmefene hydrochloride injection was approved as an ANDA in February 2022 for opioid reversal though not for community use; it was previously marketed until 2008 but was removed for business reasons and not for safety or efficacy reasons	• There are FDA-approved and marketed treatment options for opioid overdose • Opvee is the first non-naloxone opioid antagonist available for use by lay persons in a community setting • Opvee may be more effective in reversing certain opioid overdoses (e.g., carfentanil)
Benefit	• The efficacy of Opvee is supported by two studies: 1) pharmacokinetic (PK) study OPNT003-PK-001, which provides a scientific bridge to the LD, nalmefene hydrochloride injection, and 2) Pharmacokinetic-Pharmacodynamic (PK-PD) Study OPNT003-OOD-001 which confirmed onset of action at critical, early timepoints and duration of action in non-dependent healthy volunteers with prior opioid exposure • Study OPNT003-OOD-001 demonstrated Opvee was numerically better in both minute ventilation and change from baseline of minute ventilation during the first 20 minutes post-treatment and were similar during the 30 to 120 minutes post-treatment; the study met the pre-defined noninferiority (NI) margin for the primary endpoint • Efficacy and safety in pediatric patients aged 12 years and older is supported by extrapolation from adult as well as population PK modeling data	• The Applicant provided PK, PD, and popPK modeling data to support the safety and effectiveness of Opvee for community use for opioid reversal in adults and pediatric patients aged 12 years and older • Safety of Opvee in patients with physical dependence to opioids, including OUD, is also supported by the Agency's previous findings of safety for LD nalmefene hydrochloride injection

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Nalmefene's attributes of high affinity for the mu opioid receptor and long duration of action may be advantageous in reversing higher potency synthetic opioids and antagonizing longer-acting opioids as compared to current treatment options • Preliminary translational modeling performed by the Office of Clinical Pharmacology demonstrated the following advantages in opioid antagonization for Opvee 3 mg compared to Naloxone NS 4 mg: o Faster rise in plasma concentration and longer duration of action o Slower dissociation from the mu opioid receptor o Faster return of minute ventilation and end-tidal CO2 to pre-opioid levels o Prevention of renarcotization	
Risk and Risk Management	• Nalmefene is a long-acting opioid antagonist that has an inherent risk of protracted opioid withdrawal in patients with physical dependence on opioids; precipitated withdrawal from opioids may be more severe and/or more prolonged as compared with naloxone • Severe opioid withdrawal and/or excessive wait times for emergency medical services could result in attempts by the patient to overcome the opioid blockade with additional opioids that then accumulate and cause re-narcotization and/or death • If Opvee is more effective in reversing certain opioid overdoses (e.g., carfentanil), an unintended consequence may be an increase in non-fatal opioid overdoses with significant morbidity (i.e., hypoxia or anoxic brain injury)	• Opioid-dependent individuals who receive Opvee may experience precipitated withdrawal that is severe and/or prolonged; this can be managed in a medically supervised setting • Due to the potency and duration of action of nalmefene vs. naloxone, Opvee potentially poses a greater risk for precipitated opioid withdrawal in physically dependent patients. Although the discussion was about naloxone, this issue was conceptually addressed in an October 2016 joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and Drug Safety and Risk Management Advisory Committee. Regarding a question about a higher starting dose for naloxone, the minutes read: "The committee members discussed that it is unclear what should be the basis to choose an absolute correct dose; however, the committee noted that the risk of not having a high enough dose is much greater than not having enough. Some committee members stated that there is concern that lower doses of naloxone might require rescuers to titrate, taking time, and risking further hypoxic injury to the patient. Many

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		committee members stated that the risk of acute withdrawal is acceptable for the benefit of saving a patient." • Opvee is not a substitute for emergency medical care which should be called immediately after the first administration of nasal spray

2. Background

2.1 Product Information

Nalmefene is a mu-opioid receptor antagonist that binds with a higher affinity to the mu-opioid receptor and has a longer plasma half-life than naloxone. The Applicant (Opiant Pharmaceuticals, Inc.) has developed Opvee (nalmefene hydrochloride nasal spray) 3 mg in 0.1mL for a proposed indication of complete or partial reversal of opioid drug effects, including respiratory depression, induced by either natural or synthetic opioids, as well as for the emergency treatment of known or suspected opioid overdose. Opvee is a single-use, drug-device combination product for community use to be administered by laypersons to rescue patients from the life-threatening effects of opioid toxicity while awaiting emergency medical care. Opiant uses a proprietary functional excipient, Intravail A3 (dodecylmaltoside, DDM), to improve the bioavailability of the API when administered by the intranasal route. Notably, Opvee uses the Aptar Unidose Nasal Spray (UDS™) system, the same system as Narcan nasal spray, with each spray delivering 2.7 mg of nalmefene in a volume of 100 µL.

The API, nalmefene, was previously approved in 1995 as REVEX (nalmefene hydrochloride injection; NDA 020459) but withdrawn from market in 2008 for business reasons and not for safety or efficacy reasons (Federal Register, Vol. 82, No 212, November 3, 2017). No post-marketing safety issues were identified by the Agency. REVEX injection was approved for intravenous, intramuscular, and subcutaneous administration for the indication of complete or partial reversal of opioid drug effects, including respiratory depression, induced by either natural or synthetic opioids. REVEX was also indicated for the management of known or suspected opioid overdose. It was used in post-operative and emergency department settings and was supplied in two concentrations: one concentration was suitable for reversal of postoperative opioid-induced respiratory depression and the other concentration was suitable for management of opioid overdose. The REVEX formulation allowed for partially reversing doses such that assessment of clinical response could be noted before administering incrementally larger doses. Notably, the FDA approved an ANDA (212955) for nalmefene hydrochloride injection in 2022 from Purdue Pharma in the 2 mg/2 mL strength for the same routes of administration and indication as REVEX, described above.

2.2 Therapeutic Context: Opioid Overdose and Nalmefene

Opvee, a drug-device combination nasal spray for community use, was developed to reverse opioid overdose, characterized by life-threatening respiratory and central nervous system depression. The inherent characteristics of nalmefene, high-affinity for the mu-opioid receptor as well as long duration of action as compared to currently marketed opioid antagonists, may prove more effective in reversing overdoses caused by licit and illicit fentanyl analogues; the latter of which has been implicated in the majority of opioid-related overdose deaths. Importantly, naloxone products that achieve higher plasma concentrations, such as KLOXXADO and ZIMHI, may be more effective than lower-dose naloxone products for these types of overdoses.

The treatment armamentarium of opioid reversal agents for community use currently is limited to those comprised of the naloxone moiety. Naloxone products are labeled for risk of recurrent

respiratory and CNS depression, precipitation of severe opioid withdrawal and risk of cardiovascular effects. The long duration of action of nalmefene is advantageous in that the risk of renarcotization is likely less than naloxone since the half-life of nalmefene is longer than that of most opioids. The risk of cardiovascular effects is expected to be comparable between nalmefene and naloxone products. And, while in theory the severity and duration of opioid withdrawal may be more pronounced with nalmefene than naloxone in patients with physical dependence to opioids, this was not demonstrated in the available data. However, the potential advantage of improved efficacy of reversal with certain potent opioids will outweigh a more severe and prolonged opioid withdrawal.

2.3 Marketing History

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

2.4 Summary of Presubmission/Submission Regulatory Activity

- **January 2020**: An opening IND pharmacokinetic study was submitted and placed on full clinical hold (b) (4) In May 2020, the full clinical hold was removed after Opiant amended the protocol to include acceptable mitigation of device-related risks. (b) (4) Subsequently, Opiant changed their device to the Aptar Unidose Nasal Spray (UDS™) device which is approved for use of Narcan nasal spray, making the (b) (4) issues regarding their originally proposed device moot.
- **April 2020**: A Type C meeting was held regarding Opiant's proposed (b) (4) The Division of Applied Regulatory Science (DARS) was consulted for input on an appropriate study design to evaluate pharmacodynamic effects of opioid antagonists. The following points were discussed:
    a. Opiant to use minute ventilation as the primary endpoint to establish efficacy; change in minute ventilation (MV) from nadir to 5 minutes post-naloxone or nalmefene
    b. (b) (4)
    c. Opiant would consult with anesthesiologists regarding study design of measuring MV in the presence of elevated carbon dioxide as a continuous assessment
    d. Opiant can propose a noninferiority-type endpoint with appropriately justified margins
    e. The Division recommended the Sponsor reconsider collecting blood samples; blood samples would help understand and establish the concentration-effect relationship
    f. Advice on the design of a PK bridging study
    g. Advice on how to support a claim (b) (4)
- **October 2020**: The first protocol version was submitted for OPNT003-OOD-001
- **December 2020**: A Type B teleconference was held, and the following points were discussed:

a. Additional study design advice from DARS on OPNT003-OOD-001
b. Division concerns (b) (4)
c. Office of Regulatory Policy to consider if Sponsor's proposed GMP-compounded version of Revex (discontinued) is acceptable
d. The Division advised that the sample size, endpoints, and noninferiority margin for Part 2 cannot be agreed on without review of results from Part 1

- **February 2021:** Protocol Version 2.0 was submitted which incorporated many Division recommendations
- **June 2021**: Advice letter issued to Sponsor after review of Protocol Versions 3.0 (submitted March 2021) and 4.0 (submitted April 2021 with the Part 1 extension)
- **June-September 2021**: Cycles of Information Requests and Responses
- **September 2021**: Sponsor submitted protocol Version 6.0 (Part 1 completed)
- **November 2021**: Fast Track designation was granted. Opiant's formulation of Opvee contains a proprietary absorption enhancer, improving bioavailability. The constellation of API attributes, high affinity for the mu-opioid receptor and longer half-life than naloxone, has potential for improvement in morbidity and mortality above that of the currently marketed naloxone opioid antagonists.
- **December 2021:** Sponsor submitted Protocol Version 8.0, the final version, which increased sample size for Part 2
- **March 2022**: Sponsor requested a rolling review which was granted during the pre-NDA stage
- **November 2022**: Priority review was requested and granted after submission of the NDA; Stamp date for submission: November 22, 2022.
- **December 2022**: The agreed pediatric study plan (PSP) was submitted.

3. Product Quality

The Office of Product Quality (OPQ) recommends approval of this NDA based on the reviews completed by the drug substance, drug product, process and facilities, and microbiology teams.

The following assessment was excerpted from the Integrated Quality assessment, dated May 1, 2023:

- Final Overall Recommendation – Approval
- Expiration Dating: The provided data supports an expiry period of 28 months when stored at controlled room temperature 15°C to 25°C (59°F to 77°F).
- Environmental Assessment: Categorical Exclusion - Adequate

For additional information, refer to the Integrated Quality Review completed by the Chemistry, Manufacturing and Controls (CMC) team dated May 1, 2023. OPQ recommends approval with no postmarketing commitments or requirements. The Division agrees with the recommendations by the OPQ review team.

4. Nonclinical Pharmacology/Toxicology

The following assessment was reproduced from the pharmacology/toxicology review, dated May 11, 2023 (verbatim).

Introduction

Opiant submitted a New Drug Application, via a 505(b)(2) regulatory pathway, for Nalmefene Nasal Spray and proposes the following indication: for the complete or partial reversal of opioid drug effects including respiratory depression induced by either natural or synthetic opioids. The NDA relies upon FDA's previous findings of safety and efficacy for Revex, which is the listed drug (LD). The Applicant has conducted bioequivalent studies as a scientific bridge to the LD. Nalmefene is an antagonist at the mu receptor. The drug product comprises a single-use nasal spray device intended for intranasal delivery of 100 mcL of nalmefene hydrochloride solution as a 2.7 mg dose of nalmefene base. The adequacy of nonclinical data to support the safety of the drug product is assessed against a maximum recommended human daily dose (MRHD) of

5.4 mg of nalmefene base delivered by two nasal sprays. At this MRHD, the associated systemic exposures are Cmax of 22.2 ng/mL and AUC0-inf of 89.5 ng*h/mL, which was reported in the human PK Study OPNT003-PK-002.

Brief Discussion of Nonclinical Findings

In support of the nalmefene nasal spray, the Applicant submitted nonclinical toxicology studies to qualify the change in route of administration, safety of the higher nalmefene systemic exposures when compared to the LD, as well as to qualify the safety of the new excipient. The Applicant also conducted PK bridging studies to allow comparisons with the listed drug, Revex, and to inform labeling.

The Applicant's specifications for the drug substance and drug product impurities are deemed acceptable. Although one drug substance impurity, (b) (4), was noted to exceed ICH Q3A(R2), this impurity is also a drug product impurity that is controlled within ICH Q3B(R2) limits. Therefore, the specification for the drug substance impurity, (b) (4), is not a safety concern given that this impurity is controlled at an acceptable limit in the drug product. Residual solvent specifications are within the levels outlined in ICH Q3C(R8). Elemental impurities are below the control threshold of 30% as recommended in ICH Q3D. To support the safety of the container closure system, the Applicant provided extractables and leachables studies. No leachable compounds were present over the 5 mcg/day qualification threshold and therefore there are no concerns with the safety of the container closure system.

The intranasal spray formulation is an aqueous solution consisting of a (b) (4) that are all within levels stated in the FDA Inactive Ingredients Database (IID). The drug product also contains Intravail® A3 (dodecylmaltoside, DDM), which is an excipient to improve the bioavailability of the drug administered by the intranasal (IN) route. DDM is not listed in the IID and thus it is considered as a new excipient.

The Applicant submitted toxicology studies for DDM and submitted a letter of authorization (LoA) to reference the DDM data in DMF (b) (4).The systemic and local safety of DDM have been adequately characterized in 28-day repeat-dose general toxicology studies in rats and dogs. There are no genotoxicity concerns with DDM. However, from the perspective of reproductive and developmental toxicity characterization, neither data submitted by the Applicant nor data in DMF (b) (4) adequately addresses all the reproductive and developmental toxicology (DART) endpoints. A study report for a preliminary embryo-fetal toxicology study (GLP) with DDM in rats was submitted, however, was not deemed acceptable. It is noted that the Applicant submitted human pharmacokinetic data that indicate administration of two nalmefene nasal sprays resulted in measurable systemic exposure to DDM. However, the Applicant has not demonstrated that the detected levels do not pose a risk to cause reproductive and developmental effects. Because the product is for a life-threatening indication and DDM did not show adverse effects in the preliminary GLP embryo-fetal toxicology study, the lack of data to characterize DDM in all of the DART endpoints was not considered an approval issue after discussions with the clinical team based on a benefit: risk analysis and given that the full battery of reproductive and developmental studies with the new excipient can be requested as a PMR for a product developed for a life-threatening indication.

Systemic and local toxicity of the drug product were evaluated in two GLP 28-day repeat-dose general toxicology studies in rats and dogs that received daily nasal administration of nalmefene for 28 days. From a local nasal tissue perspective, minimal to slight erosion/ulcer, focal hemorrhage or exudate; minimal metaplasia was observed in the rat study and minimal epithelium degeneration was observed in the dog study.

Some of the local effects were also observed in the groups treated with vehicle that consisted of the drug excipients. These local effects are considered drug product related, and reversibility was demonstrated in the dog study. Comparing to the clinical nalmefene hydrochloride concentration at 30 mg/mL, the nonclinical studies have tested concentrations up to 3.3 times higher. Therefore, the local safety of the drug product has been adequately characterized. For systemic effects, moderate hemorrhage was observed in one high dose-treated rat; minimal to mild mixed cell infiltrate, inflammation, alveolar hemorrhage or alveolar granuloma was observed in the dog study without clear dose dependency. The lung findings tended to be focal and limited in distribution and are likely associated with the nasal route of administration. Moderate to marked seminiferous tubule degeneration accompanied by cellular debris and decreased sperm in the epididymides was observed in two high dose-treated rats. The systemic safety margin calculated against human AUC0-inf was at least 2.8x in the rat study and 13x in the dog study, while the safety margin calculated against human Cmax at the MRHD was at least 12.3x in the rat study and 131x in the dog study. Taken together, the pivotal GLP 28-day repeat-dose general toxicology studies in rats and dogs have adequately characterized the local and systemic effects of nalmefene.

Recommendations

Approvability

From a nonclinical pharmacology and toxicology perspective, NDA 217430 for nalmefene nasal spray may be approved with the following recommended labeling changes and postmarketing requirements pending the final clinical benefit:risk assessment.

Additional Nonclinical Recommendations
If the drug product is approved in this review cycle, the following additional studies are recommended, as postmarketing requirements, which include safety qualification studies for DDM (i.e., reproductive and developmental studies) and juvenile animal studies to qualify safety of the API and the DDM excipient as outlined in the agreed Pediatric Study Plan (PSP):

- Conduct a fertility and early embryonic development study in rats with dodecylmaltoside (DDM).
- Conduct an embryo-fetal development study in rats with dodecylmaltoside (DDM).
- Conduct an embryo-fetal development study in rabbits with dodecylmaltoside (DDM).
- Conduct a pre- and postnatal development study in rats dodecylmaltoside (DDM).
- Conduct a juvenile animal study in rats to support the initiation of clinical studies in pediatric patients from 3 to less than 12 years of age. This study will evaluate the effect of the drug on growth and development, specifically reproductive performance/sexual maturation, local tissues including the nasal and respiratory tract, immune capacity, and central nervous system histopathology and long-term behavioral effects.
- Conduct a juvenile animal study in rats to support the initiation of clinical studies in pediatric patients from birth to less than 3 years of age. This study will evaluate the effect of the drug on growth and development, specifically reproductive performance/sexual maturation, local tissues including the nasal and respiratory tract, immune capacity, and central nervous system histopathology and long-term behavioral effects.

The Nonclinical review also included a table of recommended revisions to labeling. The Division agrees with the recommendations of the pharmacology/toxicology review team.

5. Clinical Pharmacology

The clinical pharmacology review was completed on May 8, 2023, with no concerns identified that would preclude approval. The following information is from the clinical pharmacology review (verbatim):

Pharmacology and Clinical Pharmacokinetics
This is a 505(b)(2) NDA application, which relies on the previous Agency findings of safety and efficacy for the reference listed drug REVEX (nalmefene hydrochloride injection) NDA 020459. REVEX is indicated for the complete or partial reversal of opioid drug effects, including respiratory depression, induced by either natural or synthetic opioids. REVEX is also indicated in the management of known or suspected opioid overdose. The pharmacology and pharmacokinetics (PK) of Opvee, nalmefene nasal spray, have been characterized in two Phase 1 clinical studies in healthy subjects as well as a population PK report that included data from one pharmacokinetic-pharmacodynamic study (PK-PD).

Mechanism of Action: Nalmefene is a well-known opioid antagonist that binds to opioid receptors and prevents or reverses the effects of opioids, including respiratory depression, sedation, and hypotension.

Summary of Pharmacokinetics of Opvee: Following Opvee administration, quantifiable plasma nalmefene levels were observed at the first time point of blood collection that 2.5 minutes. Plasma levels of single nasal spray of Opvee were higher at all timepoints compared to 1 mg intramuscular (IM) injection of nalmefene (lowest effective dose); thus, efficacy of Opvee is implied. Peak plasma levels of nalmefene were noted approximately 15 minutes after single nasal spray administration of Opvee. The applicant states that "While plasma concentrations following IV administration were not reported at earlier time points for REVEX, immediately (e.g., 1 minute) following IV administration plasma concentrations are likely to exceed Cmax concentrations following 1-2 doses of nalmefene nasal spray." It is reasonable to assume that peak plasma nalmefene concentrations of 0.5 to 1 mg nalmefene injection will be higher immediately post bolus administration.

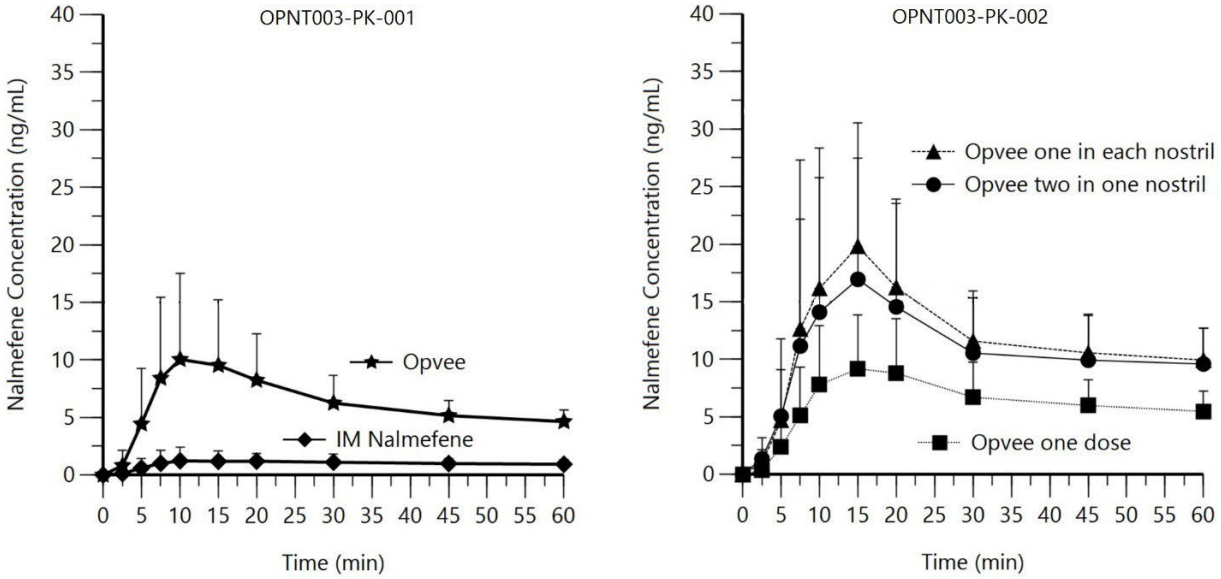


Figure 1: Pharmacokinetics of nalmefene (mean ± SD) following Opvee administration from relative bioavailability study (Left) and repeat dose PK study (Right) truncated to the first hour.

It is anticipated that if the patient does not respond, opioid overdose reversal products may be administered repeatedly until emergency services arrive. Pharmacokinetics of single spray, and two spray doses of Opvee administered as one spray in each nostril and two sprays in one nostril were evaluated in Study OPNT003-PK-002. A dose-proportional increase in Cmax and AUC is noted when comparing single dose and two doses of Opvee administered in each nostril. Approximately 21% higher Cmax was noted when two doses of Opvee were administered one in each nostril compared to two doses in one nostril; AUC was similar between these treatments. Based on Revex injection (NDA 20459) label, nalmefene exhibited dose proportional pharmacokinetics following intravenous administration of 0.5 mg to 2.0 mg. The calculated AUC of label approved dose and data from publication (Kaplan 1999) were used to compared with observed and simulated doses of Opvee nasal spray. The systemic levels (AUC) of up to three doses of Opvee nasal spray are expected to be lower than the highest safe dose of nalmefene (Table 1).

Table 1: Systemic exposure of nalmefene (observed and simulated) with Opvee nasal spray and nalmefene Injection.

Parameter	**Single Dose IV (mg)***			**Label indicated 0.5 mg followed by one dose of 1 mg (Simulation)**	**Kaplan et al., 1999, 2 mg x four doses (Simulation)**	**Nasal Spray 2.7 mg**		
						Observed		**Simulation (Three doses administered 5 minutes apart)**
	0.5	1	2			1 dose	2 doses	3 doses
AUC ng*h/mL	8.3	16.6	34.3	24.9	137.2	46.8	89.5	123.92

Source: Revex label Table 1. https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/020459s006lbl.pdf
Simulated doses of three or four doses were conducted with nalmefene nasal spray doses administered with a 5-minute gap between doses. Nonparametric superposition method was employed using Phoenix 32-bit version 8.3.4.295 to generate various PK parameters.

Since both Cmax and AUC of up to three doses of Opvee nasal spray are expected to be below the Cmax and AUC of highest safe and effective doses of IV nalmefene, the safety of two doses of Opvee nasal spray is implied.

Pharmacodynamics: In study OPNT003-OOD-001, following Opvee nasal spray administration the reversal of opioid-induced respiratory depression was noted within 2.5 to 5 minutes in an experimental clinical pharmacology study conducted in opioid-experienced but non-dependent healthy volunteers. In the same study, maximum reversal effect of nalmefene in reversing respiratory depression was noted in 15 minutes. Naloxone (Narcan nasal spray) was also included as a positive-control, or an assay sensitivity or validity measure. The observations from the PK-PD study were fit well with Office of Clinical Pharmacology's (OCP) opioid-effects model that was previously published. The OCP's opioid- effects model was developed to translate the systemic exposure of different opioid agonists and antagonists into clinically interpretable outcome such as minute ventilation, blood gas tensions, and cardiac output.

Figure 2: Pharmacologic effects of nalmefene IN 3 mg (A & C) and naloxone IN 4 mg (B & D) on minute ventilation (MV) and end-tidal CO2 (ETCO2) in Study OPNT003-OOD-001.

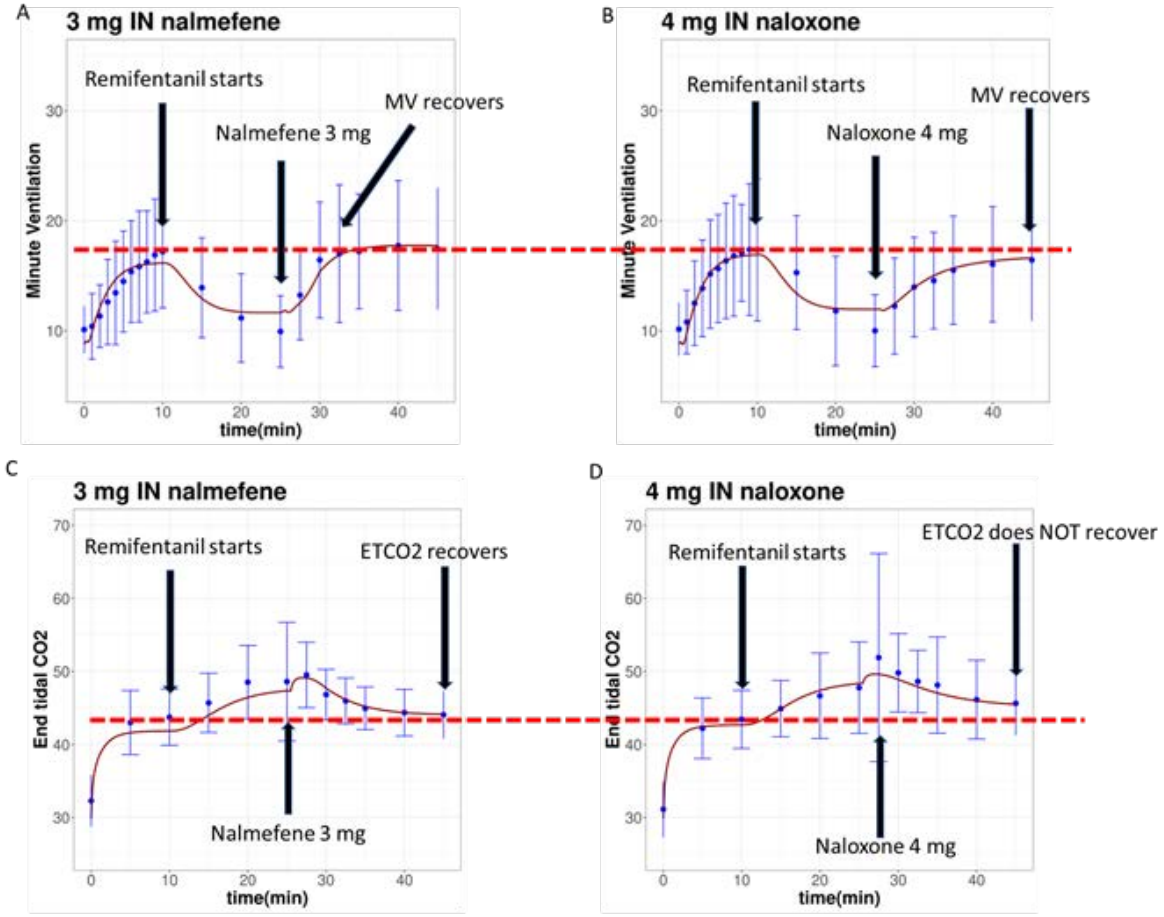


Figure 2 A and B show effects on MV. Figure 2 C and D show effects on ETCO2. Blue error bars: mean and standard deviation from the study OPNT003-OOD-001. Thin red lines: model simulation of a typical subject.

Starting from time 0, subjects breathed in a hyperoxic and hypercapnic gas mixture. This resulted in an increase of MV. Starting from 10 min, the remifentanil (0.175 ug/kg/min) infusion began, resulting in a decrease of MV. At the 25th minute, IN nalmefene (A) or naloxone (B) was administered, leading to a recovery (increase) of MV. For the nalmefene group (A), it took less than 10 min for MV to recover to the pre-opioid level (thick horizontal red dash line). For the naloxone group (B), it took at least 20 min. For the nalmefene group (C), 20 min after the IN administration, ETCO2 has recovered (decreased) to the pre-opioid level (thick horizontal red dash line). For the naloxone group (D), 20 min after the IN administration, ETCO2 has not fully recovered (still above the pre-opioid level).

In addition, OCP's Independent Modeling and Simulation confirmed the time to onset of action, duration of pharmacodynamic effects in terms of hypoxia, cardiac arrest, and preventing renarcotization in virtual population representative of opioid use disorder patients (See DARS Review appended in Section 4.3).

Opvee nasal spray was not evaluated in any specific populations. As such no dosage adjustment is needed in elderly, renal impairment patients or hepatic impairment patients. The basis for the recommendation is reliance on label for nalmefene injection. Based on population PK simulations, compared to an adult population (mean weight 75.42 kg), 12-year-old virtual subjects with a median weight 50.6 kg (range 27.6 to 126.8 kg) are expected to have 7.6% higher mean Cmax and 25.5% higher mean AUC0-∞. Since such anticipated differences in exposure may not adversely affect safety yet provide effective plasma nalmefene concentrations, dosage adjustment of Opvee nasal spray in adolescent patients is not needed.

Dosing and Therapeutic Individualization
General Dosing
Recommended dose for the reversal of known or suspected opioid overdose in patients 12 years and older is a single spray of Opvee. Emergency medical services should be called after the first dose. If the patient does not respond within two to five minutes, a second dose of Opvee may be administered. If the patient responds to Opvee, repeat dosing may not be necessary, particularly while in care of emergency services personnel.

Therapeutic Individualization
General dosing recommendations apply to patients 12 years and older. Adolescent patients (average bodyweight 50 kg) are expected to have similar exposure to nalmefene as adults. Titration or dosage adjustment with regard age, gender, bodyweight, hepatic impairment, and renal impairment is not necessary.

The Clinical Pharmacology team played a key role in revising the proposed labeling. The Division agrees with the recommendations of the clinical pharmacology review team.

6. Clinical Microbiology

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

7. Clinical/Statistical- Efficacy

The Applicant is relying on FDA's previous findings of efficacy for the listed drug REVEX (nalmefene hydrochloride injection; NDA 020459). The efficacy of Opvee is supported by a scientific bridge to the listed drug through one bioavailability pharmacokinetic study (Study OPNT003-PK-001) comparing Opvee with an Applicant manufactured intramuscular (IM) nalmefene hydrochloride injection. Study OPNT003-PK-001 demonstrated that the maximum nalmefene exposure (C_{max}), partial AUCs, and total exposure were several-fold higher after Opvee administration compared to IM administration. These findings support the Applicant's reliance on FDA's previous findings of efficacy for REVEX injection in adults.

Importantly, the Division sent an Advice Letter to Sponsors of nalmefene in 2019 informing them of concerns that must be addressed during the clinical development program as an emergency-use opioid antagonist. These concerns included a slow onset of action, a need for titration, and long duration of action. Specifically, as an emergency-use opioid antagonist in a

community setting, delayed or variable onset of action at critical early time points may result in morbidity and mortality. Regarding titration, unlike Revex (nalmefene hydrochloride injection) which can be titrated to clinical effect with incremental doses, a nasal spray formulation for community use must deliver an effective dose that does not rely on titration. Lastly, the longer half-life of nalmefene relative to naloxone may result in protracted opioid withdrawal symptoms in patients who are physically dependent on opioids.

To address the Division's concerns with the API for community use, the Applicant conducted a pharmacodynamic study, OPNT003-OOD-001 (Study OOD-001) to confirm onset of action of Opvee at critical early time points as well as to confirm the effectiveness of a single spray (i.e., titration not needed) and its duration of action under steady-state opioid agonism. The concern for long duration of action of nalmefene was related to the potential for causing prolonged precipitated opioid withdrawal. Because the patient population for Study OOD-001 consisted only of healthy volunteers with prior opioid exposure – and not opioid dependence – concerns regarding prolonged opioid withdrawal were addressed separately (refer to 'Safety' below). Though not an adequate and well-controlled study - as agreed on with the Division - the review team considered Study OOD-001 to be pivotal in demonstrating performance characteristics of Opvee, namely onset of action, to confirm its clinical effectiveness and appropriateness for use in a community setting.

Moreover, the Division acknowledged the ethical and safety challenges of conducting a study in which healthy subjects are intentionally overdosed with opioids in order to evaluate the efficacy of Opvee. The Division worked closely with Opiant to determine an acceptable trial design and patient population, and ultimately, an experimental model utilizing ventilatory response to hypercapnia (VRH) was considered adequate to safely and ethically investigate the opioid antagonist pharmacodynamic effects of nalmefene in healthy subjects while receiving a continuous infusion of opioid to simulate an opioid overdose. The Division of Applied Regulatory Science (DARS) contributed significantly to the study design given their experience with VRH and opioid-induced respiratory depression models.

Notably, before agreement on utilizing the VRH model, Opiant initially proposed to use (b) (4); however, the Division did not accept this proposal (b) (4)

The study of interest, OPNT003-OOD-001, was a two-part open-label, randomized, 2-period, 2-treatment, crossover study in healthy subjects with prior opioid exposure to demonstrate noninferiority of Opvee compared to naloxone NS on minute ventilation during steady-state remifentanil infusion. The primary endpoint for the pivotal Part 2 of the study was change in minute ventilation from a remifentanil-induced nadir to 5 minutes after administration study drug (Opvee or Naloxone NS). To safely evaluate the pharmacodynamic effect of these opioid antagonists on reversal of respiratory depression while receiving a continuous remifentanil infusion, a ventilatory response to hypercapnia (VRH) model was utilized. Subjects inspired a hypercapnic gas mixture (7% CO2) to induce hyperventilation. It was against this baseline of

hyperventilation that the Applicant could ethically and safely suppress the subjects' minute ventilation with a continuous infusion of remifentanil (steady-state opioid agonism).

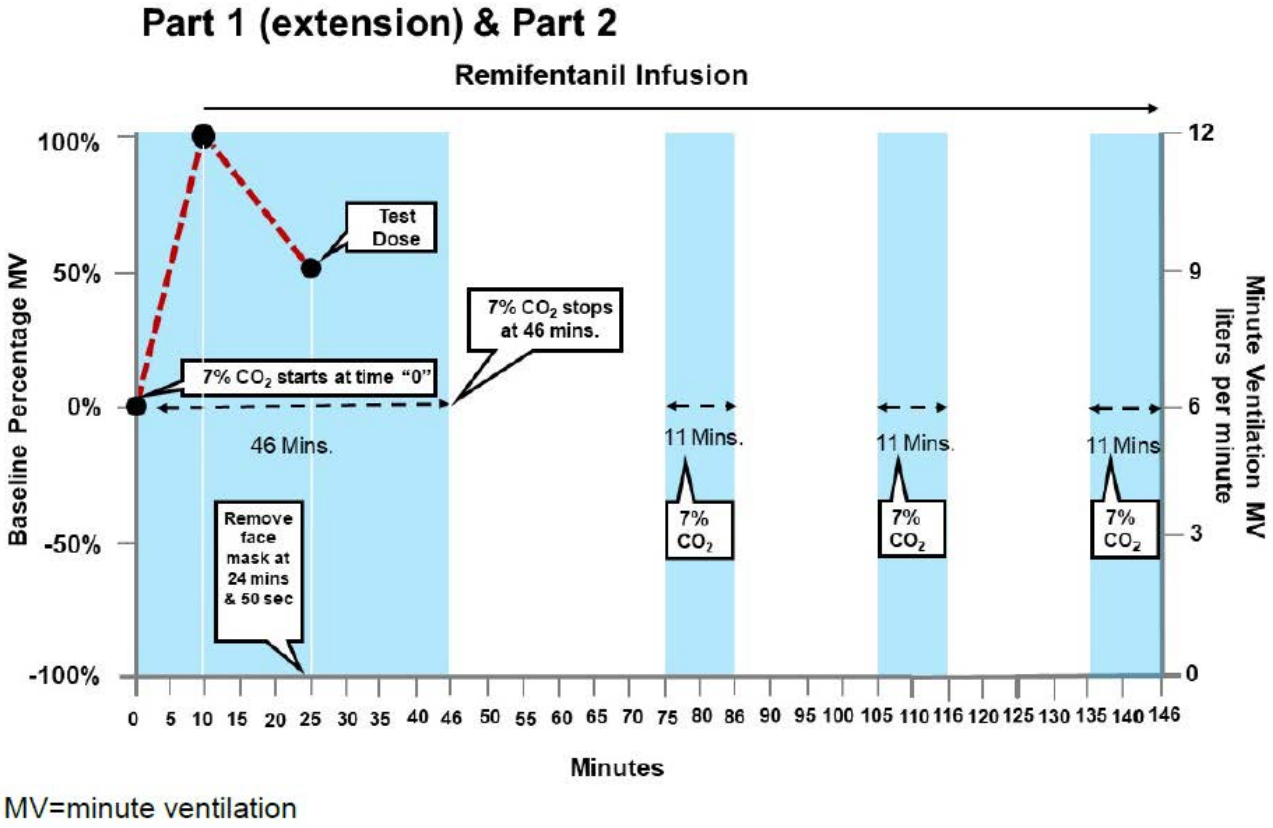
Additionally, the purpose of the non-pivotal Part 1 of Study OOD-001 was to determine two important factors: 1) the remifentanil dose required to suppress minute ventilation by at least 40% from the hyperventilated baseline and 2) that naloxone NS increases the minute ventilation by >15% but <65% over the remifentanil-induced nadir at 5 minutes. The calibration of these two factors in Part 1 would ensure that Opvee could demonstrate a treatment effect in Part 2, if one existed. Once these two factors established the necessary remifentanil dose, the study could proceed to the pivotal Part 2, an open-label, randomized, 2-period, 2-treatment crossover study to evaluate the primary endpoint of change in minute ventilation from a remifentanil-induced nadir to 5 minutes after administration of study drug, Opvee or Naloxone NS. Naloxone NS, an approved standard-of-care treatment for emergency reversal of opioid toxicity, serves as a positive control providing some measure of assay validation. PK and safety parameters were assessed as well at pre-determined timepoints.

Importantly, remifentanil (ULTIVA), indicated as an analgesic agent for use during induction and maintenance of general anesthesia and for continuation as an analgesic into the immediate postoperative period in adult patients in a monitored clinical setting, was chosen as the opioid in this study because of its especially short-acting duration; it is rapidly metabolized with a half-life of approximately nine minutes. If any subjects experienced remifentanil-related complications, cessation of the infusion would rapidly reverse the event. This was a critical safety point for subjects participating in an experimental model of opioid overdose.

Lastly, the Division advised Opiant (January 2021 Type C Meeting Minutes) that results from Part 1 would need to be submitted for review in order to formally agree on sample size, endpoints, and non-inferiority margin for Part 2. Opiant acknowledged the Division's recommendation; however, they were concerned that this delay and disruption would be detrimental to the trial conduct. Opiant subsequently did not submit study data from Part 1, and therefore, the sample size, endpoints and non-inferiority margin were never formally agreed on by the Division.

The study design for Part 1 (extension) and Part 2 is illustrated here:

Figure 2: Study Design of Part 1 (extension) & Part 2



Source: Clinical Study Protocol OPNT003-OOD-001; Version 8.0

The blue shaded areas represent times when subjects inspired a hypercapnic gas mixture ((50% O2, 43% N2, 7% CO2) to induce hyperventilation. Subjects inspired this gas mixture for 10 minutes before the intravenous remifentanil infusion was started at Minute 10. Subjects continued these two interventions, the hypercapnic gas mixture and remifentanil infusion for an additional 15 minutes before either Opvee or Naloxone NS was administered in a crossover sequence. The primary endpoint was assessed at 5 minutes after administration of the intranasal study drugs. The white areas of the figure represent breaks from the face mask in which the subjects were breathing room air. The purpose of these breaks was to improve patient comfort and minimize patient drop out.

Opiant provided the following statistical considerations for Part 2 of Study OOD-001.

- The ITT analysis set included all subjects who were randomized and received at least one dose of Opvee or Naloxone NS
- Noninferiority Margin of 0.6 L/min was chosen by the Applicant based on the following justification:

  - Naloxone IV produced a 3 L/min increase from the nadir of opioid induced depression of minute ventilation at 5 minutes post-administration in a study by Dahan et al. (2010)[1]
  - A non-inferiority margin of 80% of the estimated reversal produced by naloxone under these conditions, was chosen, which represents a difference of 0.6 L/min between treatments. Therefore, noninferiority was demonstrated if the upper limit of the 95% CI was less than 20% of the mean change in minute ventilation for naloxone hydrochloride.
  - A difference of 20% or less would not likely represent a clinically meaningful difference between treatments.
- The primary endpoint of change in minute ventilation at 5 minutes after study drug administration would be analyzed using a linear model for a two-treatment, two-period crossover trial including treatment, period, and sequence as fixed effects, and subject nested within sequence as a random effect
- Interim analyses were conducted for sample size estimation. Sixty-eight subjects were to be enrolled in Part 2 so that at least 46 subjects would complete both treatments, Opvee and Naloxone NS, at the primary endpoint for 5 minutes post-dose. A protocol amendment was submitted as Version 8 to increase the Part 2 sample size to 68 subjects.

Study Results for OPNT003-OOD-001:

Sixty-nine subjects participated in Part 2 with 61 subjects receiving 3 mg Opvee and 60 subjects receiving 4 mg Naloxone NS. These 69 subjects comprised the Part 2 analysis sets of ITT, PK and safety.

Overall, as detailed in Table 2 below, 18 subjects in Part 2 of Study OOD-001 were discontinued from the study. Four subjects discontinued due to adverse events and six subjects met a protocol-specified withdrawal criterion.

[1] Dahan A, Aarts L , Smith T. Incidence, Reversal, and Prevention of Opioid-induced Respiratory Depression. Anesthesiology. 201 0;1 12:226-238.

Table 2: Summary of Subject Disposition

	Part 1 (N=7) n (%)	Part 1 Extension (N=8) n (%)	Part 2 (N=69) n (%)	Overall (N=84) n (%)
Completed Study	5 (71.4)	8 (100.0)	51 (73.9)	64 (76.2)
Discontinued Study	2 (28.6)	0	18 (26.1)	20 (23.8)
Reason for Study Discontinuation				
Adverse Event	0	0	4 (5.8)	4 (4.8)
Protocol Deviation	0	0	0	0
Lost to Follow-Up	0	0	0	0
Withdrawal by Subject	2 (28.6)	0	5 (7.2)	7 (8.3)
Study Terminated by Sponsor	0	0	0	0
Pregnancy	0	0	0	0
Death	0	0	0	0
Physician Decision	0	0	2 (2.9)	2 (2.4)
Sponsor Request	0	0	0	0
Protocol-Specified Withdrawal Criterion Met	0		6 (8.7)	6 (7.1)
Other	0	0	1 (1.4)	1 (1.2)

N=number of subjects.
Percentages are based on the number of subjects in the Safety Set.
Source: Applicant's submission; Clinical Study Report, Version 1.0 Table S1, page 11

The primary endpoint was the change in minute ventilation from a remifentanil-induced nadir to 5 minutes after administration of the nasal spray study drugs. Statistical analyses of noninferiority were performed from the ITT set (69 subjects), using only subjects in Part 2 who took both treatments and completed the data collection for 5 minutes post-dose (50 subjects). The following results were demonstrated:

- Opvee (LS mean 5.745 L/min) demonstrated a greater change in minute ventilation at 5 minutes compared to Naloxone NS (LS mean 3.011 L/min) which was confirmed by a sensitivity analysis
- Opvee demonstrated a greater maximum increase in minute ventilation as compared to Naloxone NS
- Mean minute ventilation returned to 98.9% of pre-remifentanil levels for Opvee at 5 minutes post-dose as compared to 95% of pre-remifentanil levels for Naloxone NS at 20 minutes post-dose

The following table shows the results of post-dose minute ventilation between nalmefene and naloxone:

Table 3: Minute Ventilation and Change in Minute Ventilation from Nadir Baseline

	Naloxone				Nalmefene			
Minutes in Relation to Study Drug Administration	**n**	**Mean MV (L/min) (SD)**	**n**	**Change from Baseline (L/min) (SD)**	**n**	**Mean MV (L/min) (SD)**	**n**	**Change from Baseline (L/min) (SD)**
-15 (Remifentanil baseline)	59	17.36 (6.46)	-	-	62	17.19 (5.10)		-
0 (Nadir Baseline)	59	10.55 (4.65)	58	-0.68 (3.02)	61	10.63 (4.02)	61	-0.70 (2.46)
2.5	59	12.25 (4.37)	59	1.70 (4.05)	60	13.24 (4.06)	60	2.55 (2.97)
5	59	13.98 (4.53)	59	3.43 (4.70)	60	16.44 (5.27)	60	5.74 (4.83)
7.5	59	14.56 (4.39)	59	4.01 (4.82)	61	17.01 (6.26)	61	6.38 (5.51)
10	59	15.51 (4.91)	59	4.96 (5.30)	61	17.21 (5.22)	61	6.58 (5.17)
15	59	16.05 (5.23)	59	5.55 (4.94)	61	17.75 (5.90)	61	7.12 (6.00)
20	59	16.44 (5.55)	59	5.93 (5.24)	60	17.46 (5.55)	60	6.79 (5.53)
30	59	8.55 (1.81)	58	-1.95 (4.61)	60	8.50 (2.66)	60	-2.18 (3.93)
45	59	8.02 (1.89)	58	-2.53 (4.59)	59	8.06 (2.15)	59	-2.56 (3.92)
60	59	12.99 (4.22)	58	2.52 (4.39)	60	13.60 (4.55)	60	2.92 (4.36)
90	57	12.67 (3.93)	56	2.14 (4.66)	59	13.42 (4.38)	59	2.71 (4.56)
95	57	8.23 (3.55)	56	-2.32 (6.16)	59	8.10 (2.92)	59	-2.61 (4.26)
100	56	7.00 (1.89)	55	-3.56 (4.93)	59	7.81 (2.48)	59	-2.91 (4.03)
110	55	7.93 (2.20)	54	-2.53 (4.20)	59	8.59 (2.27)	59	-2.13 (4.05)
120	57	12.49 (3.91)	56	2.02 (3.86)	59	13.59 (4.60)	59	2.88 (4.60)

MV = Minute Ventilation; SD = Standard Deviation
Source: Statistical primary review by Yunfan Deng, Ph.D. / Tables 14.2.1.3.1, 14.2.1.3.2, and 14.2.1.3.3 of Study OPNT0003-OOD-001 Clinical Study Report (CSR)

Furthermore, at the primary endpoint the upper limit of the 95% CI (-1.175) for nalmefene was less than 20% of the Least Squares (LS) mean change in minute ventilation for naloxone (0.6022). The Applicant noted that the point estimate favored Opvee, demonstrating both noninferiority and superiority. These results were confirmed by the Applicant's sensitivity analysis.

Additionally, the proportion of subjects with extreme responses to the two treatments at 5 minutes post-administration were compared using the Pearson chi-square test. The proportion of subjects administered Naloxone NS with a change in minute ventilation that was less than 50% of the change in minute ventilation following Opvee was significantly greater ($p = 0.0003$) than the proportion of the subjects administered Opvee with a change in minute ventilation that was less than 50% of the change in minute ventilation following Naloxone NS.

As a sensitivity analysis, the primary analysis was rerun excluding the subjects for which the change in minute ventilation from remifentanil-induced nadir to 5 minutes was more than 1.5 interquartile range (IQR) below first quartile (Q1) or more than 1.5 IQR range above third quartile (Q3).

An unexpected observation was that the PK plasma concentrations from Study OOD-001 were lower than that of the two PK studies, PK-001 and PK-002. All three studies were conducted

in healthy volunteers; therefore, the Applicant hypothesized that the gas mixture administered through the tightly sealed facemask dried the nasal mucosa and subsequently attenuated the effect of the nasal absorption enhancer. Importantly, the Clinical Pharmacology and DARS review teams confirmed that plasma PK of Naloxone NS in Study OOD-001 was comparable to the PK in other Naloxone NS studies. Therefore, the PK and PD results of Opvee in Study OOD-001, while demonstrating noninferiority and superiority on the primary endpoint in this experimental model, represent a worst-case scenario despite the statistically significant and clinically important results. The efficacy of Opvee under real-world conditions will likely have earlier onset of action and greater change from baseline in minute ventilation at early timepoints and beyond compared to this experimental model.

The Applicant has provided substantial evidence of effectiveness to support approval of Opvee as an emergency-use opioid antagonist for community use based on reliance of the Agency's previous findings of efficacy for the listed drug REVEX (nalmefene hydrochloride injection; NDA 020459) in combination with the study results of OPNT003-OOD-001 (pharmacodynamic study) and OPNT003-PK-001 (scientific bridge). Study OPNT003-OOD-001, though not an adequate and well-controlled study as agreed on with the Division, addresses and obviates concerns regarding onset of action, titration, and duration for this new dosage form in the proposed indication.

8. Safety

The Applicant is relying on the Agency's previous findings of safety for the listed drug (LD) REVEX (nalmefene hydrochloride injection; NDA 020459) as well as three clinical studies from the Opvee development program described in detail below.

Overview of clinical studies included in the safety evaluation:

- OPNT003-PK-001:
  - Established the scientific bridge by demonstrating systemic exposure comparable to an approved intramuscular dose
- OPNT003-PK-002:
  - Provided pharmacokinetic and safety data on repeat dosing. The plasma concentrations of repeat dosing represent the maximum exposure of Opvee in the clinical development program. The nasal sprays were administered in immediate succession which is different than the proposed labeling for repeat dosing in Dosage and Administration (repeat every 2 to 5 minutes if the patient does not respond)
- OPNT003-OOD-001:
  - A pharmacodynamic study designed to address concerns regarding onset of action, titration, and duration of action of Opvee when administered under steady-state opioid agonism

OPNT003-PK-001 was an open-label, randomized, two-period, two-treatment, two-sequence, crossover study in 68 healthy volunteers. Subjects were randomly assigned to receive two treatments during the two dosing periods: Opvee 3 mg dose and nalmefene hydrochloride 1 mg intramuscularly (IM) with a 4-day washout period between doses. The primary objective

was to determine the PK of Opvee 3 mg compared to a 1 mg dose of nalmefene hydrochloride delivered as an IM injection, to demonstrate systemic exposure comparable to an approved IM dose. The secondary objective was to evaluate the safety and tolerability of Opvee in healthy volunteers.

Subjects remained in the inpatient facility for seven days to complete the treatment phase of the study and were discharged following completion of the discharge procedures at the end of the last period. Subjects were phoned three to five days after discharge to query adverse events and concomitant medications since discharge.

A total of 66 out of 68 subjects completed both study periods. Two subjects discontinued from the study for reasons unrelated to study drug.

OPNT003-PK-002 was an open-label, randomized, six-sequence, three-treatment, three-period crossover study in which 24 healthy subjects received three separate administrations of Opvee. Subjects were randomly assigned to one of six sequences (four subjects per sequence). Each subject received one of the three treatments in each of the three treatment periods below.

Table 4: Identity of Study Treatments

Treatment	Dose
Treatment 1 (T1)	3 mg (one 0.1 mL spray of 30 mg/mL nalmefene hydrochloride in one nostril)
Treatment 2 (T2)	6 mg (one 0.1 mL sprays of 30 mg/mL nalmefene hydrochloride in each nostril)
Treatment 3 (T3)	6 mg (two 0.1 mL sprays of 30 mg/mL nalmefene hydrochloride in one nostril)

Source: Summary of Clinical Pharmacology Studies, pg. 9 (PDF)

Drug administration was separated by a six-day washout period. Subjects remained in the inpatient facility for 15 nights to complete the entire study and were discharged on the second day after the last dose. Subjects were called three to five days after discharge to query adverse events and concomitant medications since discharge.

The primary objective was to compare the PK of Opvee following three different dosing regimens of 30 mg/mL Opvee. The secondary objective was to evaluate the safety and tolerability of Opvee in healthy volunteers.

A total of 23 out of 24 subjects completed all three study periods. One subject discontinued from the study for reasons unrelated to study drug.

OPNT003-OOD-001 is described in Section 7, Clinical/Statistical Efficacy. Briefly, Part 1 was conducted under steady-state opioid agonism with remifentanil as a continuous infusion and consisted of seven subjects who received Naloxone NS on Day 1 and Day 5 with a 4-day washout period between doses. The Part 1 extension consisted of eight subjects who received Naloxone NS on Day 1. The primary objective of Part 1 and Part 1 extension was to assess the relationship between the dose of remifentanil and suppression of CO_2-induced increases in minute ventilation.

Part 2 consisted of 69 subjects, 61 of whom received Opvee and 60 who received Naloxone NS in a randomized 2-period crossover manner with a 4-day washout period between study drug doses on Day 1 and Day 5. The primary objective of Part 2 was to demonstrate non-inferiority of Opvee compared to Naloxone NS on minute ventilation during steady-state remifentanil infusion. A secondary objective of this study was to evaluate the safety and tolerability of Nalmefene IN during remifentanil infusion.

Safety Population:
A total of 151 subjects were included in the safety population. They received at least one dose of Opvee in studies OPNT003-PK-001, OPNT003-PK-002, and OPNT003-OOD-001. The breakdown of subjects exposed to Opvee in each study was 66, 24, and 61, respectively. The safety population appears to have adequate representation of sex, race, and ethnicity to allow generalizability to the U.S. target population and will allow for an accurate assessment of safety in the proposed population.

A pooling strategy was not specified by the Agency in advance of the NDA submission. In the Summary of Clinical Safety and the Integrated Summary of Safety, the Applicant has pooled the safety data by treatment group (i.e., 3 mg in one nostril, 6 mg total with 1 spray in each nostril, or 6 mg total with 2 sprays in one nostril).

Table 5: Study Subject Drug Exposure by Cumulative Dose Safety Population

Nalmefene hydrochloride IN				Comparators	
3 mg one nostril[1] (N=150)	**6 mg 1 spray in each nostril[2] (N=23)**	**6 mg 2 sprays in one nostril[3] (N=24)**	**6 mg Combined [4] (N=47)**	**Nalmefene 1 mg IM (N=68)**	**Naloxone Hydrochloride 4 mg IN[1] (N=75)**
n(%)	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**
150 (100%)	23 (100%)	24 (100%)	47 (100%)	68 (100%)	75 (100%)

[1] Subjects in the OPNT003-OOD-001 study received hypercapnic gas mixture and remifentanil infusion in addition to 3 mg nalmefene hydrochloride and 4 mg naloxone hydrochloride.
[2] 6 mg nalmefene hydrochloride IN (3 mg in each nostril)
[3] 6 mg nalmefene hydrochloride IN (3 mg twice in one nostril)
[4] 6 mg nalmefene hydrochloride IN dose includes subjects that received two 3 mg doses one in each nostril and 3 mg doses twice in one nostril
Source: Table 2.7.4.1
Source: Applicant's Integrated Summary of Safety, Table 2 pg. 10 (PDF)

Key Safety Results:
There were no deaths in any clinical studies conducted with Opvee and there were no serious adverse events (SAEs) in clinical studies PK-001, PK-002, or OOD-001. There were no dropouts or discontinuations due to adverse events in Studies PK-001 or PK-002. However, Study OOD-001 reported four discontinuations due to adverse events, all of which occurred during the pivotal Part 2. With further review, Subject (b) (6) developed a "mild hypercapnia event" that occurred during the 2nd period after the designated washout period and prior to study drug administration. Temporally, the study interventions (breathing of a hypercapnic gas mixture and remifentanil-induced respiratory suppression) appear to be the causes and not

Naloxone NS from the previous treatment period. The remaining three adverse dropouts received Opvee.

Table 6: Display of Dropouts due to Adverse Events

Subject No.	Treatment	Date of Discontinuation	Adverse Event	Outcome	TEAE
(b) (6)	Nalmefene	(b) (6)	Headache	Recovered/Resolved	Y
	Naloxone		Hypercapnia	Recovered/Resolved	Y
	Nalmefene		Headache	Recovered/Resolved	Y
	Nalmefene		Apnoeic attack	Recovered/Resolved	N

Source: Table 2.7.4.3.9, Table 2.7.4.5.1, Listing 5.3.5.3.15.1, Listing 5.3.5.3.15.3

Systemic Safety by Adverse Events:
Rates of adverse events varied between System Organ Classes (SOCs) for the three clinical studies, PK-001, PK-002, and OOD-001. For example, the pharmacokinetic studies, PK-001 and PK-002, in which administration of Opvee was the only study intervention, subjects experienced adverse events categorized in the following SOCs in order of decreasing incidence:
1) Respiratory, thoracic, and mediastinal disorders
2) Nervous system disorders
3) Gastrointestinal disorders

Conversely, the pharmacodynamic study, Study OOD-001, which contained several study interventions, showed adverse events in the following SOCs in order of decreasing incidence:
1) Nervous system disorders
2) Gastrointestinal disorders
3) Respiratory, thoracic, and mediastinal disorders

Adverse events appeared to be influenced by the study interventions of Study OOD-001 including the continuous infusion of remifentanil, breathing a hypercapnic gas mixture inducing a physiologic response of hyperventilation, and premedication with ondansetron, famotidine, and sodium citrate. These study interventions appear to be the cause for the increased incidence of AEs within the Nervous system and Gastrointestinal SOCs, whereas the administration of Opvee alone in studies PK-001 and PK-002 resulted in a higher incidence of adverse events categorized under respiratory, thoracic, and mediastinal disorders. Arguably, the adverse events observed in Study OOD-001 may be more reflective of those observed in a real-world situation of opioid intoxication/overdose and hypercarbia.

Throughout the clinical development program, there were no clinically significant abnormalities in clinical labs, physical exams, ECGs, or nasal examinations; nor was there any observed impact on olfactory effects in any study. The Applicant noted some clinically significant out-of-range vital signs; however, these were not associated with adverse events.

Table 7: Relative Frequencies of Treatment-Related Common Adverse Events That Occurred in Greater Than 1% of Healthy Adult Volunteers

Adverse Event	Nalmefene 2.7 mg	Nalmefene 5.4 mg (1 spray in each nostril)	Nalmefene 5.4 mg (2 sprays in one nostril)
	N=150	N=23	N=24
Nasal Discomfort	28.7%	13.0%	12.5%
Headache	26.7%	4.3%	0%
Nausea	16.7%	21.7%	4.2%
Dizziness	9.3%	0%	4.2%
Hot flush	8.0%	0%	0%
Vomiting	6.0%	4.3%	0%
Anxiety	4.7%	0%	0%
Fatigue	4.0%	0%	0%
Nasal congestion	4.0%	4.3%	16.7%
Throat irritation	4.0%	0%	0%
Rhinalgia	2.7%	8.7%	25.0%
Decreased appetite	2.0%	0%	0%
Erythema	2.0%	4.3%	4.2%
Hyperhidrosis	2.0%	0%	0%
Abdominal pain	1.3%	0%	0%
Agitation	1.3%	0%	0%
Chills	1.3%	0%	0%
Claustrophobia	1.3%	0%	0%
Dysgeusia	1.3%	0%	0%
Dyspnea	1.3%	0%	0%
Oropharyngeal pain	1.3%	4.3%	4.2%
Paresthesia	1.3%	4.3%	4.2%
Dry mouth	0.7%	4.3%	0%
Insomnia	0.7%	4.3%	0%
Rhinitis	0.7%	4.3%	0%
Chest discomfort	0%	4.3%	0%
Constipation	0%	0%	4.2%
Dry eye	0%	4.3%	0%
Presyncope	0%	4.3%	0%
Tachycardia	0%	4.3%	0%
Urticaria	0%	0%	4.2%

Source: Clinical Overview, pp. 29-30 (PDF), Applicant's submission, NDA 217470

Table 8: Incidence of Adverse Events with 2.7 mg Opvee in PK-001 compared to OOD-001

Adverse Event	Nalmefene 2.7 mg PK-001	Nalmefene 2.7 mg OOD-001	Naloxone 4 mg OOD-001
	N=66	N=61	N=75
Nasal Discomfort	56.1%	8.2%	0%
Headache	4.5%	59%	56%
Nausea	3%	39.3%	37.3%
Dizziness	6.1%	18%	18.7%
Hot flush	0%	23%	9.3%
Vomiting	1.5%	11.5%	18.7%
Anxiety	0%	16.4%	5.3%
Fatigue	4.5%	9.8%	2.7%
Nasal congestion	3%	3.3%	0%
Throat irritation	4.5%	4.9%	0%
Rhinalgia	0%	1.6%	0%

Reviewer generated Table; Information retrieved from ISS Tables; Tables 2.7.4.4.1 and 2.7.4.4.2; pp 60-66 (PDF)

Pharmacokinetic support for Systemic Safety

The systemic safety of Opvee is supported by Study PK-002 (repeat dose administration), Revex injection labeling, and published literature of nalmefene injection, namely Frye (1997).

The safety of Opvee with respect to peak plasma concentration is supported by Study PK-002, Revex injection labeling, and Frye (1997). The following was reproduced from the Clinical Pharmacology Review on May 8, 2023.

> In the Revex injection labeling, plasma drug concertation at 5 min following a 1 mg intravenous dose was reported, with a mean value of 3.7 ng/mL in young subjects and 5.8 ng/ml in elderly subjects. Additionally, a publication reported nalmefene plasma concentrations at 5 minutes after bolus dose of 2 mg nalmefene injection at an average of 17.3 ng/mL in healthy volunteers (Frye R.E. et al., Clin. Pharm. Ther. 1997, 61(1):15-23. For an intravenous injection product, the highest plasma drug concentration should be observed right after injection, and then drop quickly mainly due to drug distribution. Therefore, it is reasonable to assume that the drug concentration immediately after intravenous administration of nalmefene will be higher than the reported values at 5 min after injection. In addition, considering dose proportionality and accumulation after multiple-dose administration, the plasma concentration immediately after 4 repeated intravenous doses of 2 mg nalmefene injection, five minutes apart, will be even higher. Therefore, based on totality of evidence, the applicant's rationale is justified on a scientific basis. It is reasonable to conclude that the Cmax value after three doses of Opvee nasal spray (approximately 31.78 ng/mL) will be comparable or lower compared to 4 repeated intravenous administrations of 2 mg IV nalmefene injection.

Moreover, safety of Opvee with respect to AUC or overall exposure is supported by Study PK-002 as well as clinical pharmacology PK simulations of dosing regimens referenced in published literature. Specifically, Opiant submitted a publication (Kaplan, 1999)[2] of a controlled trial that evaluated the efficacy, safety, and withdrawal outcomes of nalmefene and naloxone in emergency department patients with suspected narcotic overdose. Patients received up to four doses of study drug intravenously (either 1 mg of nalmefene, 2 mg of nalmefene, or 2 mg of naloxone) as often as every 5 minutes based on clinical need. This publication supplements the support for safety with respect to AUC or overall exposure since the AUC of up to three doses of Opvee nasal spray are expected to be lower than the highest safe regimen of nalmefene injection, 2 mg nalmefene IV injection of up to four doses administered 5 minutes apart.

Foreign Postmarketing Safety:
An oral formulation of nalmefene hydrochloride dihydrate, Selincro, was approved in 2013 and marketed in the European Union for treatment of alcohol use disorder (AUD) for patients with no active physical withdrawal symptoms and not in need of immediate detoxification. The maximum dose is 18 mg (one tablet) per day. Patients may take this dose on days when they think there is a risk they may drink alcohol. No new safety signals were identified by the Applicant in the foreign postmarketing experience.

Of note, while Selincro and Opvee have different PK profiles (Selincro: Tmax 90 minutes vs. Opvee: Tmax 15 minutes), the Cmax and AUC of Selincro is higher than the Cmax and AUC of a single administration of Opvee. Moreover, the AUC of Selincro is approximately 1.5 times higher than the AUC of a second dose of Opvee (131 ng.h/mL vs. 89.5 ng.h/mL). Later in this section, the clinical experience of Selincro is leveraged to inform the severity and duration of precipitated opioid withdrawal in patients with physical dependence to opioids.

Local Toxicity:
Nasal irritation assessments were conducted in all three clinical studies, PK-001, PK-002, and OOD-001; however, nasal pain, through Nasal Rating Scale (NRS) assessments was only assessed in PK-001 and PK-002, and not OOD-001.

Overall, considering nasal irritation and nasal pain, Opvee appears to be well-tolerated with no concerns from the clinical perspective on local safety. A summary of nasal irritation results for the entire clinical program, shows that on a scale from 0 to 5 (noted below), no subjects experienced irritation beyond a 1 out of 5. Across all treatment arms, the 1-hour (PK-001 and PK-002) and 2-hour (OOD-001) post-dose time checks appeared to have the highest incidence of abnormal nasal irritation exams at 1 out of 5. At 48-hours post-dose, all subjects returned to 0 out of 5 with normal appearing nasal mucosa.

0 = Normal appearing mucosa, no bleeding
1 = Inflamed mucosa (erythema/edema), no bleeding

[2] Kaplan JL, Marx JA, Calabro JJ, Gin-Shaw SL, Spiller JD, Spivey WL, Gaddis GM, Zhao N, Harchelroad FP Jr. Double-blind, randomized study of nalmefene and naloxone in emergency department patients with suspected narcotic overdose. Ann Emerg Med. 1999 Jul;34(1):42-50.

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 medication intervention
5 = Ulcerated lesions, bleeding which requires medical intervention

Furthermore, nasal pain evaluations based on the Nasal Rating Scale (NRS) were only assessed for studies PK-001 and PK-002. In Study PK-001, 6% of subjects experienced severe pain (rated 7 and higher) 15 minutes post-dose. At 1-hour post-dose, the highest NRS was 6 out of 10 experienced by 3% of subjects. Despite the severe pain rating at 15-minutes post-dose, as correlated with the nasal irritation assessments above, subjects only developed inflamed mucosa with no bleeding. We note that the irritation assessments were not performed at the time point of maximal reported pain. For Study PK-002, out of the three treatment arms, no one subject experienced greater than a 4 out of 10 in pain severity. The observation of a difference in nasal pain between studies (PK-001 and PK-002) cannot be explained.

Evaluation of Safety of Opvee in OUD/Physical Dependence to Opioids:
The safety of Opvee in OUD/physical dependence to opioids is supported by pharmacokinetic data (Cmax and AUC) of Opvee and REVEX injection and the correlation with narratives of patients receiving nalmefene for suspected opioid overdose (later confirmed to be opioid-positive on toxicology and/or have physical dependence on opioids). This data was reviewed to discern the severity and duration of precipitated opioid withdrawal. Additionally, clinical experience with Selincro, an oral nalmefene formulation, is leveraged to inform the severity and duration of precipitated opioid withdrawal in patients with physical dependence to opioids.

The FDA review of Revex contained two efficacy studies that were considered substantial evidence by the reviewing Medical Officer to support efficacy of reversal of opioid overdose, Study 05 and Study JF-1-201. The results of Study 05 were published in Kaplan et al. The safety results from these studies were reviewed for key safety events, namely deaths and narratives reporting withdrawal due to opioids. Briefly, the patient narratives were reviewed, and of the few deaths reported between these two studies, none were attributed to nalmefene or naloxone administration. Opioid withdrawal did not appear to play a role in the deaths which were found to be attributable to the significant primary comorbidities. Moreover, the Revex clinical review noted that the overall incidence of withdrawal symptoms among the studies submitted to the NDA, including opioid overdose and post-anesthesia reversal of opioid depression, was comparable between the nalmefene and naloxone groups.

Opioid withdrawal was assessed as part of Kaplan et al., noted above as Study 05. This was a double-blind, randomized, controlled trial of nalmefene and naloxone in emergency department patients with suspected opioid overdose. There were 176 subjects evaluated with suspected opioid overdose. The patients were randomized to one of three intravenous treatment groups; nalmefene 1 mg, nalmefene 2 mg, and naloxone 2mg. Efficacy, safety, and withdrawal outcomes were assessed. Of the 176 subjects evaluated, 77 were later determined through toxicology testing to be opioid-positive. The Opioid Withdrawal Scale (OWS) score was reported at baseline, 5 minutes, 20 minutes, and 240 minutes after study drug administration. The OWS ranges from 0-13 with a patient receiving a point for each opioid

withdrawal sign and/or symptom that is demonstrate. A higher score indicates a more severe opioid withdrawal. Notably, in the opioid-positive patients, the assessment of opioid withdrawal did not demonstrate any between-group differences in the 0 to 20- or 0 to 240-minute changes. No subjects discontinued the study due to adverse events and the incidence of adverse events with nalmefene increased as the dose increased from 1 mg to 2 mg intravenously.

Additionally, as noted in the foreign postmarketing safety, Selincro is an oral formulation of nalmefene indicated for the treatment of alcohol use disorder (AUD). The published literature contains reports of precipitated opioid withdrawal when Selincro was prescribed for AUD in patients with co-occurring OUD on either medication-assisted treatment (MAT) with methadone/buprenorphine or with unrecognized physical dependence. Since the AUC of Selincro 18 mg exceeds the AUC of 2 sprays of Opvee (Study PK-002) the clinical team considered that the published literature containing narratives of precipitated opioid withdrawal was relevant to our understanding of Opvee's safety in opioid dependent patients.

Therefore, Opiant was asked to submit summaries of relevant literature including an assessment and conclusion regarding the relevance to their application. Opiant concluded that given the considerably higher exposures with Selincro, the patient cases of withdrawal are not considered relevant to the application. Nonetheless, of the 15 submitted case reports, no deaths were reported. Methadone and buprenorphine were the most frequently antagonized opioids with withdrawal symptoms noted as 'sometimes severe.' Most withdrawal episodes started 1-2 hours after ingestion and lasted approximately 10-12 hours. Clinical Opiate Withdrawal Scale (COWS) score was not reliably reported for all cases but ranged from mild to moderately severe withdrawal symptoms. Two patients were reported as having severe withdrawal; one of these patients took 36 mg of nalmefene (instead of 18 mg) and the other patient had a medical history of paranoid schizophrenia with alcohol and codeine abuse. This patient required admission to the ICU where he was treated for 3 days with several intravenous drugs to control withdrawal symptoms. It is not explicitly clear from the narrative if this patient was also experiencing alcohol withdrawal which contributed to the severity and need of an ICU admission. This data provides support of the safety of Opvee in patients with physical dependence to opioids. As the AUC of 18 mg Selincro is 1.5 times the AUC of 2 doses of Opvee, the duration of withdrawal (and perhaps the severity of withdrawal) is not expected to surpass that seen with Selincro.

Additionally, the Revex label cites the results of a brain receptor occupancy study within the Clinical Pharmacology section of Distribution. The study noted that following a 1 mg parenteral dose, nalmefene was rapidly distributed and blocked over 80% of brain opioid receptors within 5 minutes after administration. The review team considered the implications of these findings on the severity of precipitated withdrawal in opioid-dependent subjects. Given high percentage of occupied opioid receptors within 5 minutes with a parenteral formulation, the review team estimates that the severity of precipitated withdrawal from Opvee, with a slower rise in plasma concentration over time than nalmefene injection, should be comparable to that observed in clinical studies conducted with Revex in opioid overdose. Increases in the severity and seriousness of opioid withdrawal precipitated by Opvee are not expected to significantly different than what has already been observed in clinical studies and

clinical practice. Moreover, the rapidity and extent of opioid receptor occupancy in addition to slower dissociation of nalmefene from the mu-opioid receptor, may account for why a total dose of Revex greater than 1.5 mg did not increase therapeutic response in clinical studies.

Undoubtedly, any opioid antagonist carries the risk of precipitated opioid withdrawal in opioid-dependent patients. As described above, the available data do not suggest that nalmefene has demonstrably more risk with regard to precipitated withdrawal compared to naloxone. However, the pharmacology of nalmefene implies greater risk for duration and severity of withdrawal. Ideally, the armamentarium against opioid overdose would include a variety of strengths of antagonists for titration. This is the case in an Emergency Department setting where an injectable formulation can be titrated in a monitored patient.

However, in a patient found down with suspected opioid overdose, it is reasonable to assume that the person's degree of opioid-dependence and the quantity and the actual opioid(s) responsible are not known. It also seems unlikely that a rescuer will have an assortment of opioid antagonists from which to choose. Thus, while severe precipitated withdrawal can be very uncomfortable for patients and is to be avoided, this must be weighed against rapid reversal of hypoxia and the potential for death.

In October 2016, the Agency convened a joint meeting of the Anesthesia and Analgesia Drug Product and Drug Safety and Risk Management Advisory Committees. The subject of the meeting was naloxone-containing products for use in the community. The pertinent question posed to the Committee was "Discuss how to balance the need for rapid reversal of an opioid overdose with the risk for precipitating an acute opioid withdrawal syndrome when selecting the minimum naloxone exposure that forms the basis for approval of novel products." The Meeting Minutes read:

> The committee members did not come to a consensus on the appropriateness of a higher starting dose of naloxone versus the current dose. The committee members discussed that it is unclear what should be the basis to choose an absolute correct dose; however, the committee noted that the risk of not having a high enough dose is much greater than not having enough. Some committee members stated that there is concern that lower doses of naloxone might require rescuers to titrate, taking time, and risking further hypoxic injury to the patient. Many committee members stated that the risk of acute withdrawal is acceptable for the benefit of saving a patient.

In response to a question of whether minimal acceptable naloxone exposure (comparable to that from naloxone injection) should be increased, the Minutes read:

> A slight majority of the committee voted for "B", in favor of increasing the minimum acceptable naloxone exposure to that comparable to or greater than a higher dose of naloxone injection. The committee members who voted to continue with the current minimum standard dose of naloxone stated that, as previously discussed, there was no indication that the current standard was failing the Agency or industry. Those voting for an increase opined that the current standard was set in 1971 and reflected inpatient use rather than use in the community where time to resuscitate may be minimal. These

committee members also stated that given the wide availability of potent opioids in the community requiring multiple doses of naloxone, an increase in the minimum standard dose of naloxone seemed appropriate.

The proposed prescribing information contains sections regarding patients physically dependent on opioids, precipitation of severe opioid withdrawal, risks of attempting overcome the opioid blockade by administering high or repeated doses of exogenous opioids as well as patient counseling information. These sections provide guidance for risk mitigation in opioid and non-opioid dependent individuals.

9. Advisory Committee Meeting

There were no issues that needed to be discussed with an advisory committee (AC); therefore, an AC meeting was not convened.

10. Pediatrics

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

Opiant submitted their initial pediatric study plan on December 27, 2021, at which time they requested the following:

(b) (4)

The review team and the Pediatric Review Committee (PeRC) disagreed with Opiant's (b) (4) The review team notes that clinical experience is abundant with naloxone in both controlled and uncontrolled studies down to birth. The Division advised Opiant that efficacy cannot be extrapolated for subjects under 12 years of age. Additional PK, safety, and efficacy data would be needed to support an indication in < 12 years old. Moreover, nonclinical PK and repeat dose toxicity studies will need to be completed prior to initiation of clinical studies in < 12 years old.
However, the Division advised Opiant that it would be acceptable to extrapolate the adult pharmacokinetic (PK) data to the 12 to < 18-year-old pediatric population as no PK

differences are expected between these two populations. Furthermore, as it would be unethical to conduct clinical studies in healthy pediatric volunteers due to their deriving no direct benefit from participation, the Division advised that an "at risk" population be identified for which clinical studies could be completed in the < 12-year-old population. The Division and PeRC agreed with Opiant to defer the clinical assessments of PK, safety, and efficacy of nalmefene in patients < 12 years of age (all age groups down to birth) because the drug will be ready for approval in patients > 12 years of age prior to the completion of pediatric studies. The Agreed Initial Pediatric Study Plan (iPSP), reviewed under IND 136851, as finalized on December 8, 2022.

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

There is an injection formulation of nalmefene available (generic of REVEX) which is unlikely to be confused with Opvee because Opvee will be the only nalmefene-containing community-use product available in the US. Furthermore, these two drug products have different distribution channels.

11. Other Relevant Regulatory Issues

The Office of Scientific Investigations (OSI) inspection of the analytical site for Study OPNT003-OOD-001 was completed under a BLA and the results were determined to be adequate. There are no other relevant regulatory issues.

12. Labeling

The following high-level labeling issues were discussed among the review team:

1) INDICATIONS AND USAGE: The Applicant proposed an Indication and Usage (I&U) statement that was identical to the LD (nalmefene hydrochloride injection). To improve accuracy of the indication, the I&U statement was modified to align with that of community-use opioid reversal products such as Narcan nasal spray. Specifically, the I&U of the LD noted an indication "…for the complete or partial reversal of opioid drug effects…" This statement is accurate for the LD, an injection product, since it can be incrementally titrated to effect; however, Opvee cannot be titrated to effect in this way. Opvee was formulated to deliver an effective fixed dose in one spray. The I&U statement was also modified to reflect safe and effective use in "…pediatric patients aged 12 years and older…" as proposed by DPMH. Furthermore, the Division ultimately agreed with the Applicant in retaining the phrase "...induced by natural or synthetic opioids..." since the Opvee program conducted Study OOD-001 under steady-state opioid agonism with remifentanil. The Division agreed with DARS's

rationale that the successful antagonism of remifentanil in Study OOD-001 could be extrapolated to other synthetic opioids.

The final agreed on Indication is, "Opvee nasal spray is indicated for the emergency treatment of known or suspected overdose, induced by natural or synthetic opioids in adults and pediatric patients aged 12 years and older, as manifested by respiratory and/or central nervous system depression."

2) REPEAT DOSING: Safety data and a clinical pharmacology simulation show that two doses of Opvee are reasonably safe. There are substantial data on very high dose naloxone available that were discussed at the October 2016 Advisory Committee and significant adverse reactions to an opioid antagonist alone do not appear likely.

However, the duration and severity of precipitated withdrawal in opioid-dependent patients is expected to be correlated with the number of doses received during rescue. Similar to the analogous naloxone-containing products, the proposed labeling for Opvee allows for dosing to be repeated every 2 to 5 minutes without an upper limit. As discussed in Section 8 (subsection entitled Evaluation of Safety of Opvee in OUD/physical dependence to opioids), the review team carefully considered the pharmacology, pharmacokinetics, and safety data available to inform whether a Limitation of Use was warranted. We also considered the discussion at the October 2016 Advisory Committee and current trends in the opioid epidemic. At some point, the potency and quantities of opioid in medically significant overdoses may plateau. All of this considered, a limit to the maximum number of doses of Opvee to be used in a rescue is not justified at this time.

Additionally, there are some tangential data to support that patients are unlikely to receive more than two doses of Opvee. The analogous community-use naloxone-containing products are packaged as 2-packs, as is Opvee. We consulted the Drug Use team who assessed Symphony Health's IDV to obtain a sample of dispensed data for naloxone spray products. Only (b) (4)% of these prescriptions were for more than one box. Thus, the inference is that persons prescribed naloxone nasal sprays do not have more than two doses available to dose in a single rescue.

3) CLINICAL STUDIES: (b) (4) The guidance for industry *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* notes the circumstances in which studies should and should not be included in the CLINICAL STUDIES section. (b) (4) the study results are reported in Section 12.2 PHARMACODYANMICS. Moreover, the review team

determined that the Applicant's proposed [redacted] (b) (4) appeared promotional [redacted] (b) (4) Ultimately, the review team agreed that a Figure showing the recovery of respiratory drive with Opvee [redacted] (b) (4) represented as the percent change in minute ventilation from baseline as well as the variability at assessed timepoints, captured the results in an interpretable way for health care clinicians.

13. Postmarketing Recommendations

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

4451-1 Conduct a clinical pharmacokinetic, pharmacodynamic, and safety study of Opvee in pediatric patients aged 3 to less than 12 years of age.

Draft Protocol Submission:	10/2024
Final Protocol Submission:	02/2025
Study Completion:	03/2027
Final Report Submission:	09/2027

4451-2 Conduct a clinical pharmacokinetic, pharmacodynamic, and safety study of Opvee in pediatric patients from birth to less than 3 years of age.

Draft Protocol Submission:	12/2026
Final Protocol Submission:	03/2027
Study Completion:	09/2028
Final Report Submission:	03/2029

4451-3 Conduct a juvenile animal study in rats to support the initiation of clinical studies in pediatric patients from 3 to less than 12 years of age. This study will evaluate the effect of the drug on growth and development, specifically reproductive performance/sexual maturation, local tissues including the nasal and respiratory tract, immune capacity, and central nervous system histopathology and long-term behavioral effects.

Draft Protocol Submission:	09/2023
Final Protocol Submission:	01/2024
Study Completion:	05/2024
Final Report Submission:	02/2025

4451-4 Conduct a juvenile animal study in rats to support the initiation of clinical studies in pediatric patients from birth to less than 3 years of age. This study will evaluate the effect of the drug on growth and development, specifically reproductive

performance/sexual maturation, local tissues including the nasal and respiratory tract, immune capacity, and central nervous system histopathology and long-term behavioral effects.

Draft Protocol Submission:	09/2023
Final Protocol Submission:	01/2024
Study Completion:	06/2024
Final Report Submission:	03/2025

The following PMRs will be required under FDAAA.

4451-5 Conduct a fertility and early embryonic development study in rats with dodecylmaltoside (DDM).

Draft Protocol Submission:	08/2023
Final Protocol Submission:	11/2023
Study Completion:	10/2024
Final Report Submission:	04/2025

4451-6 Conduct an embryo-fetal development study in rats with dodecylmaltoside (DDM).

Draft Protocol Submission:	08/2023
Final Protocol Submission:	11/2023
Study Completion:	02/2024
Final Report Submission:	08/2024

4451-7 Conduct an embryo-fetal development study in rabbits with dodecylmaltoside (DDM).

Draft Protocol Submission:	08/2023
Final Protocol Submission:	11/2023
Study Completion:	09/2024
Final Report Submission:	03/2025

4451-8 Conduct a pre- and postnatal development study in rats with dodecylmaltoside (DDM).

Draft Protocol Submission:	08/2023
Final Protocol Submission:	12/2023
Study Completion:	01/2025
Final Report Submission:	07/2025

14. Comments to the Applicant

The following enhanced pharmacovigilance request will be communicated to the Applicant in the NDA approval letter.

ENHANCED PHARMACOVIGILANCE REQUEST

We request that for Opvee you submit all serious and non-serious occurrences of severe, prolonged, and/or precipitated opioid withdrawal in cases where more than two doses of Opvee are used in a single rescue as 15-day "Alert reports" (described under 21 CFR 314.80(c)(1)) through the 5th year following initial U.S. approval.

Provide a separate narrative summary and analysis of these adverse events, apart from your required analysis of 15-day "Alert reports," in each required postmarketing periodic safety report [e.g., periodic adverse drug experience report (PADER) required under 21 CFR 314.80(c)(2)], quarterly during the first 3 years post-approval and annually thereafter, through the 5th year following initial U.S. approval.

These narrative summary and analyses should include an assessment of all new information obtained during the reporting interval and cumulatively since initial U.S. approval related to these adverse events (i.e., severe, prolonged, and/or precipitated opioid withdrawal in cases where more than two doses of Opvee are used in a single rescue) with the aim of further characterizing these risks (e.g., indication, temporal association, action taken, outcome, confounders, underlying risk factors, use in unapproved populations, and assessment of causality).

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

/s/

TANYA L BRESCIA-ODDO
05/22/2023 03:19:28 PM

ROBERT B SHIBUYA
05/22/2023 03:24:06 PM

RIGOBERTO A ROCA
05/22/2023 03:53:44 PM