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<th>Application Type</th>
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<tr>
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<tr>
<td>Submit Date(s)</td>
<td>December 20, 2013</td>
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<td>Received Date(s)</td>
<td>December 20, 2013</td>
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<td>PDUFA Goal Date</td>
<td>June 20, 2014</td>
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<td>Division / Office</td>
<td>DAAAP/ODE II</td>
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<tr>
<td>Reviewer Name(s)</td>
<td>Steven Galati M.D.</td>
</tr>
<tr>
<td>Review Completion Date</td>
<td>March 19, 2014</td>
</tr>
<tr>
<td>Established Name</td>
<td>Naloxone Injection</td>
</tr>
<tr>
<td>(Proposed) Trade Name</td>
<td>Evzio</td>
</tr>
<tr>
<td>Therapeutic Class</td>
<td>Opioid Antagonist</td>
</tr>
<tr>
<td>Applicant</td>
<td>Kaleo Inc.</td>
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<tr>
<td>Formulation(s)</td>
<td>Injection</td>
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<tr>
<td>Dosing Regimen</td>
<td>0.4 mg single-dose</td>
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<tr>
<td>Indication(s)</td>
<td>Opioid Overdose</td>
</tr>
<tr>
<td>Intended Population(s)</td>
<td>Out-of-Hospital Treatment of Opioid Overdose</td>
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Clinical Review
Steven Galati
NDA - 205787
Evzio Naloxone Auto-Injector

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval with revisions to the proposed labeling.

1.2 Risk Benefit Assessment

This application is to support the product, Evzio [Naloxone Auto-Injector (NAI)], utilizing the 505(b)(2) pathway with the reference drug Narcan (NDA 016636). The product offers an out-of-hospital treatment option for patients who suffer from an opioid overdose. Given it would be unethical to evaluate a novel formulation/route of administration for naloxone in the setting of a clinical trial in patients with an opioid overdose when there are previously-approved formulations of naloxone available, the Applicant’s required clinical program consisted of demonstrating comparable (or higher) pharmacokinetics in healthy volunteers in relation to an approved route of administration for naloxone in lieu of efficacy studies. In addition, based on the known safety profile and wide safety margin of naloxone, the greatest concern for treating the acutely life-threatening incident of an opioid overdose in any population is undertreating this potentially fatal event. The Applicant submitted the results of a pivotal comparative bioavailability trial (IJ-900DV-03O) and the results of this trial showed the reference product delivers naloxone at levels equal to (bioequivalent) or greater than the comparator. Therefore, the trial provided an adequate scientific bridge to the Agency’s previous findings of safety and efficacy. Therefore, the Applicant may rely on the Agency’s previous findings of safety and efficacy for Narcan as a 505(b)(2) application. Additional safety data was collected in the trial IJ-900DV-03O, and after review, no new safety signals were identified.

Naloxone is reserved mostly for use in the hospital setting for opioid overdose. This product provides a mechanism for treatment of opioid overdose in the outpatient setting, and to be administered by caregivers with or without medical training. In the outpatient setting, patients may intentionally or unintentionally overdose on opioids. Also, patients may accidentally ingest an opioid and require emergent treatment. Given these instances are medical emergencies, a treatment option that is effective in this environment may have a substantial impact on patient safety from a public health perspective. The Applicant proposed an indication discussed in more detail in Section 6.1. The Division is currently still reviewing the most appropriate indication for this drug product at the time of this review.

In addition to the pivotal comparative bioavailability trial, the Applicant also completed a Human Factors Engineering (HFE) development program to support approval of Evzio,
naloxone auto-injector (NAI). The device component was tested through the Applicant’s human factors development program which included the following three studies:

- NAI Formative User Needs Study (IJ-1000FE-03O)
- NAI Formative Usability and Label Evaluation Study (IJ-1001FE-03O)
- Summative Design Validation Study of the User Interface (IJ-1025SE-03O)

The HFE provides additional supportive information in the final risk-benefit analysis of the product. These studies assist in an assessment of the drug-device’s potential success in real world usage. A thorough review of the studies was performed by Quynh Nhu Nguyen, Biomedical Engineer/Human Factors Reviewer, dated October 2, 2013. The review stated “the consultant finds the human factors study acceptable, and no further optimization on the design and/or labeling is necessary.”

Overall, the risk-benefit profile of the Evzio in this population, and treatment environment, is favorable.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

I have identified no further safety issues in review of this application that warrant additional postmarket risk evaluation and mitigation strategies.

1.4 Recommendations for Postmarket Requirements and Commitments

No postmarket requirements are recommended at this time.

2 Introduction and Regulatory Background

2.1 Product Information

Naloxone is a narcotic antagonist, a synthetic congener of oxymorphone.

The Applicant developed Evzio (NAI) as a combination drug-device product being submitted under Section 505(b)(2) of the Food, Drug, and Cosmetics Act (FD&C Act). Evzio is a single-use auto-injector that delivers 0.4 mg naloxone hydrochloride (HCl) via subcutaneous or intramuscular injection. Evzio is intended for patients who receive opioids out-of-the hospital and develop acute, opioid-related, central nervous system or respiratory depression. Evzio is designed for a caregiver or layperson to administer naloxone in the out-of-hospital setting for the treatment of an opioid overdose.

The Device Constituent Component of Evzio is a compact, user-actuated, auto-injection system.
2.2 Tables of Currently Available Treatments for Proposed Indications

Narcan (naloxone) was originally approved in 1971 intended for administration in patients who suffered harm from an opioid overdose or suspected overdose.

2.3 Availability of Proposed Active Ingredient in the United States

Multiple approved drug products containing the active ingredient naloxone are available and marketed in the United States (Table 1). Most of the approved products are combination products used for maintenance of opioid dependence. The naloxone component of the approved combination drug products is generally included to deter intravenous abuse.

<table>
<thead>
<tr>
<th>Drug Product Name</th>
<th>NDA</th>
<th>Approval Date</th>
<th>Dose Form</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narcan</td>
<td>016636</td>
<td>4/13/1971</td>
<td>Injection</td>
<td>Complete or partial reversal of opioid depression, including respiratory depression</td>
</tr>
<tr>
<td>Talwin NX (pentazocine/naloxone)</td>
<td>018733</td>
<td>12/06/1982</td>
<td>Tablet</td>
<td>Relief of moderate to severe pain</td>
</tr>
<tr>
<td>Suboxone (Buprenorphine/naloxone)</td>
<td>020733</td>
<td>10/08/2011</td>
<td>Tablet</td>
<td>Maintenance treatment of opioid dependence</td>
</tr>
<tr>
<td>Suboxone (Buprenorphine/naloxone)</td>
<td>022410</td>
<td>8/20/2010</td>
<td>Film</td>
<td>Maintenance treatment of opioid dependence</td>
</tr>
<tr>
<td>Zubsolv (Buprenorphine/naloxone)</td>
<td>204242</td>
<td>7/3/2013</td>
<td>Tablet</td>
<td>Maintenance treatment of opioid dependence</td>
</tr>
</tbody>
</table>

2.4 Important Safety Issues With Consideration to Related Drugs

Naloxone may cause an abrupt and complete reversal of opioid effects leading to withdrawal symptoms (e.g., abdominal cramping, muscle aches, sweating, anxiety, nausea, vomiting, diarrhea). Several instances of hypotension, hypertension, ventricular tachycardia and fibrillation, and pulmonary edema have been associated with use postoperatively and naloxone should be used with caution in patients with pre-existing cardiac disease or who have received potentially cardiotoxic drugs.
## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

### Table 2: Key Presubmission Regulatory Activity

<table>
<thead>
<tr>
<th>Date</th>
<th>Meeting/ Submission Type</th>
<th>Key Comments</th>
</tr>
</thead>
</table>
| 7/02/2011  | Type B Meeting (pre-IND)         | • EVZIO will be regulated as a drug/device combination product  
• 505(b)(2) pathway appropriate  
• A relative bioavailability or bioequivalence study with listed product required to demonstrate pharmacokinetic (PK) comparability  
• Efficacy and safety based on comparability of PK data  
• Considering naloxone has a relatively large therapeutic index window, the concern would be greater if EVZIO delivers less drug |
| 1/8/2013   | Memorandum to File              | • Fast Track designation granted  
• (b)(4) |
| 6/4/2013   | Type B Meeting (pre-NDA)         | • Division agreed the NDA may be submitted as a rolling submission  
• Addition of “(b)(4)” proposed in labeling required defining  
• EVZIO is subject to PREA |
| 7/19/2013  | Initial submission to rolling review | • Pivotal PK study  
• Clinical overview and summary |
| 10/29/2013 | Draft labeling submitted        | |
| 11/6/2013  | Teleconference with Applicant    | • Discussed appropriateness of product’s indication  
• Determined that definition of |
2.6 Other Relevant Background Information

There is no additional information to be discussed in this section.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

All data and documents in this application were electronically submitted following the guidances for electronic submission. The documents were organized in electronic Common Technical Document (eCTD) format. The datasets were not in Study Data Tabulation Model (SDTM) format. The overall quality of the submission was adequate. The organization and the ability to navigate the NDA were acceptable.

3.2 Compliance with Good Clinical Practices

The Applicant stated that all studies were conducted in accordance with Guidelines for Good Clinical Practice and the Declaration of Helsinki and in compliance with the United States Food and Drug Administration regulations for informed consent and protection of patient rights as described in 21 Code of Federal Regulations Parts 50, 56, and 312. The Applicant also states that the studies were approved by Institutional Review
Boards/Independent Ethics Committees and that all studies underwent regular monitoring by the Applicant or an appointed Contract Research Organization.

### 3.3 Financial Disclosures

The Applicant submitted Form FDA 3454 “Certification: Financial Interests and Arrangements of Clinical Investigator”, certifying that they had no financial interests or arrangements to disclose (see Appendix for Clinical Investigator Financial Disclosure). A total of six investigators were listed and the study was performed through the contract research organization, Parexel International Early Phase Clinical Unit-Baltimore.

### 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

There was no clinically relevant data for the following disciplines: chemistry, manufacturing and controls, clinical microbiology, preclinical and pharmacology/toxicology review disciplines.

#### 4.4 Clinical Pharmacology

**4.4.1 Mechanism of Action**

Naloxone is an opioid antagonist, a synthetic congener of oxymorphone.

**4.4.2 Pharmacodynamics**

When naloxone hydrochloride is administered intravenously the onset of action is generally apparent within two minutes; the onset of action is only slightly less rapid when it is administered subcutaneously or intramuscularly.

**4.4.3 Pharmacokinetics**

Overall, the bioavailability is comparable between the between the two delivery systems; Evzio (0.5 inch needle) and standard syringe (5/8 of an inch needle). For both area under the curve (AUC) parameters, naloxone administered from Evzio is bioequivalent to naloxone administered from the standard syringe (Table 3). The $C_{\text{max}}$ is similar, but not bioequivalent to the reference test. Table 3 shows the geometric mean ratio was 1.15 with a 90% CI of (0.97, 1.37). The $C_{\text{max}}$ is slightly higher for the naloxone delivered through the Evzio, however, this should not relate to any safety concern given the therapeutic safety margin for naloxone and is consistent with the
Division’s requirements. See Dr. Wei Qiu’s full report for full details of the study results and design.

Table 3: Statistical Analysis of Relative Bioavailability for Naloxone Plasma Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Parameter (unit)</th>
<th>IMP</th>
<th>N</th>
<th>Geometric LS Means</th>
<th>Geometric LS Means 95% CI</th>
<th>Treatment Ratio (Test/Reference)</th>
<th>90% CI for Ratio of Geometric LS Means</th>
<th>Within Subject %CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (pg/mL)</td>
<td>Test</td>
<td>30</td>
<td>1100</td>
<td>(918, 1320)</td>
<td>1.15</td>
<td>(0.97, 1.37)</td>
<td>40.9</td>
</tr>
<tr>
<td>Reference</td>
<td>30</td>
<td>957</td>
<td>(797, 1150)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$AUC_{0-1}$ (pg.h/mL)</td>
<td>Test</td>
<td>30</td>
<td>1780</td>
<td>(1620, 1960)</td>
<td>0.993</td>
<td>(0.94, 1.05)</td>
<td>12.6</td>
</tr>
<tr>
<td>Reference</td>
<td>30</td>
<td>1800</td>
<td>(1640, 1970)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$AUC_{0-\text{inf}}$ (pg.h/mL)</td>
<td>Test</td>
<td>30</td>
<td>1880</td>
<td>(1710, 2070)</td>
<td>0.983</td>
<td>(0.937, 1.03)</td>
<td>10.9</td>
</tr>
<tr>
<td>Reference</td>
<td>30</td>
<td>1910</td>
<td>(1740, 2110)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI = Confidence interval; %CV = Percentage coefficient of variation; LS: Least squares; N = Number of subjects exposed to treatment; HCl = Hydrochloride; USP = United States Pharmacopeia

Data source: Section 14.2, Table 14.2.4

Source: Clinical study report p. 60

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The studies conducted in support of this NDA for Evzio are listed below (Table 4).

Table 4: Clinical Studies Submitted in Support of this Application

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Population</th>
<th>Number of Subjects</th>
<th>Relevance</th>
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</thead>
<tbody>
<tr>
<td><strong>Pivotal Comparative Bioavailability Study</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IJ-900DV-03O</td>
<td>Healthy volunteers</td>
<td>N = 30</td>
<td>Pivotal comparative bioavailability trial to support efficacy and safety of this application.</td>
</tr>
<tr>
<td><strong>Human Factors Studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IJ-1000FE-03O</td>
<td>Caregivers caring for individual taking opioid</td>
<td>N = 9 caregivers</td>
<td>Formative study to optimize NAI interface (user needs study)</td>
</tr>
</tbody>
</table>
Clinical Trial | Population | Number of Subjects | Relevance |
--- | --- | --- | --- |
IJ-1001FE-03O | Patients taking opioids and caregivers caring for individual taking opioid medication | N = 7 patients and 7 caregivers | Formative study to evaluate NAI and various labeling designs and instructions for use |
IJ-1025SE-03O | Untrained volunteers | N = 40 (20 Juveniles, aged 12-19, and 20 Adults, aged 20-65) | Summative design validation study of the user interface. Results showed majority of untrained users could effectively administer naloxone |

Source: Derived from Applicant's submission, NDA 205787

As described in Section 1.2, the pivotal comparative bioavailability study was the only required clinical study. The PK parameters were found to either bioequivalent (AUC) or greater (Cmax) than the comparator naloxone administered via a standard syringe and described in Section 4.4.3, Clinical Pharmacology. Therefore the Applicant was able to rely on the Agency’s previous findings of safety and efficacy for the reference product Narcan.

The device component was tested through the Applicant’s human factors development program which included three of the studies listed in Table 4. These studies assist in an assessment of the drug-device’s potential success in real world usage. A thorough review of the studies was performed by Quynh Nhu Nguyen, Biomedical Engineer/Human Factors Reviewer, dated October 2, 2013.

5.2 Review Strategy

IJ-1000FE-03O is the pivotal comparative bioavailability trial which provided a scientific bridge to the Agency’s previous findings of safety and effectiveness for Narcan, for this 505(b)(2) NDA. As described in Section 1.2, for ethical reasons of studying novel drug products in life-threatening situations, such as an opioid overdose when approved treatment exists, the Applicant’s clinical program consisted of demonstrating comparable (or higher) pharmacokinetics in healthy volunteers in relation to an approved route of administration for naloxone in lieu of efficacy studies. Given the wide safety margin of naloxone, the concern would be undertreating an opioid overdose. A brief description of the design of IJ-1000FE-03O is discussed in Section 5.3, Discussion of Individual Studies/Clinical Trials. In the description of the trial, Evzio will be referred to as NAI given the protocol predated the proposed tradename. Detailed information regarding the design and findings are discussed by Dr. Wei Qiu, clinical pharmacologist.
5.3 Discussion of Individual Studies/Clinical Trials

**Trial IJ-1000FE-03O**

“A Randomized, Single-Blind, Two-Sequence, Two-Period Comparative Bioavailability Study of Two Naloxone Hydrochloride Products in Healthy Human Volunteers”

Conducted from January 8, 2013 to February 26, 2013

One clinical site in Baltimore, MD

**Protocol**

**Objective/Rationale**
Primary: To compare the pharmacokinetics (PK) of 0.4 mg naloxone hydrochloride (HCl) following a single intramuscular (IM) or subcutaneous (SC) injection administered using either the naloxone auto-injector (NAI) or a standard syringe

Secondary: To assess the safety and tolerability of naloxone injection by NAI compared to standard syringe.

**Overall Design**
This was to be a Phase 1, randomized, single-blind, single-dose, two-sequence, two-period crossover bioavailability, safety and tolerability study in 30 healthy male and female subjects to evaluate the PK of 0.4 mg of naloxone administered by injection using either NAI or a standard syringe. The study consisted of a several week screening period and a 3 day inpatient admission to complete both dosing periods. Safety assessments were conducted throughout the study, including physical examinations (PE), pregnancy tests, routine clinical laboratory assessments (chemistry, hematology, urinalysis), ECGs, adverse event (AE) assessments, vital sign assessments and evaluation of the injection site.

**Treatment**
Each subject was to receive two doses of 0.4 mg of naloxone, either through NAI (0.5 inch needle) or a standard syringe (5/8 of an inch needle) on Day 1 and the alternate on Day 2.

**Population and Procedures**
Planned enrollment was to be 30 healthy subjects. Subjects were randomized to receive either method of injection and then crossover to the alternate method on Day 2.

**Inclusion Criteria**
- Male or female ≥ 18 and ≤ 45 years of age
- Able to provide written informed consent
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• Willing and able to participate in all required study activities
• Body mass index (BMI) between 18.5 and 29.9 kg/m², inclusive and a weight ≥50 kg and ≤100 kg
• If female and of childbearing potential, must have had negative pregnancy tests at screening and Day -1 (admission) and must have been using highly effective contraception¹ and committed to continue its use for 28 days after final naloxone administration
• Male subjects and their female spouses/partners of childbearing potential must have been using highly effective contraception consisting of two forms of birth control (one of which must have been a barrier method) which started at Screening and committed to continue its use for 28 days after final naloxone administration
• No clinically significant abnormal findings on PE, medical history, ECG or clinical lab results during screening or admission
• Vital signs were within clinically acceptable ranges at screening and admission

Exclusion Criteria
• Clinically significant medical conditions²
• Diabetes Mellitus or cardiac risk factors³ or the prior use of potentially cardiotoxic drugs
• History of allergic or adverse responses to naloxone
• History of unusual bruising or prolonged bleeding
• Consumption of xanthines during the 24 hours preceding Day –1 (admission) or during the study
• Blood donation within 56 days or plasma donation within 14 days of admission
• Participation in a clinical trial within 30 days of admission
• Use of any over-the-counter (OTC) or prescription medication or grapefruit within 14 days admission or during the study⁴
• Use of any enzyme altering drug (e.g., barbiturates, phenothiazines, cimetidine, carbamazepine) within 30 days before admission or during study⁵
• Smoking or use of tobacco products within 6 months of admission or during study⁶

¹ Established, consistent use of oral, injected or implanted hormonal methods of contraception established for at least 90 days before admission. Examples included placement of an intrauterine device or intrauterine system, barrier methods of contraception such as condom or occlusive cap (diaphragm or cervical/vault caps] with spermicidal foam/gel/film/cream/suppository), double-barrier method or abstinence.
² Gastrointestinal, renal, hepatic, neurologic, hematologic, endocrine, oncologic, pulmonary, immunologic, psychiatric or cardiovascular disease or any other condition which, that in the opinion of the investigator, would compromise the safety of the subject or impacted the validity of the results
³ Examples include family history, hypertension, hypercholesterolemia
⁴ Exception is acetaminophen under 1 gram per day and use of OTC contraceptive products
⁵ Determined by a urine cotinine concentration >200 ng/mL

Reference ID: 3473511
Females trying to conceive, donated ova, were pregnant, or were lactating or breast feeding at screening or throughout study
Males who donated sperm at screening or throughout the study
Positive serum pregnancy test at Screening or admission (Day -1)
Positive blood screen for HIV, HBV, or HCV
Positive urine screen for drugs-of-abuse or breath alcohol test at screening or admission
Alcohol use within 72 hours of admission
History of any substance abuse within 6 months prior to admission

Procedures
The study was to consist of a screening period and a 3-day, inpatient treatment period. The subjects were to receive the study medication after eligibility confirmed and randomized to receive either NAI or a standard syringe on Day 1, then crossover to the alternate treatment on Day 2. There was to be a 24 hour washout period between doses. PK assessments were to be collected for each dosing period. After subjects were to receive a second dose of naloxone, additional safety assessments were to be completed prior to discharge from the unit.

Subject Withdrawal
Subjects were to be free to withdraw from participation in this study at any time and for any reason. Subjects who experienced an AE were to be followed until the AE resolved or until 30 days from the end of the study.

Evaluations/Endpoints
The primary objective of this study was to compare the PK parameters of naloxone administered from NAI and a standard syringe. Subjects were to have PK assessments ($C_{\text{max}}$, $T_{\text{max}}$, AUC parameters) collected 5 minutes prior to dosing and at 5, 10, 15, 20, 30, 40 and 50 minutes, and 1, 1.25, 1.5, 2, 3, 4 and 6 hours post-dose for each dosing period.

Safety Assessments
- Incidence of TEAEs throughout study period
- Vital sign measurements\(^6\)
- Physical examination (screening, admission or Day -1 and Day 2)\(^7\)
- Laboratory tests(screening, admission or Day -1 and Day 2):
  - Chemistry
  - Hematology

\(^6\) Blood pressure, pulse, respiratory rate and body temperature were to be collected at screening, admission, 60 minutes pre-dose and approximately 6 hours post-dose and were taken in the supine position after resting for ≥5 minutes, and before discharge
\(^7\) Includes inspection of the injection sites between 5 minutes pre-dose and immediately prior to dosing and between 60 and 120 minutes post-dose on each dosing day and at end-of-study

Reference ID: 3473511
Subject Overview
A total of 30 subjects were screened met all the eligibility criteria and were subsequently randomized in the study. All the subjects completed the study and were included in both the PK and safety analyses.

Subject Disposition
All 30 subjects that were randomized completed the study.

Demographics
The demographic characteristics are displayed in Table 5. The population was diverse, consisting of Black or African American, White, Hispanic or Latino, Native Hawaiian or other Pacific Islander males and females with ages ranging from 20 to 43 years of age. The trial population was predominantly female (18 subjects [60%]) and Black or African American (20 subjects [66.7%]). The mean body mass index (BMI) was 24.91 kg/m², ranging from 20 to 29.8 m/kg². Given the Applicant is relying on the agency’s previous findings of safety for Narcan, this appears to be an appropriate population for this PK trial.

---

8 Performed at screening, admission, and after collection of final blood sample for PK analysis
Protocol Violations
The protocol deviations consisted of non-significant events (e.g., pre-dose injection site examine 1 minute early, fasting requirements deviated by 1-37 minutes in several subjects) and should not impact the study results.

Dosing Information
The planned dosing consisted of two, single doses of 0.4 mg of naloxone separated by 24 hours. The exposed needle length for the test product (NAI) was a nominal 0.5 inches and 5/8 of an inch for the reference product. Naloxone was delivered either subcutaneously or intramuscularly depending on the amount of subcutaneous tissue present in a particular subject.

Table 5: Summary of Demographic Parameters (Study IJ-900DV-03O)

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Mean or Percentage*</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30</td>
<td>30.8</td>
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<tr>
<td>Race: Native Hawaiian or other Pacific Islander</td>
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<tr>
<td>Race: Black/African American</td>
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<tr>
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</table>

n = number of subjects; BMI = Body mass index
*Continuous variables are summarized by mean; categorical variables are summarized by percentage
Data source: IJ-900DV-03O CSR Tables 14.1.2 and 14.1.3

Source: Applicant's Clinical Summary p. 21
Safety Findings
A brief summary of the safety findings for this clinical trial is provided herein. A complete discussion of safety can be found in Section 7.

Deaths
No subjects died during the trial.

Serious Adverse Events (SAEs)
No SAEs occurred during the trial.

Discontinuations Due to Adverse Events
No subject discontinued due to an AE during the trial.

6 Review of Efficacy

Efficacy Summary
The Applicant utilized the 505(b)(2) pathway, relying on the Agency’s previous efficacy and safety findings for the naloxone product, Narcan (NDA016636), and bridged to those previous findings by performing a successful comparative bioavailability study. An efficacy study is not required by the Division for the following reasons. It would be unethical to administer a novel formulation/route of administration for naloxone to patients with an opioid overdose in the setting of a clinical trial when there are already-approved formulations of naloxone available. Therefore, as discussed in the pre-IND meeting, the Applicant’s clinical program consisted of demonstrating comparable (or higher) pharmacokinetics in healthy volunteers in relation to an approved route of administration for naloxone in lieu of efficacy studies. The Division agreed this could be accomplished through a successful, single, pivotal, comparative bioavailability trial. Based on the review of the pivotal comparative bioavailability trial, IJ-1000FE-03O, naloxone delivered by the Evzio and the standard syringe, delivered via the SC or IM route, showed comparable pharmacokinetics and met the requirements set forth by the Division (Table 3). Therefore, the Applicant may rely on the Agency’s previous findings of safety and efficacy for the Narcan.

Deleted sections:
6.1.4 Analysis of Primary Endpoint(s); 6.1.5 Analysis of Secondary Endpoints(s); 6.1.6 Other Endpoints; 6.1.7 Subpopulations; 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations; 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects; and 6.1.10 Additional Efficacy Issues/Analyses were all deleted since the Division did not require the Applicant to conduct efficacy studies.
6.1 Indication

The Applicant proposed the following language within their product’s prescribing information:

- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]

The Division does not agree with the Applicant’s proposed language for the proposed indication as it does not necessarily reflect the intended target population. Furthermore, the Division recognizes the importance of this product in addressing a major public health crisis and would not want to unintentionally limit its use. Product labeling discussions are currently ongoing at the time of the report’s completion. However, below is proposed new language for the indication to be included in the product labeling.

- EVZIO is an opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.
- EVZIO is intended for immediate administration as emergency therapy in settings where opioids may be present.
- EVZIO is not a substitute for immediate medical care.

I believe this language better represents the indication for the intended target population and addresses the two concerns identified above.

6.1.1 Methods

See Section 5.3.

6.1.2 Demographics

See Section 5.3.
6.1.3 Subject Disposition

See Section 5.3.

7 Review of Safety

Safety Summary

The Applicant submitted a 505(b)(2) application referencing the approved drug, Narcan (NDA 016636), to support the clinical efficacy and safety of Evzio in the treatment of opioid related overdose. As previously described in Section 1.2 and Section 6, the Division agreed with the Applicant’s plan to submit data from a PK study in lieu of efficacy and safety studies if the PK parameters (i.e., AUC and Cmax) were found to be bioequivalent or show greater values. The PK data was found to be bioequivalent or greater as described in Section 4.4 and shown in Table 3. Therefore, the Applicant may rely on the Agency’s previous findings of safety and efficacy for Narcan (NDA 016636) for this application. Additional safety data was collected from the pivotal comparative bioavailability trial (IJ-900DV-03O) and discussed below. Overall, the safety data from trial IJ-900DV-03O did not show any new safety signals. There were no deaths, serious adverse events (SAE) or withdrawals.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The pivotal comparative bioavailability trial (IJ-900DV-03O) consisted of 30 healthy adult subjects aged 18-45 years of age. The safety data discussed below are from trial IJ-900DV-03O and provide additional support to the Agency’s previous findings of safety for the reference drug Narcan. The entire 30 subjects were included in the safety group. As described in Section 4.4.3, the trial showed the AUC parameters were bioequivalent between both naloxone delivery systems. The $C_{\text{max}}$ is slightly higher for the naloxone delivered through the Evzio, however, this should not relate to any safety concern given the wide therapeutic safety margin for naloxone. Given this application is a 505(b)(2), and the results of trial IJ-900DV-03O showed naloxone used in Evzio were comparable to the reference drug, the Agency’s previous findings of safety for the reference product Narcan (NDA 016636) may be relied upon for this application. A number of subsections below are not relevant and reference to the deleted sections is listed below. The Applicant also performed an analysis of the literature to support the safety of Evzio. Literature references are briefly discussed in Section 7.7.

Deleted Sections
7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence. This section was not relevant to this application because there was no relevant data to be pooled.

7.2.2 Explorations for Dose Response. This section was not relevant since only a single dose was studied and this product is designed to be a single-fixed dose product.

7.2.3 Special Animal and/or In Vitro Testing. No data was submitted to inform a discussion for this section.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class. No data was submitted to inform a discussion for this section.

7.4.6 Immunogenicity was deleted because no data was submitted to inform a discussion for this section.

7.5.3 Drug-Demographic Interactions, 7.5.4 Drug-Disease Interactions, 7.5.5 Drug-Drug Interactions, and 7.6.1 Human Carcinogenicity were all deleted. No data was submitted to inform a discussion for this section.

7.5.2 Time Dependency for Adverse Events. This trial only includes a single dose of medication, therefore, this section was irrelevant.

7.2.5 Metabolic, Clearance, and Interaction Workup. This section was deleted because only a comparative PK trial was required and the Applicant could rely on the Agency’s previous findings for Narcan.

7.3.5 Submission Specific Primary Safety Concerns. This section was deleted because there were no specific primary safety concerns in this PK study.

7.5 Other Safety Explorations. This section is not relevant given the drug was only given as a single, fixed-dose in the trial.

7.6 Human Reproduction and Pregnancy Data. This section was deleted because no new data was submitted for an analysis.

7.1.2 Categorization of Adverse Events

All treatment emergent adverse events (TEAEs) were coded by using the Medical Dictionary for Regulatory Activities (MedDRA), version 15.1. If the same AE (using the MedDRA Preferred Term) was reported more than once for the same subject within a dosing period, it was to only appear once for that specified treatment. For subjects with multiple AEs within a dosing period of the same MedDRA Preferred Term and of different severities, the AE with the highest assessment of severity was used for that dosing period. Adverse events that emerged in one dosing period and carried over into the next period were attributed to only the period in which the AE emerged.
7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Exposure

Thirty subjects received naloxone in study IJ-DV900-03O, and all the subjects received both the investigational medicinal product (Evzio/NAI - naloxone 0.4 mg) and reference product (naloxone 0.4 mg via syringe). Because the Applicant is utilizing the 505(b)(2) pathway and relying on the Agency’s previous findings of Narcan, the exposure to 30 subjects is adequate for the purposes of this safety evaluation.

Demographics

Demographics are discussed in Section 5.3.

7.2.4 Routine Clinical Testing

The safety monitoring plan is outlined for the pivotal trial in Section 5.3, which appears adequate for this population.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in this trial.

7.3.2 Nonfatal Serious Adverse Events

There were no serious adverse events (SAE).

7.3.3 Dropouts and/or Discontinuations

There were no dropouts or discontinuations in the study.

7.3.4 Significant Adverse Events

All of the TEAEs were of mild intensity and no notable differences between the test groups. There were no marked laboratory abnormalities, and no events led to
substantial intervention. I also reviewed the submitted ECG data for all subjects and found no relevant changes between test groups.

### 7.4 Supportive Safety Results

#### 7.4.1 Common Adverse Events

The Applicant defined the safety population as all subjects who received at least one dose of study drug. No adverse event was reported by more than 2 subjects in the pivotal study IJ-900DV-03O. Dizziness (n=2) was the most common event associated with the test drug (Table 6). No subject experienced a TEAE that resulted in their withdrawal from the trial. Overall, there are no newly identified safety signals. I reviewed the Applicant’s dataset and found no substantial differences that would affect my perception of the adverse event profile.

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<tr>
<th>System Organ Class</th>
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<tbody>
<tr>
<td>Preferred Term</td>
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<tr>
<td>Gastrointestinal Disorders</td>
<td>1 (3.3%)</td>
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<tr>
<td>Nausea</td>
<td>1 (3.3%)</td>
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<td>General Disorders and Administration Site Conditions</td>
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<td>Vessel Puncture Site Haematoma</td>
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<td>Nervous System Disorders</td>
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<tr>
<td>Anosmia</td>
<td>1 (3.3%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (6.7%)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>1 (3.3%)</td>
</tr>
<tr>
<td>Headache</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Presyncope</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Skin And Subcutaneous Tissue Disorders</td>
<td>1 (3.3%)</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>1 (3.3%)</td>
</tr>
</tbody>
</table>

N = number of subjects exposed to treatment; n = number of subjects

Data source: IJ-900DV-03O CSR Table 14.3.1.2

Source: Clinical Summary – Summary of Clinical Safety p. 22
7.4.2 Laboratory Findings

In Study IJ-900DV-03O, no clinically significant findings were noted for any clinical chemistry, hematology or urinalysis results in either group. I reviewed through the data tables provided by the Applicant and did not identify any clinically relevant laboratory findings.

7.4.3 Vital Signs

There were no observable treatment-related trend in vital sign parameters and median absolute values were similar for both groups. No TEAEs were related to vital sign measurements.

7.4.4 Electrocardiograms (ECGs)

ECGs were performed on each subject at screening, Day -1, and Day 2 (6 hours post dose). I reviewed the combined and individual ECG data submitted by the Applicant, and none of the abnormalities appeared to be clinically relevant. No subject developed a prolonged QTcF and the mean QTcF was not increased. The PR interval did not show any significant changes from the subject's baseline values. Several subjects developed a heart rate slightly out of the normal range (e.g., subject 117 heart rate was 49, 52, and 57). This likely represents a subject’s normal range and not related to the study drug.

7.4.5 Special Safety Studies/Clinical Trials

No special safety trials were included in this application. The prescribing information describes several instances of hypotension, hypertension, ventricular tachycardia and fibrillation, and pulmonary edema in post-operative patients. Many of these patients had pre-existing cardiovascular disorders or received a drug(s) which may affect the cardiovascular system. This information is not particularly relevant to Evzio given the product is proposed for out-of-hospital use.

7.6.3 Pediatrics and Assessment of Effects on Growth

The Division outlined the requirements for the Applicant’s pediatric plan during the pre-NDA meeting (June 4, 2013). The Applicant proposed a single-dose regimen of 0.4 mg. However, the current labeling for Narcan provides separate dosing and administration regimens for adults and children, including a weight-based dosing regimen. The Division stated the new dosing regimen triggered the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), and the Applicant is required to provide an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Also, the Applicant was informed if they believe a waiver for any pediatric age group is appropriate, they must
Although the product will be prescribed to a patient taking opioids out of the hospital, the product may also be used for anyone, including children, who may be exposed to opioids. The concern for the pediatric age range includes a number of situations including, but not limited to the following: accidental use or ingestion, intentional misuse, and exposure to duragesic patches. Similarly to the adult population, there is a wide safety margin for naloxone, and the clinical consequences of not treating an opioid overdose are grave, and it is not practical to deliver pediatric weight-based dosing for naloxone (as is currently recommended in the Narcan labeling) in a community setting. The benefit of a potentially life-saving drug product with a wide safety margin considerably outweighs the risk of not treating an opioid overdose which may result in death. Therefore, the risk/benefit ratio convincingly demonstrates support for labeling the proposed product containing a 0.4 mg fixed dose of naloxone for all pediatric age ranges.

There are several concerns about the product’s use in pediatric population, especially the very young age groups. Given there is some force needed to administer the drug, there is the potential for the needle to strike bone and potentially break off within the subcutaneous or muscle tissue and possibly not deliver the dose. The Applicant submitted information justifying the safety of the exposed needle length of 0.5 inches on 2/18/2014. The safety concern is whether this needle length may over penetrate the intramuscular space leading to the needle striking bone, especially in the younger pediatric population who possess less subcutaneous tissue. The Applicant submitted the Center for Disease Control (CDC) recommendations based on intramuscular injection of vaccines. The CDC recommends 5/8” needle length for intramuscular injections, based on injection of vaccines, into the anterolateral thigh muscle in the newborn (0-28 days old) age group. The Applicant also submitted a literature reference which examined the safety of needle lengths injected into the subcutaneous fat and muscle in 100 children aged 0 – 6 years old relative to the CDC recommended needle lengths for vaccinations requiring intramuscular injection. The reference stated a 7/8 inch needle would result in 4% over penetration within this age group. Therefore, the shorter exposed needle length or 0.5 inches, such as the one for Evzio, should result in substantially less than 4% over penetration in this population; however, Evzio may require additional force compared to vaccine administration resulting in compression of the soft tissue layer. Based on the CDC recommendations for needle length, the literature reference, and the likely rare event of requiring Evzio in a newborn and the needle breaking off, as well as the risk/benefit of the clinical scenario, I believe the potentially life-saving benefit far outweighs the risk of these events.
However, I do recommend routine postmarketing surveillance, and if a signal arises, the Applicant may need to perform additional safety studies and adjust the language in the product labeling. At the current time, I recommend language be included within the product labeling for this young, vulnerable age group (i.e., age less than 1 year old). For example, recommendations may include a follow-up inspection of the injection site by a health professional or an x-ray to assess for needle fragments. The Pediatric and Maternal Health Service (PMHS) has been consulted and will assist in the pediatric labeling section prior to approval.

The above information was discussed with the Pediatric Review Committee (PeRC) on 3/5/2014, and the committee was in agreement with the Division on the above discussion.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no instances of overdose in the pivotal comparative bioavailability study IJ-900DV-03O. The currently approved Narcan product labeling states there is no clinical experience with naloxone overdosage in humans. The Applicant referenced literature which concluded high doses of naloxone have been administered in clinical trials with minimal toxicity. Naloxone does not have any known abuse potential since it does not produce subjective effects or physical dependence and precipitates abstinence in morphine-dependent subject. There is no data available regarding withdrawal and rebound.

7.7 Additional Submissions / Safety Issues

No additional safety studies or updates were submitted for review.

8 Postmarket Experience

Although Evzio includes a device component, there is considerable experience with naloxone and published literature to support its safety and effectiveness. A brief review of the literature submitted by the Applicant is described in Section 9.1.

9 Appendices

9.1 Literature Review/References

The Applicant submitted an analysis of a PubMed database search for published data relevant to the safety and efficacy of naloxone through June 9, 2013. The analysis of the literature supports the safety and effectiveness of naloxone for the treatment of respiratory depression secondary to opioid overdose. Naloxone is the standard of care,
with no absolute contraindications, for the treatment of opioid-related respiratory depression regardless of age, sex or ethnicity. Cardiovascular events, pulmonary edema, and seizures have been reported and studied in the literature. However, separating the effects of naloxone from the effects of concomitant medications and pre-existing disorders has been problematic. High doses of naloxone have been administered in clinical trials and generally have been well tolerated. Overall, naloxone is considered to have a wide safety margin even at doses higher than the proposed fixed dose of 0.4 mg. Review of the provided literature reveals no new safety signals that would alter the risk-benefit profile of Evzio in this population.

An additional submission was submitted 3/17/14 which included an analysis of the literature, in combination with the safety data collected from the pivotal pharmacokinetic trial (IJ-DV900-030) for this application, to be included in Section 6 of the product labeling. The safety profile of naloxone in the literature is biased towards settings of use in opioid withdrawal. The Division requested the Applicant attempt to characterize the safety of naloxone based on the drug and not the effects of opioid withdrawal. The Applicant provided a summary of their findings and proposed language for Section 6 of the product labeling. The Applicant based the language for Sections 6 by combining AEs associated with naloxone use in opioid naïve subjects in the literature and possibly related AEs reported in the clinical trial IJ-900DV-030. I agree that the literature is sparse regarding characterizing the direct AEs caused by naloxone and not a consequence of opioid withdrawal. The Applicant’s proposal appears reasonable.

Cardiac Disorders
- palpitations

Gastrointestinal Disorders
- nausea, vomiting, dyspepsia

Nervous System Disorders
- tremor, dystonia, dizziness, headache, drowsiness (sedation), yawning

Psychiatric Disorders
- agitation, anxiety, anger, confusion, dysphoria, dysesthesia

Skin and Integumentary Disorders
- injection site reaction, diaphoresis (hyperhidrosis and sweating)

Vascular Disorders
- pallor, flushing

Details of the frequency of the AEs were not reported in all the literature and could not be estimated. After a review of the literature submitted and my own review of PubMed, the literature is sparse regarding the AEs that may be directly linked to naloxone, excluding opioid withdrawal symptoms and post-operative events.
9.2 Labeling Recommendations

Product labeling is still under review at the completion of this report. However, labeling recommendations are included within the relevant sections of this report.

9.3 Advisory Committee Meeting

There was no advisory committee for this drug product.

APPENDIX 9.4 Clinical Investigator Financial Disclosure
Clinical Investigator Financial Disclosure
Review Template

Application Number: 205787
Submission Date(s): December 20, 2013
Applicant: Kaleo INC.
Product: Evzio (naloxone auto-injector)
Reviewer: Steven Galati
Date of Review: March 19, 2014
Covered Clinical Study (Name and/or Number): IJ-1000FE-03O

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<th>No ☐ (Request list from applicant)</th>
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</thead>
<tbody>
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<td>Total number of investigators identified:</td>
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<td></td>
</tr>
<tr>
<td>Number of investigators who are sponsor employees (including both full-time and part-time employees):</td>
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<td></td>
</tr>
<tr>
<td>Number of investigators with disclosable financial interests/arrangements (Form FDA 3455):</td>
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</tr>
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<tr>
<td>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study:</td>
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<td>Significant payments of other sorts:</td>
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<td>Proprietary interest in the product tested held by investigator:</td>
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<td>Significant equity interest held by investigator in sponsor of covered study:</td>
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<tr>
<td>Is an attachment provided with details of the disclosable financial interests/arrangements:</td>
<td>Yes ☐</td>
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<tr>
<td>Is a description of the steps taken to minimize potential bias provided:</td>
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<td>No ☐ (Request information from applicant)</td>
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<tr>
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<tr>
<td>Is an attachment provided with the reason:</td>
<td>Yes ☐</td>
<td>No ☐ (Request explanation from applicant)</td>
</tr>
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</table>
Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.1 Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

*The Applicant submitted Form FDA 3454 “Certification: Financial Interests and Arrangements of Clinical Investigator”, and stated a total of six investigators were listed and the study was performed through the contract research organization, Parexel International Early Phase Clinical Unit-Baltimore. The form certified that they had no financial interests or arrangements to disclose.*

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

*Given no investigator had financial interests or arrangements to disclose, the possibility of bias in the results based on financial interests is unlikely.*

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1 See [web address].
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STEVEN A GALATI
03/19/2014

JOSHUA M LLOYD
03/19/2014
CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 205787  Applicant: Kaleo INC  Stamp Date: 12/20/13

Drug Name: Naloxone Auto-injector  NDA/BLA Type: Priority/Fast Track

On initial overview of the NDA/BLA application for filing:

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<td>eCTD</td>
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<td>5. Are all documents submitted in English or are English translations provided when necessary?</td>
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<td>6. Is the clinical section legible so that substantive review can begin?</td>
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<tr>
<td><strong>LABELING</strong></td>
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<tr>
<td>7. Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?</td>
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<td><strong>SUMMARIES</strong></td>
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<tr>
<td>8. Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?</td>
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<td>9. Has the applicant submitted the integrated summary of safety (ISS)?</td>
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<tr>
<td>10. Has the applicant submitted the integrated summary of efficacy (ISE)?</td>
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<tr>
<td>11. Has the applicant submitted a benefit-risk analysis for the product?</td>
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File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

Reference ID: 3434657
## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

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<th>Yes</th>
<th>No</th>
<th>NA</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>12. <strong>DOSE</strong></td>
<td></td>
<td>X</td>
<td></td>
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</tr>
<tr>
<td>Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?</td>
<td>X</td>
<td></td>
<td></td>
<td>505(b)(2) with reference to Narcan NDA 016636</td>
</tr>
<tr>
<td>13. If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Number:</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Study Title:</td>
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<tr>
<td>Sample Size:</td>
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<tr>
<td>Arms:</td>
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<td></td>
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<tr>
<td>Location in submission:</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>14. <strong>Efficacy</strong></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do there appear to be the requisite number of adequate and well-controlled studies in the application?</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pivotal Study #1</td>
<td></td>
<td></td>
<td></td>
<td>Indication:</td>
</tr>
<tr>
<td>Pivotal Study #2</td>
<td></td>
<td></td>
<td></td>
<td>Indication:</td>
</tr>
<tr>
<td>15. Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?</td>
<td></td>
<td>X</td>
<td></td>
<td>No efficacy studies required.</td>
</tr>
<tr>
<td>16. Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.</td>
<td></td>
<td>X</td>
<td></td>
<td>No efficacy studies required.</td>
</tr>
<tr>
<td>17. Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18. <strong>Safety</strong></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19. Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20. Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?</td>
<td></td>
<td>X</td>
<td></td>
<td>The Applicant conducted a literature review pertaining to the safety of naloxone in humans through June 2013.</td>
</tr>
</tbody>
</table>
## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>21. For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure(^1)) been exposed at the dose (or dose range) believed to be efficacious?</td>
<td></td>
<td>X</td>
<td></td>
<td>Not a chronic indication.</td>
</tr>
<tr>
<td>22. For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?</td>
<td>X</td>
<td></td>
<td></td>
<td>The Division required a pivotal relative BA study between the proposed product and the reference product, to support this application, and the Applicant collected safety data in this study.</td>
</tr>
<tr>
<td>23. Has the applicant submitted the coding dictionary(^2) used for mapping investigator verbatim terms to preferred terms?</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24. Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25. Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?</td>
<td>X</td>
<td></td>
<td></td>
<td>There were no deaths, discontinuations, or SAEs in the pivotal PK study</td>
</tr>
</tbody>
</table>

### OTHER STUDIES

| 26. Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions? | X   |    |    |                                                                         |
| 27. For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)? | X   |    |    |                                                                         |

### PEDIATRIC USE

| 28. Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral? | X   |    |    |                                                                         |

### ABUSE LIABILITY

| 29. If relevant, has the applicant submitted information to assess the abuse liability of the product? | X   |    |    |                                                                         |

### FOREIGN STUDIES

| 30. Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population? | X   |    |    |                                                                         |

### DATASETS

| 31. Has the applicant submitted datasets in a format to allow reasonable review of the patient data? | X   |    |    |                                                                         |
| 32. Has the applicant submitted datasets in the format agreed to | X   |    |    |                                                                         |

\(^1\) For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

\(^2\) The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908
CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

<table>
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<tr>
<td>previously by the Division?</td>
<td></td>
<td></td>
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<tr>
<td>33. Are all datasets for pivotal efficacy studies available and complete for all indications requested?</td>
<td>X</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>34. Are all datasets to support the critical safety analyses available and complete?</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>35. For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?</td>
<td></td>
<td>X</td>
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</table>

CASE REPORT FORMS

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<thead>
<tr>
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<tbody>
<tr>
<td>36. Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?</td>
<td>X</td>
<td></td>
<td></td>
<td>None required. There were no deaths, discontinuations, or SAEs in the pivotal PK study.</td>
</tr>
<tr>
<td>37. Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
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FINANCIAL DISCLOSURE

<table>
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<tr>
<td>38. Has the applicant submitted the required Financial Disclosure information?</td>
<td></td>
<td>X</td>
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</table>

GOOD CLINICAL PRACTICE

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<tr>
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<tbody>
<tr>
<td>39. Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?</td>
<td>X</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ________

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. We note that you have submitted integrated summary information (i.e., efficacy and safety) in the clinical overview and clinical summary. However, you must cross-reference this information in Module 5.3.5.3 (i.e., the integrated summary of safety [ISS] and integrated summary of effectiveness [ISE]).

Reviewing Medical Officer Date

Clinical Team Leader Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

Reference ID: 3434657
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

---------------------------------------
STEVEN A GALATI
01/10/2014

JOSHUA M LLOYD
01/10/2014