

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**209862Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## CLINICAL PHARMACOLOGY REVIEW

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NDA: 205787 S007	Submission Date(s): April 19, 2016
Proposed Brand Name	EVZIO Naloxone Auto-Injector (NAI)
Generic Name	Naloxone HCl Injection, USP
Reviewer	Wei Qiu, Ph.D.
Team Leader	Yun Xu, Ph.D.
OCP Division	DCPII
OND division	DAAAP
Sponsor	Kaleo Inc
Relevant IND(s)	IND 112,292
Submission Type	Efficacy Supplement to add 2 mg Strength
Formulation; Strength(s)	Solution for injection via autoinjector; 2.0 mg
Indication	 (b) (4)

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## 1 Executive Summary

### 1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed the NDA submissions dated April 19, 2016 and finds them acceptable from clinical pharmacology perspective.

### 1.2 Phase IV Commitments

None.

### 1.3 Summary of Clinical Pharmacology Findings

#### **Key clinical pharmacology findings:**

Dose proportionality for naloxone AUC<sub>t</sub> and AUC<sub>inf</sub> was demonstrated between approved 0.4 mg NAI and proposed 2.0 mg NAI because the 90% CIs (1.02-1.11 for AUC<sub>0-t</sub> comparison and 1.01-1.09 for AUC<sub>inf</sub> comparison) for the geometric mean ratios of dose normalized AUC<sub>t</sub> or AUC<sub>inf</sub> were contained within the bioequivalence criteria (0.80, 1.25). Naloxone C<sub>max</sub> values were slightly greater than dose proportional for the same comparison because the geometric mean ratio of the dose normalized C<sub>max</sub> values was 1.24 with the upper bound of the 90% CI (1.04, 1.49) greater than 1.25.

Kaleo Inc. submitted an efficacy supplement (S-007) to propose the addition of 2.0 mg strength of Naloxone Auto-Injector (NAI) for intramuscular (IM) or subcutaneously (SC) administration. The 2.0 mg NAI was developed at a concentration of 5 mg/mL naloxone HCl to deliver 2.0 mg per single 0.4 mL injection. The 2.0 mg dose is the recommended maximum initial dose of naloxone HCl given intravenously (IV) (or IM/SC administration if IV route is not available) as specified in the approved labeling for Narcan (naloxone HCl injection, NDA 16636). The proposed formulation for 2.0 mg NAI is identical to the approval 0.4 mg NAI formulation except for naloxone concentration. The proposed indications are the same as that for 0.4 mg NAI.

Per the Pre-NDA meeting held on December 23, 2014, Division recommended sponsor

(b) (4) characterization of the

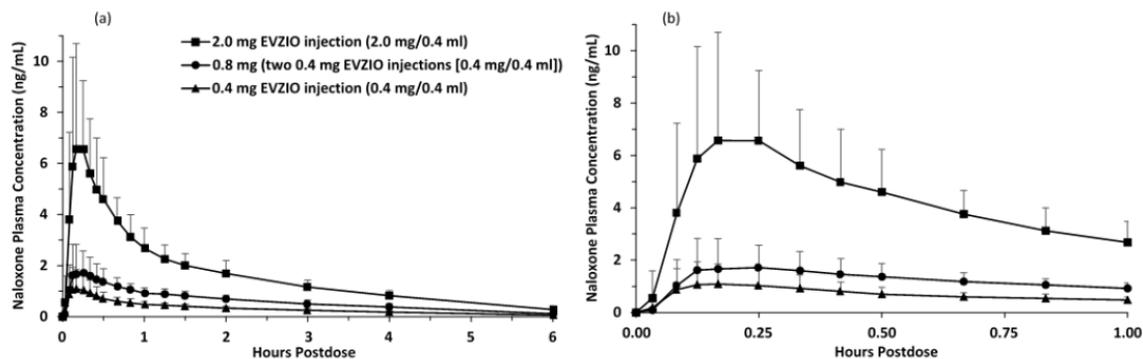
pharmacokinetic (PK) profile for the new 2.0 mg strength NAI, and documentation of PK linearity over the therapeutic dose range.

In this current submission, sponsor characterized the PK of 2 mg NAI and dose linearity over dose range of 0.4 to 2 mg NAI in Study KA-900DV-05V. Study KA-900DV-05A is a randomized, single-dose, three-sequence, three-period crossover dose proportionality study in 24 healthy subjects. All 24 subjects completed the study. The treatments include a single 0.4 mg NAI, a 0.8 mg naloxone HCl using two 0.4 mg NAI given 2 minutes apart, and a single 2.0 mg NAI. Study drug was administered on Day 1, Day 2, and Day 3. All injections were given in the mid-anterolateral aspect of the thighs. Blood samples for PK determination were collected pre-dose and at 2, 5, 7.5, 10, 15, 20, 25, 30, 40, and 50 min and 1, 1.25, 1.5, 2, 3, 4, and 6 h post-dose.

Naloxone plasma concentration was determined by a validated LC/MS/MS analytical method which was utilized for the comparative BA Study IJ-900DV-03O submitted in the original NDA. Lower limit of quantification is 2 pg/mL. For all QCs (5.00, 12.0, 45.0, 160, and 750 pg/mL), inter-assay precision (%CV) is 3.33 to 5.06% and inter-assay accuracy (% bias) is -2.13 to 1.22% difference from theoretical.

Mean naloxone plasma concentration time profiles (N = 24) for a single 0.4 mg NAI, 0.8 mg naloxone HCl using two 0.4 mg NAI given 2 minutes apart, and a 2.0 mg NAI are shown in **Figure 1**. Naloxone PK parameters from all 24 subjects and statistical analysis of dose proportionality are shown in **Table 1**.

**Figure 1** Mean Naloxone Plasma Concentration Time Profiles, (a) 0-6 h and (b) 0-1 h



**Table 1** Summary of Naloxone Pharmacokinetic Parameters and Statistical Analysis of Dose Proportionality

Treatment	Statistic	C <sub>max</sub> (pg/mL)	T <sub>max</sub> (h)	T <sub>1/2</sub> (h)	AUC <sub>0-t</sub> (pg.h/mL)	AUC <sub>0-inf</sub> (pg.h/mL)
Pharmacokinetic Parameters						
Reference (0.4 mg NAI)*	Mean (SD)	1328 (836)		1.58 (0.457)	1817 (290)	1995 (326)
	%CV	62.9		28.9	16.0	16.3
	Median (Min-Max)	980 (503-4220)	0.25 (0.09-0.84)	1.47 (1.05-2.76)	1864 (1322-2269)	1991 (1427-2688)
Test (0.8 mg naloxone HCl [two 0.4 mg NAIs])*	Mean (SD)	2156 (1021)		1.52 (0.360)	3498 (691)	3776 (720)
	%CV	47.4		23.7	19.8	19.1
	Median (Min-Max)	1855 (913-4160)	0.21 (0.09-0.85)	1.40 (1.11-2.39)	3435 (2334-5186)	3776 (2584-5438)
Test (2.0 mg NAI)	Mean (SD)	7905 (3617)		1.53 (0.382)	9657 (1488)	10330 (1565)
	%CV	45.8		25.0	15.4	15.2
	Median (Min-Max)	6950 (3020-14900)	0.25 (0.13-0.67)	1.47 (0.90-2.31)	9703 (6896-12760)	10410 (7420-13150)
Statistical Assessments of Dose Proportionality						
Dose normalized 2.0 mg / 0.4 mg <sup>†</sup>	GMR	1.24			1.06	1.05
	90% CI for ratio	1.04, 1.49			1.02, 1.11	1.01, 1.09
Dose normalized 0.8 mg / 0.4 mg	GMR	0.85			0.96	0.94
	90% CI for ratio	0.71, 1.02			0.92, 1.00	0.91, 0.98
Power Model (linear regression)	Slope	1.15			1.04	1.03
	95% CI	0.97, 1.33			0.98, 1.11	0.97, 1.09

The PK of a single 2.0 mg NAI is adequately characterized in Study KA-900DV-05A. Mean C<sub>max</sub> of 7.90 ng/mL was reached at a median T<sub>max</sub> of 15 min. The mean T<sub>1/2</sub> is 1.53 h. The median T<sub>max</sub> and mean T<sub>1/2</sub> values were similar for the 2.0 mg NAI and 0.4 mg NAI. At each time points, naloxone concentrations for the 2.0 mg NAI are greater than the 0.4 mg NAI.

Dose proportionality for naloxone AUC<sub>t</sub> and AUC<sub>inf</sub> was demonstrated between 0.4 mg NAI and 2.0 mg NAI because the 90% CIs for the geometric mean ratios of dose normalized AUC<sub>t</sub> or AUC<sub>inf</sub> were contained within the bioequivalence criteria (0.80, 1.25). Naloxone C<sub>max</sub> values were slightly greater than dose proportional for the same treatment comparison because the geometric mean ratio of the dose normalized C<sub>max</sub> values was 1.24 with the upper bound of the 90% CI (1.04, 1.49) greater than 1.25. It is also noted that the naloxone concentrations at each time point after administration are much higher for the 2.0 mg NAI than the 0.4 mg NAI.

Dose proportionality for naloxone AUC<sub>t</sub> and AUC<sub>inf</sub> was also demonstrated between 0.4 mg NAI and 0.8 mg naloxone HCl (two 0.4 mg NAI given 2 min apart) because the 90% CIs for the geometric mean ratios of dose normalized AUC<sub>t</sub> or AUC<sub>inf</sub> were within the bioequivalence criteria (0.80, 1.25). C<sub>max</sub> was slightly less than dose proportional because the geometric mean ratio of the dose normalized C<sub>max</sub> values (90% CI) for C<sub>max</sub> was 0.85 with the lower bound of the 90% CI (0.71, 1.02) less than 0.80.

From clinical pharmacology perspective, sponsor has adequately characterized the PK of the proposed new strength of NAI (2 mg) and dose proportionality between 0.4 mg NAI and 2 mg NAI. According to the approved labeling for Narcan (naloxone HCl injection), the list drug product identified for NAI in the original NDA submission, an initial dose of 0.4 to 2.0 mg is given IV (or via IM/SC administration if IV route is not available). In the original NDA, the 0.4 mg NAI exhibited slightly (15%) greater C<sub>max</sub> and equivalent AUC values of naloxone in comparison to the 0.4 mg naloxone HCl delivered via a standard syringe. The 2.0 mg NAI showed about 5-fold AUC and C<sub>max</sub> values compared to the the 0.4 mg NAI; and the naloxone concentrations at each time point after administration are much higher for the 2.0 mg NAI than the 0.4 mg NAI. These PK results support the addition of the new strength for the indication of opioid overdose.

## 2 Labeling Recommendations

(~~RED Strikeout~~ text should be removed from labeling; Blue underlined text should be added to labeling)

The following edits are per discussion within the review team and as of today (9/22/16) labeling negotiation with sponsor is still ongoing.

Under Section 12.3 CLINICAL PHARMACOLOGY: Pharmacokinetics

In a pharmacokinetic study in 30 healthy subjects, a single 0.4 mg subcutaneous or intramuscular naloxone injection administered using EVZIO provides equivalent naloxone AUC and 15% greater naloxone C<sub>max</sub> in comparison to a single 0.4 mg subcutaneous or intramuscular naloxone injection administered using a standard syringe.

Following a single 0.4 mg EVZIO injection, the median T<sub>max</sub> of naloxone was reached at 0.25 hours (range 0.08 to 1.23 hours), with a mean (CV%) C<sub>max</sub> value of 1.24 (51.4% CV) ng/mL. The mean (CV%) plasma half-life of naloxone in healthy adults was 1.28 (38.0% CV) hours. In the same study, following administration of a single dose of 0.4 mg naloxone injection using a standard syringe, the median T<sub>max</sub> was 0.33 hours (range 0.08 to 2.03 hours) and the mean (CV%) C<sub>max</sub> value was 1.07 (45.1% CV) ng/mL. The mean <sup>(b) (4)</sup> plasma half-life was 1.36 (23.5% CV) hours.

A second pharmacokinetic study in 24 healthy subjects using a crossover design, evaluated a single 0.4 mg EVZIO injection, a single 2.0 mg EVZIO injection, and two 0.4 mg EVZIO injections administered two minutes apart (0.8 mg naloxone hydrochloride total). The pharmacokinetic parameters obtained in this study are shown in Table 1 and the plasma concentration time profiles of naloxone are in Figure 1.

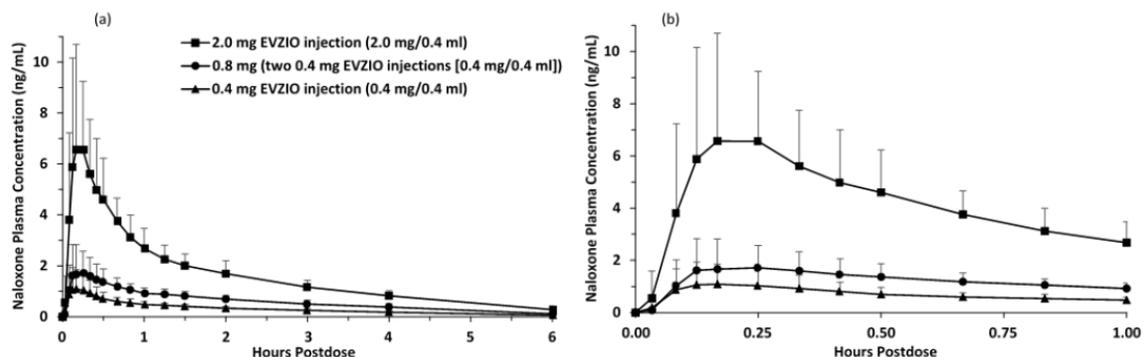
**Table 1 Mean Pharmacokinetic Parameters (CV%) for Naloxone Following EVZIO (Naloxone HCl) Intramuscular/Subcutaneous Administration to Healthy Subjects**

Parameter	0.4 mg EVZIO (N=24)	0.8 mg (two 0.4 mg EVZIO) (N=24)	2 mg EVZIO (N=24)
T <sub>max</sub> (h) <sup>†</sup>	0.25 (0.09, 0.84)	0.21 (0.09, 0.85)	0.25 (0.13, 0.67)
C <sub>max</sub> (ng/mL)	1.33 (62.9)	2.16 (47.4)	7.91 (45.8)
AUC <sub>0-t</sub> (ng h/mL)	1.82 (16.0)	3.50 (19.8)	9.66 (15.4)
AUC <sub>0-inf</sub> (ng h/mL)	2.00 (16.3) <sup>††</sup>	3.78 (19.1) <sup>††</sup>	10.33 (15.2)
T <sub>1/2</sub> (h)	1.58 (28.9) <sup>††</sup>	1.52 (23.7) <sup>††</sup>	1.53 (25.0)

<sup>†</sup> T<sub>max</sub> reported as median (minimum, maximum)

<sup>††</sup> N=23 for AUC<sub>0-inf</sub> and T<sub>1/2</sub>

**Figure 1 Mean ± SD Plasma Concentration of Naloxone, (a) 0-6 h and (b) 0-1h Following Intramuscular/Subcutaneous Administration using EVZIO**



## Distribution

(b) (4)

Following parenteral administration, naloxone is distributed in the body and readily crosses the placenta. Plasma protein binding occurs but is relatively weak. Plasma albumin is the major binding constituent but significant binding of naloxone also occurs to plasma constituents other than albumin. It is not known whether naloxone is excreted into human milk.

## Elimination

Following a single 0.4 mg EVZIO injection, the mean (CV%) plasma half-life of naloxone in healthy adults was 1.58 (28.9% CV) hours and 1.53 (25% CV) hours following a single 2 mg EVZIO injection. In a neonatal study of naloxone injection, the mean ( $\pm$  SD) plasma half-life was observed to be 3.1 ( $\pm$  0.5) hours.

## *Metabolism*

Naloxone hydrochloride is metabolized in the liver, primarily by glucuronide conjugation with naloxone-3-glucuronide as the major metabolite.

## (b) (4) Excretion

After an oral or intravenous dose, about 25-40% of naloxone is excreted as metabolites in urine within 6 hours, about 50% in 24 hours, and 60-70% in 72 hours

### 3 Appendix

#### 3.1 Clinical Pharmacology Filing Memo

<b>Office of Clinical Pharmacology</b>				
<i>New Drug Application Filing and Review Form</i>				
<i>General Information About the Submission</i>				
	Information	Proposed Brand Name	Information	
NDA/BLA Number	205-787 S007	EVZIO	Naloxone Auto-Injector (NAI) HD 2.0 mg	
OCP Division (I, II, III, IV, V)	II	Generic Name	Naloxone HCl injection, USP	
Medical Division	DAAAP	Drug Class	Opioid Antagonist	
OCP Reviewer	Wei Qiu, Ph.D.	Indication(s)	(b) (4)	
OCP Team Leader	Yun Xu, Ph.D.	Dosage Form, Strength	Solution for injection, 2.0 mg (0.4 mL of 5 mg/mL)	
Pharmacometrics Reviewer	N/A	Dosing Regimen	Opioid antagonist	
Date of Submission	April 19, 2016	Route of Administration	IM or SC injection	
Primary Review Goal Date (GRMP)	Sept 25, 2016	Sponsor	Kaleo Inc	
PDUFA Due Date	October 19, 2016	Priority Classification	Priority	
		Relevant INDs	IND 112292	
<i>Clin. Pharm. and Biopharm. Information</i>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	1		Dose proportionality study KA-900DV-05A
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				

PD -				
Phase 1:				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:	x	(1)		See above
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		1		

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

	Content Parameter	Yes	No	N/A	Comment
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			√	(b) (4) to-be-marketed product was used in the dose proportionality study
2	Has the applicant provided metabolism and drug-drug interaction information?			√	No new findings in the proposed label.
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	√			(b) (4) dose proportionality study was conducted to compare the proposed product (2 mg) and the approved product (0.4 mg).
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	√			
5	Has a rationale for dose selection been submitted?			√	Match the exposure of the list drug
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	√			

7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	√			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	√			
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	√			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			√	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?	√			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			√	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			√	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			√	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			√	Submitted agreed initial pediatric study plan
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			√	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	√			
<b>General</b>					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	√			
19	Was the translation (of study reports or			√	

other study information) from another language needed and provided in this submission?				
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**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?**

YES

This NDA is fileable from clinical pharmacology perspective.

No OSI inspection needs to be requested because usually OSI inspection is not requested for supplemental NDA. OSI inspection on the pivotal comparative BA study IJ-900DV-03O comparing 0.4 mg auto-injection and 0.4 mg injection of Narcan included in the original NDA was acceptable. This sNDA introduces an auto injector with 2 mg dose and its PK profile looks reasonable compared to the already approved 0.4 mg auto injector.

If the NDA/BLA is not fileable from the clinical pharmacology 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.

There are no comments for sponsor at this time.

\_\_\_\_\_  
Reviewing Clinical Pharmacologist

\_\_\_\_\_  
Date

\_\_\_\_\_  
Team Leader/Supervisor

\_\_\_\_\_  
Date

**Background:**

Kaleo Inc submitted a NDA 205787 S007 to seek approval of a new 2.0 mg strength of Naloxone Auto Injection (NAI) for IM or SC administration. The formulation is identical to the approval 0.4 mg NAI formulation except it is formulated to a higher drug concentration of 5 mg/mL. The proposed indication is the same as the approved one. (b) (4)

(b) (4)

Sponsor (b) (4) conducted a dose proportionality study (KA-900DV-05A) comparing the proposed 2.0 mg auto injection and the approved 0.4 mg auto injection.

Study KA-900DV-05A is randomized, single-dose, three-sequence, three-period crossover dose proportionality study in healthy subjects. In this study, Dose normalized C<sub>max</sub> for the test (2.0 mg NAI) was 24% greater than the reference (0.4 mg NAI), while dose normalized AUC values were equivalent.

Please find the filing slides for more details.

## NDA 205-787 S007: EVZIO (Naloxone Hydrochloride Injection)

- **Sponsor:** Kaleo Inc.
- Naloxone Auto Injector (NAI) delivering 0.4 mg naloxone HCl (naloxone HCl concentration of 1 mg/mL) via SC or IM injection was approved on April 3, 2014 under 505(b)(2)
  - Reference product: ANDA 72076 to the RLD (NDA 16636 Narcan® which has been discontinued), 1 mg/mL for IV, IM and SC injection.
  - Narcan® PI: "An initial dose of 0.4 mg to 2 mg of naloxone HCl may be administered intravenously. ....IM or SC administration may be necessary if IV route is not available."
- **Current submission:** Seeking approval of a new 2.0 mg strength NAI or NAI-HD which is designed to deliver an approved dose strength by approved routes of administration via an approved auto-injector
  - (b) (4)
  - Formulation is identical to the 0.4 mg NAI formulation except it is formulated to a drug concentration of 5 mg/mL
  - Device constituent component same for 0.4 mg or 2.0 mg injection (0.4 mL injection of 1 mg/mL or 5 mg/mL)

## Pre-NDA MM (12/23/2014)

Question 15. (b) (4)

(b) (4)

(b) (4) we strongly recommend that you perform a pharmacokinetic (PK) study to better understand the PK profile of your product and to inform labeling and prescribers. (b) (4)

(b) (4)

## Pre-NDA MM (12/23/2014)

*Question 15A. In general, does FDA believe a 2-period, 2-treatment (Evzio 0.4 mg and NAI-HP 2.0 mg), crossover pharmacokinetic (PK) study in 8 to 12 subjects will be sufficient to inform labeling and prescribers and provide the information recommended by FDA pertaining to linearity of the pharmacokinetics over the therapeutic dose range?*

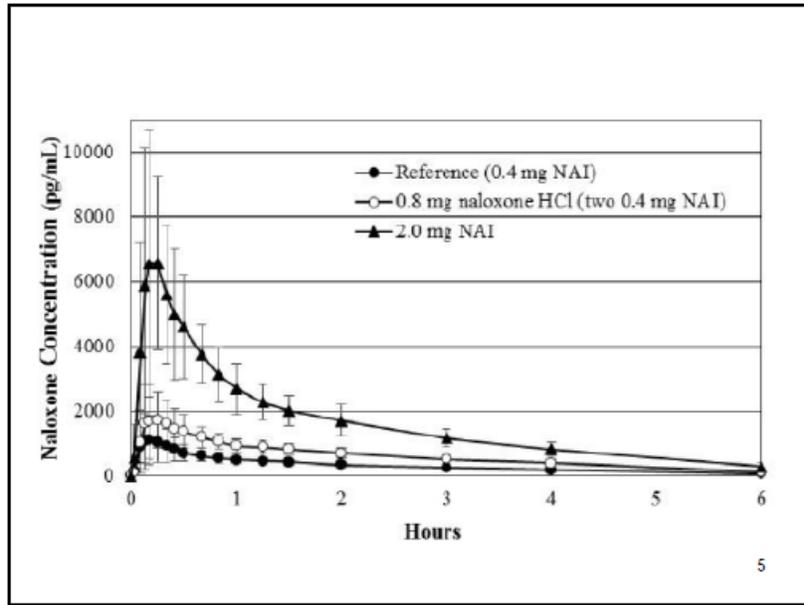
The Agency stated agreement with the Sponsor's proposal and added that the minimum final analyzable sample size is 12 subjects for each treatment group to establish dose proportionality. Furthermore, the Sponsor should include a dose normalized AUC and C<sub>max</sub> to target the 80 - 125 range for the 90% confidence intervals in the dose proportionality linearity analysis. The Agency requested this analysis; however, the Agency is mainly interested in the PK profile for the 2 mg dose and how the product will perform. Dose proportionality outside of the 80 - 125 range will not necessarily preclude approval. The Agency stated that the Sponsor must use the final to-be-marketed product in the PK study.

3

## Dose Proportionality Study KA-900DV-05A

- R, 3-Seq, 3-Per CO Dose Proportionality Study in Healthy Subjects (n = 24) with a washout period of 24 h
  - Treatment A (Reference): IM/SC injection of 0.4 mg naloxone HCl with a single injection using an NAI (EVZIO)
  - Treatment B (Test 1): IM/SC injection of 0.8 mg naloxone HCl using two 0.4 mg NAIs (EVZIO) given 2 minutes apart.
  - Treatment C (Test 2): IM/SC administration of 2.0 mg naloxone HCl with a single injection using a NAI.
  - Injection site: anterolateral aspect of the thigh. IM or SC depending on the tissue layer thickness of the subject
    - Treatment A and C: right thigh
    - Treatment B: left thigh
- PK sampling: pre-dose and 2, 5, 7.5, 10, 15, 20, 25, 30, 40, and 50 min and 1, 1.25, 1.5, 2, 3, 4, and 6 h post-dose

4



Treatment	Scheduled Dose (mg)	n	Descriptive Statistics			Geometric		Median	Min	Max
			Mean	SD	CV	Mean	CV			
0.4 mg NAI	0	24	1.677	1.728	119.0	3.131	36.2	1.960	0	7.17
	0.0393	24	176.0	229.1	129.4	73.21	205.9	51.95	3.47	848
	0.0685	24	375.6	461.1	121.7	136.0	62.3	491.0	166	3640
	0.105	24	1060	876.9	82.7	107.4	86.7	791.0	276	4220
	0.1647	24	1099	759.7	69.9	180.1	76.4	781.0	287	3490
	0.25	24	1028	429.1	41.0	172.4	46.1	841.0	184	2420
	0.3331	24	924.0	509.7	55.0	114.2	52.0	801.0	49	2420
	0.4167	24	896.2	380.1	46.6	78.4	46.4	741.0	147	1890
	0.5	24	490.9	259.7	52.2	152.5	40.9	451.0	243	1210
	0.667	24	590.0	353.1	59.4	180.3	55.0	551.0	300	1030
	0.9331	24	520.0	349.5	66.6	118.0	50.4	521.0	236	1090
	1	24	476.2	224.1	46.0	162.7	22.9	491.0	292	732
	1.25	24	443.2	50.89	20.5	134.2	21.2	451.0	368	634
	1.5	24	406.5	80.95	19.6	100.0	20.4	407.0	266	549
2	24	330.9	73.84	22.2	122.0	22.1	391.0	233	476	
3	24	264.2	76.88	28.9	126.0	32.0	231.0	149	377	
4	24	276.0	61.96	25.1	164.7	26.4	271.0	99.4	324	
6	24	61.97	31.92	51.5	65.09	52.1	51.10	19.9	154	
2.0 mg NAI	0	24	1.342	0.8346	229.7	2.175	10.9	0	0	2.55
	0.0393	24	881.0	1038	116.0	161.4	88.6	168.4	7.25	4760
	0.0685	24	1769	1429	80.0	246	123.5	271.5	450	13100
	0.105	24	1973	4285	72.0	427.1	128.2	508.5	823	14900
	0.1647	24	1947	4129	62.9	614.7	86.8	689.9	1129	14900
	0.25	24	1541	2007	42.0	590.3	46.2	608.5	2440	11300
	0.3331	24	1593	2151	39.2	519.1	49.1	669.0	2289	9500
	0.4167	24	1977	212.0	10.6	462.2	46.0	490.0	2129	3600
	0.5	24	1601	1022	35.3	430.1	31.0	390.0	1020	6911
	0.667	24	1957	306.8	24.1	365.9	23.7	307.0	2493	5550
	0.9331	24	1122	172.2	27.3	302.2	27.6	290.5	1949	4920
	1	24	1081	181.8	28.3	288.1	28.4	280.5	1339	5180
	1.25	24	1259	148.3	24.3	216.9	24.6	220.0	1220	3150
	1.5	24	1083	465.5	53.2	194.9	25.2	197.5	1020	2500
2	24	1694	507.9	36.0	162.7	29.0	170.0	665	3200	
3	24	1141	266.8	23.3	113.9	25.0	113.0	561	1420	
4	24	921.1	201.9	24.9	78.2	24.4	78.2	465	1150	
6	24	271.0	131.1	48.0	249.9	47.0	209.5	124	422	

Treatment	Statistic	C <sub>max</sub> (pg/mL)	T <sub>max</sub> (h)	T <sub>1/2</sub> (h)	AUC <sub>0-t</sub> (pg·h/mL)	AUC <sub>0-inf</sub> (pg·h/mL)
<b>Pharmacokinetic Parameters</b>						
Reference (0.4 mg NAI)*	Mean (SD)	1328 (836)		1.58 (0.457)	1817 (290)	1995 (326)
	%CV	62.9		28.9	16.0	16.3
	Median (Min-Max)	980 (503-4220)	0.25 (0.09-0.84)	1.47 (1.05-2.76)	1864 (1322-2269)	1991 (1427-2688)
Test (0.8 mg naloxone HCl [two 0.4 mg NAIs])*	Mean (SD)	2156 (1021)		1.52 (0.360)	3498 (691)	3776 (720)
	%CV	47.4		23.7	19.8	19.1
	Median (Min-Max)	1855 (913-4160)	0.21 (0.09-0.85)	1.40 (1.11-2.39)	3435 (2334-5186)	3776 (2584-5438)
Test (2.0 mg NAI)	Mean (SD)	7905 (3617)		1.53 (0.382)	9657 (1488)	10330 (1565)
	%CV	45.8		25.0	15.4	15.2
	Median (Min-Max)	6950 (3020-14900)	0.25 (0.13-0.67)	1.47 (0.90-2.31)	9703 (6896-12760)	10410 (7420-13150)
<b>Statistical Assessments of Dose Proportionality</b>						
Dose normalized 2.0 mg / 0.4 mg <sup>†</sup>	GMR	1.24			1.06	1.05
	90% CI for ratio	1.04, 1.49			1.02, 1.11	1.01, 1.09
Dose normalized 0.8 mg / 0.4 mg	GMR	0.85			0.96	0.94
	90% CI for ratio	0.71, 1.02			0.92, 1.00	0.91, 0.98
Power Model (linear regression)	Slope	1.15			1.04	1.03
	95% CI	0.97, 1.33			0.98, 1.11	0.97, 1.09

## Recommendation

- Fileable from clin pharm perspective
  - Datasets for concentrations and PK parameters are included
  - Analytical report and validation report are included
  - NO OSI inspection will be requested because usually OSI inspection is not requested for sNDA. OSI inspection was requested for the original NDA for the PK study between the 0.4 mg auto-injection and 0.4 mg Narcan and the study was acceptable. This sNDA plans to introduce an auto injector with 2 mg dose, and its PK profile looks reasonable compared to the 0.4 mg auto-injector.

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## 3.2 Individual Study Summary

### 2 SYNOPSIS

<b>Name of Sponsor/Company:</b> kaleo, Inc.	<b>Individual Study Table Referring to Part of the Dossier</b>	<b>(For National Authority Use Only)</b>
<b>Name of Finished Product:</b> EVZIO (naloxone HCl injection)		
<b>Name of Active Ingredient:</b> naloxone hydrochloride USP		
	<b>Volume:</b> Not applicable	
	<b>Page:</b> Not applicable	
<b>Title of Study:</b>	A Randomized, Three-Sequence, Three-Period, Pharmacokinetic Bioavailability and Dose Proportionality Study of Naloxone Hydrochloride Administered Using a Naloxone Auto-Injector in Healthy Human Volunteers	
<b>Principal Investigator:</b>	Ronald Goldwater MDCM, MSc(A)	
<b>Study Center:</b>	PAREXEL Early Phase Clinical Unit, Baltimore, USA	
<b>Publication:</b>	None at the time of writing this report	
<b>Development Phase:</b>	Phase 1, comparative bioavailability and safety study	
<b>Studied Period:</b>	First subject enrolled:	26 Aug 2015
	Last subject completed:	13 Sep 2015
<b>Study Objectives:</b>	<p>The primary objectives of the study were:</p> <ul style="list-style-type: none"> <li>To evaluate the dose proportionality of 0.4 mg and 2.0 mg naloxone hydrochloride (HCl) following intramuscular (IM)/subcutaneous (SC) injection using a naloxone auto-injector (NAI).</li> <li>To characterize the pharmacokinetic (PK) profiles of 0.4 mg, 0.8 mg (two 0.4 mg injections) and 2.0 mg naloxone HCl following IM/SC injection using NAIs.</li> </ul> <p>The secondary objective of the study was:</p> <ul style="list-style-type: none"> <li>To assess the safety and tolerability of 0.4 mg, 0.8 mg and 2.0 mg naloxone HCl injection using NAIs.</li> </ul>	
<b>Study Design and Methodology:</b>	<p>This was a randomized, open-label, single-dose, 3-period crossover study in fasted, healthy male and female subjects to evaluate the dose proportionality of 0.4 mg and 2.0 mg naloxone HCl administered using an NAI and characterize the PK profiles of 0.4 mg, 0.8 mg and 2.0 mg naloxone HCl administered using NAIs. Twenty-four adult volunteers were planned to be enrolled and receive study drug. Subjects were randomized to receive the following study treatments in 1 of 6 sequences (ABC, ACB, BCA, BAC, CAB or CBA). Study drug was administered on Day 1, Day 2 and Day 3:</p> <ul style="list-style-type: none"> <li>Treatment A: IM/SC administration of 0.4 mg naloxone HCl with a single injection using an NAI (EVZIO).</li> <li>Treatment B: IM/SC administration of 0.8 mg naloxone HCl using two 0.4 mg NAIs (EVZIO) given 2 minutes apart. The first injection defined time 0 for the purpose of Treatment B PK sampling.</li> <li>Treatment C: IM/SC administration of 2.0 mg naloxone HCl with a single injection using an NAI.</li> </ul> <p>During the Screening Visit (Day -28 to Day -2), subjects signed the informed consent and then completed procedures to determine eligibility. Eligible subjects reported to the clinic on the day before dose administration and remained in the clinic until the final postdose blood sample was collected and all discharge procedures were completed for the third dosing period (Day 3). Subjects were randomly assigned to treatment sequence. There was a washout period between doses of approximately 24 hours. Safety assessments were conducted throughout the study.</p>	

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<b>Name of Active Ingredient:</b> naloxone hydrochloride USP	<b>Page:</b> Not applicable	
<b>Number of Subjects (Planned and Analyzed):</b>		
	<b>Safety Population</b>	<b>Pharmacokinetic Population</b>
Planned	24	24
Randomized	24	24
Evaluable	24	24
<b>Diagnosis and Main Criteria for Inclusion:</b>		
<b>Criteria</b>	<b>Range for Inclusion</b>	
Age	18 to 55 years of age, inclusive	
Weight; Body Mass Index	≥ 50 kg and ≤ 100 kg; 18.5 and 32 kg/m <sup>2</sup> , inclusive	
Sex	Male and female	
Pathology/other criteria	Not applicable, healthy subjects	
<b>Study Drugs:</b>		
<ul style="list-style-type: none"> <li>Reference: Naloxone HCl for injection at a concentration of 1.0 mg/mL (i.e., 0.4 mg/0.4 mL administered using an NAI [sourced from commercial supplies of EVZIO]), Lot Number F0115414AA.</li> <li>Test: Naloxone HCl for injection at a concentration of 5.0 mg/mL (i.e., 2.0 mg/0.4 mL administered using an NAI), Lot Number F0119415BB.</li> </ul>		
<b>Duration of Treatment:</b>		
The duration of study participation for each subject was less than 5 weeks (up to 4 weeks for the screening period and 4 days for in-subject admission to complete the 3 dosing periods [i.e., Treatment A, Treatment B and Treatment C]). Subjects were randomly assigned to receive the study treatments in 1 of 6 sequences (ABC, ACB, BCA, BAC, CAB or CBA).		
<b>Criteria for Evaluation:</b>		
<b>Safety:</b>		
Routine safety monitoring was conducted during the in-house phase of the study. Safety and tolerability were evaluated by:		
<ul style="list-style-type: none"> <li>Vital signs (blood pressure [BP], pulse, respiratory rate and oral body temperature)</li> <li>Twelve-lead electrocardiograms (ECGs)</li> <li>Clinical laboratory testing (hematology, clinical chemistry and urinalysis)</li> <li>Physical examination</li> <li>Adverse event (AE) assessments</li> <li>Injection site evaluation</li> <li>Concomitant medication assessments</li> </ul>		
<b>Pharmacokinetics:</b>		
Blood samples for PK assessment were collected 5 minutes predose and 2, 5, 7.5, 10, 15, 20, 25, 30, 40 and 50 minutes and 1, 1.25, 1.5, 2, 3, 4 and 6 hours postdose for each treatment period (18 time points).		
The following PK parameters were estimated from plasma naloxone concentrations:		
<ul style="list-style-type: none"> <li>Maximum plasma concentration (C<sub>max</sub>)</li> <li>Time to C<sub>max</sub> (T<sub>max</sub>)</li> <li>Terminal elimination half-life (T<sub>1/2</sub>)</li> <li>Elimination rate constant (Lambda z)</li> </ul>		

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<b>Name of Finished Product:</b> EVZIO (naloxone HCl injection)		
<b>Name of Active Ingredient:</b> naloxone hydrochloride USP		
<ul style="list-style-type: none"> <li>• Area under the concentration-time curve from baseline to the last measurable concentration (<math>AUC_{0-t}</math>)</li> <li>• Area under the plasma concentration-time curve from time 0 extrapolated to infinity (<math>AUC_{0-inf}</math>)</li> </ul>		
<b>Statistical Methods:</b>		
<b>Sample Size Estimation:</b>		
<p>Sample size estimates were based on PK data obtained in 30 subjects following administration of 0.4 mg naloxone using an NAI (EVZIO) and a standard syringe. Reference estimates of within subject variability using the NAI and a standard syringe were 12.6% for AUC and 40.9% for <math>C_{max}</math>. Due to the high variability of <math>C_{max}</math>, the within subject variability for AUC provided the basis for the projections of power described below.</p> <p>The sample size estimation was performed based on AUC within subject variability using SAS PROC POWER as a multiplicative equivalence test for mean ratio with lognormal data. Analysis was based on the two 1-sided testing procedure.</p> <p>The power calculations estimated a total sample size of 12 would have over 95% power to reject the null hypotheses. Due to the wide range in the expected variability of naloxone between AUC and <math>C_{max}</math>, the total sample size for this study was selected as 24 subjects total, with replacements to ensure 24 subjects complete all 3 treatment periods.</p>		
<b>Data Presentation/Descriptive Statistics:</b>		
<p>All demographic, safety and PK data are listed and summarized in tabular format by descriptive statistics as appropriate. Pharmacokinetic data are also displayed graphically as appropriate.</p> <p>Pharmacokinetic parameters for naloxone were estimated using noncompartmental analysis. The <math>C_{max}</math> and <math>T_{max}</math> were determined directly from the data, and <math>\lambda_z</math> and <math>T_{1/2}</math> were estimated from a linear regression of the terminal log-linear concentrations versus time. The <math>AUC_{0-t}</math> was calculated using the linear-log trapezoidal method and extrapolated to infinity (<math>AUC_{0-inf}</math>).</p> <p>The natural logarithmic transformation was applied to the PK parameters <math>C_{max}</math>, <math>AUC_{0-t}</math> and <math>AUC_{0-inf}</math>, which were analyzed via a mixed-effects linear model for the 3-period crossover design. Summary statistics based on the model were used to document bioavailability.</p>		
<b>Dose Proportionality:</b>		
<p>For each of the naloxone PK parameters <math>C_{max}</math>, <math>AUC_{0-t}</math> and <math>AUC_{0-inf}</math>, a linear mixed model analysis of variance (ANOVA) was used to test the significance of the effects of sequence, period and treatment. In this analysis, subject nested within sequence was assumed to be a random effect; sequence, period and treatment were modeled as fixed factors.</p> <p>A 90% confidence interval (CI) for each treatment ratio was obtained by taking the anti-logarithm of the 90% CI endpoints for each mean difference. Evidence of dose proportionality was obtained if the 90% CI for the primary comparison (Treatment C versus Treatment A) was contained within the interval (0.8, 1.25).</p> <p>A power model approach was also used for the PK parameters <math>C_{max}</math>, <math>AUC_{0-t}</math> and <math>AUC_{0-inf}</math> to assess for evidence of dose proportionality. In this analysis it was assumed the natural logarithm of the PK variable was linearly related to the natural logarithm of the dose. This model was fit with a simple linear regression to produce an estimate and a 2-sided 95% CI for the slope coefficient. Estimated values of the slope close to 1 were evidence of dose proportionality. All dose levels (0.4 mg, 0.8 mg, and 2.0 mg) were included in this analysis.</p>		

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<b>Name of Active Ingredient:</b> naloxone hydrochloride USP	<b>Page:</b> Not applicable	
<b>Results:</b>		
<b>Pharmacokinetics Results:</b>		
<p>Naloxone plasma concentrations were quantifiable over the 6-hour sampling period postdose for all subjects in all treatment groups. Naloxone concentrations were highest following the single 2.0 mg NAI injection for the entire mean naloxone concentration-time profile. There were no significant concentration outliers observed, and there were no significant sampling time deviations. Seventeen subjects had at least 1 period where the predose naloxone concentration was above the lower limit of quantitation (2.0 pg/mL); in each instance, the concentration represented 1.1% or less of <math>C_{max}</math> for the treatment and the values were not considered significant.</p> <p>The median <math>T_{max}</math> for naloxone for all 3 treatment groups was similar (0.2094 hour to 0.2531 hour). Peak plasma concentrations of naloxone were greatest after administration of a single 2.0 mg NAI injection, with a geometric mean (GM) <math>C_{max}</math> (gCV%) of 7113 pg/mL (50.7%), compared with the GM of two 0.4 mg NAI injections (0.8 mg naloxone HCl) or a single 0.4 mg NAI injection, 1942 pg/mL (49.3%) and 1146 pg/mL (57.2%), respectively.</p> <p>Plasma concentrations declined over the 6-hour sampling period with a similar <math>T_{1/2}</math> across all treatment groups; the GM <math>T_{1/2}</math> (gCV%) values following a single 2.0 mg NAI injection, two 0.4 mg NAI injections (0.8 mg naloxone HCl) and a single 0.4 mg NAI injection were 1.479 hours (25.9%), 1.481 hours (22.3%) and 1.526 hours (26.8%), respectively.</p> <p>Both <math>AUC_{0-t}</math> and <math>AUC_{0-inf}</math> naloxone exposure was greatest following a single 2.0 mg NAI injection, compared with two 0.4 mg NAI injections (0.8 mg naloxone HCl) or a single 0.4 mg NAI injection. For <math>AUC_{0-t}</math>, the GM (gCV%) was 9547 pg.h/mL (15.6%), 3434 pg.h/mL (19.8%) and 1793 pg.h/mL (17.0%) following administration of 2.0 mg, 0.8 mg and 0.4 mg naloxone HCl using NAIs, respectively. Similarly, for <math>AUC_{0-inf}</math>, the geometric mean (gCV%) was 10210 pg.h/mL (15.5%), 3713 pg.h/mL (19.0%) and 1969 pg.h/mL (16.8%) following administration of 2.0 mg, 0.8 mg and 0.4 mg naloxone using NAIs, respectively.</p> <p>Total (AUC) systemic naloxone exposure was dose proportional for the primary comparison of a single 2.0 mg naloxone HCl injection and a single 0.4 mg naloxone HCl injection administered using NAIs. The geometric mean ratio (GMR) (90% CI) was 1.06 (1.02, 1.11) for <math>AUC_{0-t}</math> and 1.05 (1.01, 1.09) for <math>AUC_{0-inf}</math>. Maximum (<math>C_{max}</math>) exposure was slightly greater than dose proportional for the same treatment comparison. The GMR (90% CI) for <math>C_{max}</math>, 1.24 (1.04, 1.49), was within the target interval but the upper 90% confidence bound exceeded the upper target of 1.25.</p>		

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<b>Name of Active Ingredient:</b> naloxone hydrochloride USP	<b>Page:</b> Not applicable								
<b>Statistical Assessment of Dose Proportionality Using Dose-Normalized Pharmacokinetic Parameters for 0.4 and 2.0 mg Naloxone HCl Following Intramuscular/Subcutaneous Injection Using a Naloxone Auto-Injector</b>									
	<b>Treatment A</b>			<b>Treatment C</b>			<b>Treatment C/Treatment A</b>		
<b>Parameter</b>	<b>N</b>	<b>GM</b>	<b>95% CI</b>	<b>N</b>	<b>GM</b>	<b>95% CI</b>	<b>GMR</b>	<b>90% CI</b>	<b>rMSE</b>
$C_{max}$ (pg/mL/mg)	24	2865.4	(2381.39, 3447.80)	24	3556.4	(2955.68, 4279.26)	1.24	(1.04, 1.49)	37.4
$AUC_{0-t}$ (pg.h/mL/mg)	24	4483.3	(4177.97, 4810.91)	24	4773.6	(4448.49, 5122.40)	1.06	(1.02, 1.11)	8.5
$AUC_{0-inf}$ (pg.h/mL/mg)	23	4877.1	(4551.13, 5226.39)	24	5106	(4766.72, 5469.32)	1.05	(1.01, 1.09)	7.8
<p>CI = confidence intervals; GM = geometric mean; GMR = ratio of geometric means; rMSE = square root of the residual error from the model</p> <p>Treatment A = 0.4 mg naloxone (single 0.4 mg injection); Treatment C = 2.0 mg naloxone (single 2.0 mg injection)</p> <p>Pharmacokinetic parameters (<math>AUC_{0-inf}</math>, <math>AUC_{0-t}</math> and <math>C_{max}</math>) for naloxone were natural log-transformed prior to analysis and evaluated separately using a linear mixed effects model with fixed effects terms for sequence, period and treatment. In this analysis, subject nested within sequence is considered a random effect</p> <p>Dose proportionality was also assessed for 0.8 mg naloxone HCl (two 0.4 mg NAI injections, Treatment B) and 0.4 mg naloxone HCl (Treatment A). Total (AUC) systemic naloxone exposure was dose proportional for the comparison of 0.8 mg naloxone HCl and 0.4 mg naloxone HCl administered using NAIs. The GMR (90% CI) was 0.96 (0.92, 1.00) for <math>AUC_{0-t}</math> and 0.94 (0.91, 0.98) for <math>AUC_{0-inf}</math>. Maximum (<math>C_{max}</math>) exposure was slightly less than dose proportional for the same treatment comparison. The GMR (90% CI) for <math>C_{max}</math>, 0.85 (0.71, 0.98), was within the target interval but the lower 90% confidence bound was below the lower target of 0.80.</p> <p>A simple linear regression of the natural logarithm of <math>C_{max}</math> and AUC on the natural logarithm of the dose was also performed to assess the dose proportionality/linearity of the relationship of 0.4 mg, 0.8 mg and 2.0 mg naloxone HCl administered with NAIs. The results indicate that <math>C_{max}</math> and AUC are dose proportional, as the point estimate of the slope was close to 1.0 for each parameter (1.03 for <math>AUC_{0-inf}</math>, 1.04 for <math>AUC_{0-t}</math> and 1.15 for <math>C_{max}</math>). A range of possible values for the slope was provided by a 95% CI estimate, and each range contained 1, indicating dose-proportionality: <math>AUC_{0-inf}</math> = (0.97, 1.09), <math>AUC_{0-t}</math> = (0.98, 1.11) and <math>C_{max}</math> = (0.97, 1.33).</p> <p><b>Safety Results:</b></p> <p>There were no serious adverse events (SAEs), deaths or treatment-emergent AEs (TEAEs) that led to discontinuation from the study. Overall, 10 subjects experienced 15 TEAEs. The most frequently reported TEAE was mild erythema observed in all treatment groups and noted as localized erythema due to pressure markings from the device (10 events reported in 7 subjects). Events of catheter site swelling, injection site bruising, dizziness, headache and contact dermatitis were reported in 1 subject each. All TEAEs were considered mild by the Investigator except for the event of headache that was considered moderate in intensity. The events of erythema, injection site bruising and headache were considered possibly related or related to study drug. All events had an outcome of resolved.</p> <p>With the exception of erythema, no TEAEs occurred in more than 1 subject and no treatment-specific trends in TEAEs were noted between the 3 treatments. The number of subjects experiencing erythema was similar between the treatments given the fact that Treatment B involved 2 injections.</p> <p>There were no clinically significant safety laboratory values, vital signs, ECGs values or physical examinations findings.</p>									

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<b>Name of Active Ingredient:</b> naloxone hydrochloride USP		
<p><b>Volume:</b> Not applicable</p> <p><b>Page:</b> Not applicable</p>		
<p><b>Conclusions:</b></p> <p>This was a randomized, open-label, single-dose, 3-period crossover study in fasted, healthy male and female subjects to evaluate the dose proportionality of 0.4 mg and 2.0 mg naloxone HCl administered using an NAI and characterize the PK profiles of 0.4 mg, 0.8 mg and 2.0 mg naloxone HCl administered using NAIs. Twenty-four subjects were randomized to receive the study drug treatments (Treatment A: 0.4 mg naloxone HCl, Treatment B: 0.8 mg naloxone HCl [two 0.4 mg naloxone HCl injections], and Treatment C: 2.0 mg naloxone HCl) in 1 of 6 sequences (ABC, ACB, BCA, BAC, CAB or CBA). All 24 subjects completed the study per protocol.</p> <p><b>Pharmacokinetics Conclusions:</b></p> <p>The naloxone PK profiles of 0.4 mg, 0.8 mg and 2.0 mg naloxone HCl using NAIs were characterized over a 6-hour sampling period. Administration of a single 2.0 mg naloxone IM/SC injection using an NAI resulted in the greatest plasma concentrations compared with the single 0.4 mg NAI injection or two 0.4 mg NAI injections (0.8 mg naloxone HCl). The median <math>T_{max}</math> values were similar for all treatment groups, ranging from 0.2094 hour to 0.2531 hour. Naloxone plasma concentrations declined with similar <math>T_{1/2}</math> across all treatment groups, ranging from 1.479 hours to 1.526 hours.</p> <p>Dose proportionality was assessed using 2 approaches. The first approach used an ANOVA method, where the dose-normalized treatment ratios between groups for the PK parameters <math>C_{max}</math>, <math>AUC_{0-t}</math> and <math>AUC_{0-inf}</math> were evaluated, and evidence of dose proportionality was obtained if the 90% CI for the comparison was contained within the interval (0.8, 1.25). The primary comparison was between the single 2.0 mg NAI injection and a single 0.4 mg NAI injection. Both <math>AUC_{0-t}</math> and <math>AUC_{0-inf}</math> were dose proportional as the GMR values were near unity and the 90% CIs fell within the interval (0.8, 1.25). The overall variability for both AUC parameters was low (&lt; 20%). The comparison of <math>C_{max}</math> between the single 2.0 mg naloxone HCl injection and a single 0.4 mg naloxone HCl injection suggested that maximum naloxone exposure was slightly greater than dose proportional as the GMR and the lower 90% CI fell within the predefined limits but the upper 90% CI was greater than the upper limit (1.49 compared to 1.25).</p> <p>The 0.8 mg naloxone HCl dose (two 0.4 mg naloxone HCl injections) and a single 0.4 mg NAI injection were also assessed for dose proportionality using the ANOVA method. As observed with the primary comparison, both <math>AUC_{0-t}</math> and <math>AUC_{0-inf}</math> were dose proportional as the GMR values were near unity and the 90% CIs fell within the interval (0.8, 1.25). By contrast, comparison of <math>C_{max}</math> between 0.8 mg naloxone HCl (two 0.4 mg NAI injections) and a single 0.4 mg NAI injection suggested maximum naloxone exposure was slightly less than dose proportional, as the GMR and upper 90% CI limit fell within the predefined limits but the lower 90% CI was less than the lower limit (0.71 compared to 0.8). There was moderate variability (gCV%) averaging approximately 50% for <math>C_{max}</math> across all treatment groups that may have contributed to the slight trend towards disproportional <math>C_{max}</math> exposure assessments. In addition, the current study was powered based on the within subject variability for AUC observed in the previous NAI study (IJ-900DV-030) instead of using the more variable <math>C_{max}</math> data as the basis for the power projections.</p> <p>Linear regression of the natural logarithm of <math>C_{max}</math> and AUC on the natural logarithm of dose was also performed to assess the dose-proportionality/linearity of the relationship. Estimated slope values of the slope near unity are considered evidence of dose proportionality/linearity. All 3 parameters (<math>C_{max}</math>, <math>AUC_{0-t}</math> and <math>AUC_{0-inf}</math>) had point estimates of the slope near 1 (range 1.03 to 1.15), indicating naloxone exposure as a result of 0.4 mg, 0.8 mg and 2.0 mg naloxone HCl administration using NAIs is dose proportional and linear within the range 0.4 mg to 2.0 mg.</p> <p>In summary:</p> <ul style="list-style-type: none"> <li>• Following administration of 0.4 mg, 0.8 mg (two 0.4 mg injections) and 2.0 mg naloxone HCl using NAIs, the <math>T_{max}</math> of naloxone occurred rapidly (median 0.2094 to 0.2531 hour) and was similar for all treatment groups. Plasma concentrations declined similarly in all doses with a <math>T_{1/2}</math> of 1.479 hours to 1.526 hours.</li> <li>• Naloxone exposure was greatest following a single 2.0 mg NAI injection compared with two 0.4 mg NAI injections (0.8 mg naloxone HCl) or a single 0.4 mg NAI injection. For 0.4 mg, 0.8 mg and 2.0 mg naloxone</li> </ul>		

<b>Name of Sponsor/Company:</b> kaleo, Inc.	<b>Individual Study Table Referring to Part of the Dossier</b>	<b>(For National Authority Use Only)</b>
<b>Name of Finished Product:</b> EVZIO (naloxone HCl injection)	<b>Volume:</b> Not applicable	
<b>Name of Active Ingredient:</b> naloxone hydrochloride USP	<b>Page:</b> Not applicable	
<p>HCl administered using NAIs, the GM (gCV%) for AUC<sub>0-t</sub> was 1793 (17.0), 3434 (19.8) and 9547 (15.6) pg.h/mL, respectively and for AUC<sub>0-inf</sub> was 1969 (16.8), 3713 (19.0) and 10210 (15.5), respectively.</p> <ul style="list-style-type: none"> <li>For C<sub>max</sub>, the GM (gCV%) was 1146 (57.2), 1942 (49.3) and 7113 (50.7) pg/mL for 0.4 mg, 0.8 mg and 2.0 mg naloxone HCl administered using NAIs, respectively.</li> <li>AUC<sub>0-t</sub> and AUC<sub>0-inf</sub> were dose proportional for the primary comparison of 2.0 mg naloxone HCl and 0.4 mg naloxone HCl administered using NAIs. Geometric mean ratios and (90% CI) were 1.06 (1.02, 1.11) and 1.05 (1.01, 1.09) for AUC<sub>0-t</sub> and AUC<sub>0-inf</sub>, respectively. Maximum (C<sub>max</sub>) exposure was slightly greater than dose proportional for the same treatment comparison with GMR (90% CI) of 1.24 (1.04, 1.49).</li> <li>AUC<sub>0-t</sub> and AUC<sub>0-inf</sub> were also dose proportional for the comparison of 0.8 mg naloxone HCl (two 0.4 mg naloxone HCl injections) and 0.4 mg naloxone HCl administered using NAIs. Geometric mean ratios and (90% CI) were 0.96 (0.92, 1.00) and 0.94 (0.91, 0.98) for AUC<sub>0-t</sub> and AUC<sub>0-inf</sub>, respectively. Maximum (C<sub>max</sub>) exposure was slightly less than dose proportional for the same treatment comparison with GMR (90% CI) of 0.85 (0.71, 0.98).</li> <li>Linear regression indicates that naloxone exposure is linear within the dose range of 0.4 to 2.0 mg naloxone HCl following IM/SC administration using NAIs.</li> </ul> <p><b>Safety Conclusions:</b></p> <p>No safety concerns were noted in the safety laboratory values, vital signs, ECGs values, injection site evaluations or physical examinations findings during the study. Overall, 10 subjects experienced 15 TEAEs. The most commonly experienced TEAE was mild erythema reported in all treatment groups, in a total of 7 subjects. All TEAEs were considered mild in intensity by the Investigator except for 1 TEAE of moderate intensity (headache). All TEAEs had an outcome of resolved. There were no SAEs or discontinuations associated with study drug.</p> <p><b>Overall Summary:</b></p> <p>Administration of a single 2.0 mg naloxone HCl IM/SC injection using an NAI resulted in the greatest plasma naloxone concentrations compared to 0.8 mg naloxone HCl (two 0.4 mg NAI injections) or a single 0.4 mg naloxone HCl injection (EVZIO). The T<sub>max</sub> and T<sub>1/2</sub> were similar for the administration of 2.0 mg, 0.8 mg (two 0.4 mg NAI injections) and 0.4 mg naloxone HCl using NAIs. Total (AUC) systemic naloxone exposure was dose proportional for the primary comparison of a single 2.0 mg NAI injection and a single 0.4 mg NAI injection. The 2.0 mg NAI injection was slightly greater than dose proportional for the more variable C<sub>max</sub> parameter. All 3 treatments, 0.4 mg, 0.8 mg and 2.0 mg naloxone HCl administered using NAIs, were safe and well tolerated when administered to healthy subjects in this study.</p> <p><b>Date of Report:</b> 29 Jan 2016</p> <p>This study was conducted in compliance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki.</p>		

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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WEI QIU  
09/23/2016

YUN XU  
09/23/2016

# CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

<b>Office of Clinical Pharmacology</b>				
<i>New Drug Application Filing and Review Form</i>				
<i>General Information About the Submission</i>				
	Information			Information
NDA/BLA Number	205-787 S007	Proposed Brand Name	EVZIO Naloxone Auto-Injector (NAI) HD 2.0 mg	
OCP Division (I, II, III, IV, V)	II	Generic Name	Naloxone HCl injection, USP	
Medical Division	DAAAP	Drug Class	Opioid Antagonist	
OCP Reviewer	Wei Qiu, Ph.D.	Indication(s)		(b) (4)
OCP Team Leader	Yun Xu, Ph.D.	Dosage Form, Strength	Solution for injection, 2.0 mg (0.4 mL of 5 mg/mL)	
Pharmacometrics Reviewer	N/A	Dosing Regimen	Opioid antagonist	
Date of Submission	April 19, 2016	Route of Administration	IM or SC injection	
Primary Review Goal Date (GRMP)	Sept 25, 2016	Sponsor	Kaleo Inc	
		Priority Classification	Priority	
PDUFA Due Date	October 19, 2016	Relevant INDs	IND 112292	
<i>Clin. Pharm. and Biopharm. Information</i>				
	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<b>Healthy Volunteers-</b>				
single dose:	x	1		Dose proportionality study KA-900DV-05A
multiple dose:				
<b>Patients-</b>				
single dose:				
multiple dose:				
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				

## CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

<b>PD -</b>				
Phase 1:				
Phase 2:				
Phase 3:				
<b>PK/PD -</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability</b>				
<b>Relative bioavailability -</b>				
solution as reference:	x	(1)		See above
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
<b>Food-drug interaction studies</b>				
<b>Bio-waiver request based on BCS</b>				
<b>BCS class</b>				
<b>Dissolution study to evaluate alcohol induced dose-dumping</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>		1		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			√	(b) (4) to-be-marketed product was used in the dose proportionality study
2	Has the applicant provided metabolism and drug-drug interaction information?			√	No new findings in the proposed label.
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	√			(b) (4) dose proportionality study was conducted to compare the proposed product (2 mg) and the approved product (0.4 mg).
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	√			
5	Has a rationale for dose selection been submitted?			√	Match the exposure of the list drug
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	√			

## CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	√			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	√			
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	√			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			√	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?	√			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			√	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			√	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			√	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			√	Submitted agreed initial pediatric study plan
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			√	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	√			
<b>General</b>					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	√			
19	Was the translation (of study reports or			√	

# CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

other study information) from another language needed and provided in this submission?				
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**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?**

YES

**This NDA is fileable from clinical pharmacology perspective.**

**No OSI inspection needs to be requested because usually OSI inspection is not requested for supplemental NDA. OSI inspection on the pivotal comparative BA study IJ-900DV-030 comparing 0.4 mg auto-injection and 0.4 mg injection of Narcan included in the original NDA was acceptable. This sNDA introduces an auto injector with 2 mg dose and its PK profile looks reasonable compared to the already approved 0.4 mg auto injector.**

If the NDA/BLA is not fileable from the clinical pharmacology 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.

**There are no comments for sponsor at this time.**

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Reviewing Clinical Pharmacologist

Date

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Team Leader/Supervisor

Date

## **Background:**

Kaleo Inc submitted a NDA 205787 S007 to seek approval of a new 2.0 mg strength of Naloxone Auto Injection (NAI) for IM or SC administration. The formulation is identical to the approval 0.4 mg NAI formulation except it is formulated to a higher drug concentration of 5 mg/mL. The proposed indication is the same as the approved one. It is for the management of serious opioid-related toxicity or acute opioid overdose, including the complete or partial reversal of respiratory depression, in persons who may be intentionally or accidentally exposed to natural or synthetic opioids and certain opioid-antagonist analgesics. It is also indicated for diagnosis of suspected serious opioid toxicity or acute opioid overdose.

Sponsor (b) (4) conducted a dose proportionality study (KA-900DV-05A) comparing the proposed 2.0 mg auto injection and the approved 0.4 mg auto injection.

Study KA-900DV-05A is randomized, single-dose, three-sequence, three-period crossover dose proportionality study in healthy subjects. In this study, Dose normalized C<sub>max</sub> for the test (2.0 mg NAI) was 24% greater than the reference (0.4 mg NAI), while dose normalized AUC values were equivalent.

Please find the filing slides for more details.

# CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

## NDA 205-787 S007: EVZIO (Naloxone Hydrochloride Injection)

- **Sponsor:** Kaleo Inc.
- Naloxone Auto Injector (NAI) delivering 0.4 mg naloxone HCl (naloxone HCl concentration of 1 mg/mL) via SC or IM injection was approved on April 3, 2014 under 505(b)(2)
  - Reference product: ANDA 72076 to the RLD (NDA 16636 Narcan® which has been discontinued), 1 mg/mL for IV, IM and SC injection.
  - Narcan® PI: "An initial dose of 0.4 mg to 2 mg of naloxone HCl may be administered intravenously. ....IM or SC administration may be necessary if IV route is not available."
- **Current submission:** Seeking approval of a new 2.0 mg strength NAI or NAI-HD which is designed to deliver an approved dose strength by approved routes of administration via an approved auto-injector
  - (b) (4)
  - Formulation is identical to the 0.4 mg NAI formulation except it is formulated to a drug concentration of 5 mg/mL
  - Device constituent component same for 0.4 mg or 2.0 mg injection (0.4 mL injection of 1 mg/mL or 5 mg/mL)

## Pre-NDA MM (12/23/2014)

Question 15.

(b) (4)

(b) (4)

(b) (4) we strongly recommend that you perform a pharmacokinetic (PK) study to better understand the PK profile of your product and to inform labeling and prescribers.

(b) (4)

(b) (4)

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# CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

## Pre-NDA MM (12/23/2014)

*Question 15A. In general, does FDA believe a 2-period, 2-treatment (Evzio 0.4 mg and NAI-HP 2.0 mg), crossover pharmacokinetic (PK) study in 8 to 12 subjects will be sufficient to inform labeling and prescribers and provide the information recommended by FDA pertaining to linearity of the pharmacokinetics over the therapeutic dose range?*

The Agency stated agreement with the Sponsor's proposal and added that the minimum final analyzable sample size is 12 subjects for each treatment group to establish dose proportionality. Furthermore, the Sponsor should include a dose normalized AUC and  $C_{max}$  to target the 80 - 125 range for the 90% confidence intervals in the dose proportionality linearity analysis. The Agency requested this analysis; however, the Agency is mainly interested in the PK profile for the 2 mg dose and how the product will perform. Dose proportionality outside of the 80 - 125 range will not necessarily preclude approval. The Agency stated that the Sponsor must use the final to-be-marketed product in the PK study.

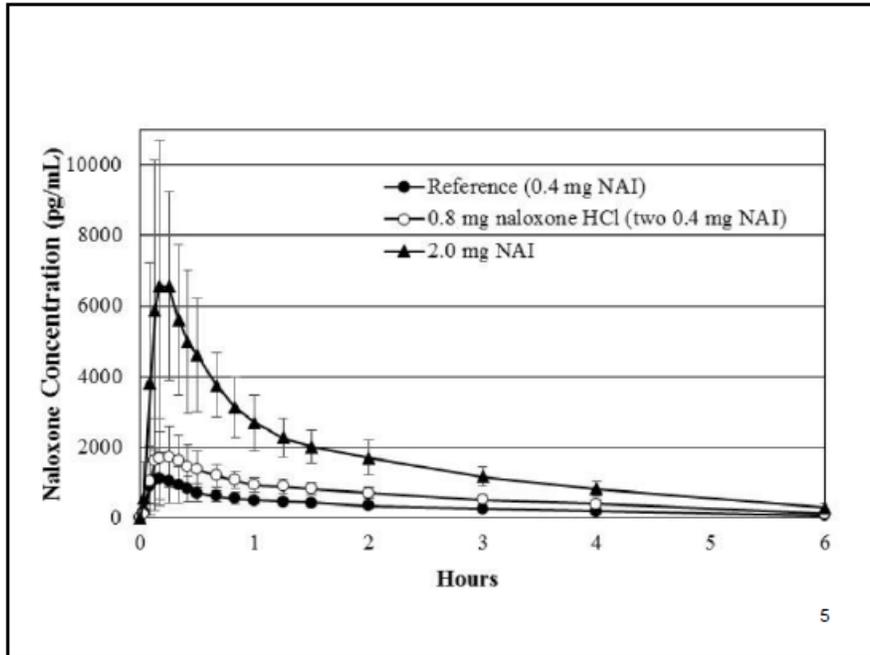
3

## Dose Proportionality Study KA-900DV-05A

- R, 3-Seq, 3-Per CO Dose Proportionality Study in Healthy Subjects (n = 24) with a washout period of 24 h
  - Treatment A (Reference): IM/SC injection of 0.4 mg naloxone HCl with a single injection using an NAI (EVZIO)
  - Treatment B (Test 1): IM/SC injection of 0.8 mg naloxone HCl using two 0.4 mg NAIs (EVZIO) given 2 minutes apart.
  - Treatment C (Test 2): IM/SC administration of 2.0 mg naloxone HCl with a single injection using a NAI.
  - Injection site: anterolateral aspect of the thigh. IM or SC depending on the tissue layer thickness of the subject
    - Treatment A and C: right thigh
    - Treatment B: left thigh
- PK sampling: pre-dose and 2, 5, 7.5, 10, 15, 20, 25, 30, 40, and 50 min and 1, 1.25, 1.5, 2, 3, 4, and 6 h post-dose

4

# CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST



Treatment	Scheduled Blood Draw Time (h)	n	Mean	SD	NCV	Geometric Mean	Geometric CV%	Median	Min	Max
0.4 mg NAI	0	24	1,670	1,998	119.0	3,131	36.2	1,960	0	7,37
	0.0833	24	136.2	229.1	129.4	73.21	293.5	50.95	3.47	865
	0.0833	24	872.3	801.3	91.7	439.2	92.3	491.0	145	2490
	0.125	24	1060	876.0	82.7	807.6	86.7	798.0	275	4220
	0.1667	24	1088	759.7	69.9	880.1	74.4	781.0	287	3490
	0.25	24	1031	629.2	61.0	872.6	64.5	866.0	356	2430
	0.25	24	926.0	599.0	65.0	914.2	59.9	895.0	409	2490
	0.4167	24	899.2	340.4	34.6	786.4	46.4	745.0	347	1690
	0.5	24	490.9	259.9	37.2	452.5	40.3	453.5	243	1210
	0.6667	24	590.6	169.1	26.4	591.3	25.9	592.0	309	1090
	0.9233	24	530.2	144.5	30.6	516.0	30.4	527.5	236	1040
	1	24	476.3	114.6	24.0	463.7	23.9	480.0	292	701
	1.25	24	463.2	90.99	20.5	434.2	21.2	453.5	249	634
1.5	24	400.5	80.05	19.6	400.8	20.4	407.5	264	589	
2	24	330.3	73.34	22.2	322.0	22.1	309.0	235	476	
3	24	246.2	75.88	30.8	238.0	32.9	235.5	149	377	
4	24	274.0	41.06	25.1	164.7	74.4	170.0	99.4	324	
6	24	61.07	31.60	51.5	55.09	52.1	54.10	19.9	141	
2.0 mg NAI	0	24	9,3642	0,9364	229.7	2,235	10.9	0	0	2,155
	0.0833	24	351.9	3038	108.0	165.4	304.3	164.5	7.24	4760
	0.0833	24	3971	3423	90.0	2561	121.5	2715	459	13100
	0.125	24	5878	4205	72.9	4274	108.2	5085	823	14900
	0.1667	24	6567	4139	62.9	5167	88.5	6150	1129	14600
	0.25	24	6541	2407	42.0	5993	48.2	6085	2460	11300
	0.25	24	5619	2141	38.2	5154	47.3	5500	2250	9500
	0.4167	24	4577	2023	46.4	4622	46.4	4460	2119	9460
	0.5	24	4601	1022	35.3	4301	31.3	3500	3023	6910
	0.6667	24	3757	966.8	24.1	3658	23.7	3870	2459	5550
	0.8333	24	3122	872.2	27.5	3012	27.6	2905	1540	4920
	1	24	2681	751.8	28.5	2581	28.4	2500	1530	5150
	1.25	24	2558	549.3	24.3	2189	24.6	2230	1020	3130
1.5	24	2003	465.5	23.2	1940	25.2	1975	1020	2960	
2	24	1694	507.9	30.0	1427	28.8	1700	865	3250	
3	24	1161	246.8	23.0	1130	25.0	1130	561	1620	
4	24	818.1	201.9	24.7	793.2	24.4	782.0	465	1190	
6	24	277.0	135.1	48.8	249.9	47.8	204.5	124	422	

# CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

Treatment	Statistic	C <sub>max</sub> (pg/mL)	T <sub>max</sub> (h)	T <sub>1/2</sub> (h)	AUC <sub>0-4</sub> (pg.h/mL)	AUC <sub>0-inf</sub> (pg.h/mL)
<b>Pharmacokinetic Parameters</b>						
Reference (0.4 mg NAD)*	Mean (SD)	1328 (836)		1.58 (0.457)	1817 (290)	1995 (326)
	%CV	62.9		28.9	16.0	16.3
	Median (Min-Max)	980 (503-4220)	0.25 (0.09-0.84)	1.47 (1.05-2.76)	1864 (1322-2269)	1991 (1427-2688)
Test (0.8 mg naloxone HCl [two 0.4 mg NADs])*	Mean (SD)	2156 (1021)		1.52 (0.360)	3498 (691)	3776 (720)
	%CV	47.4		23.7	19.8	19.1
	Median (Min-Max)	1855 (913-4160)	0.21 (0.09-0.85)	1.40 (1.11-2.39)	3435 (2334-5186)	3776 (2584-5438)
Test (2.0 mg NAD)	Mean (SD)	7905 (3617)		1.53 (0.382)	9657 (1488)	10330 (1565)
	%CV	45.8		25.0	15.4	15.2
	Median (Min-Max)	6950 (3020-14900)	0.25 (0.13-0.67)	1.47 (0.90-2.31)	9703 (6896-12760)	10410 (7420-13150)
<b>Statistical Assessments of Dose Proportionality</b>						
Dose normalized 2.0 mg / 0.4 mg <sup>†</sup>	GMR	1.24			1.06	1.05
	90% CI for ratio	1.04, 1.49			1.02, 1.11	1.01, 1.09
Dose normalized 0.8 mg / 0.4 mg	GMR	0.85			0.96	0.94
	90% CI for ratio	0.71, 1.02			0.92, 1.00	0.91, 0.98
Power Model (linear regression)	Slope	1.15			1.04	1.03
	95% CI	0.97, 1.33			0.98, 1.11	0.97, 1.09

## Recommendation

- Fileable from clin pharm perspective
  - Datasets for concentrations and PK parameters are included
  - Analytical report and validation report are included
  - NO OSI inspection will be requested because usually OSI inspection is not requested for sNDA. OSI inspection was requested for the original NDA for the PK study between the 0.4 mg auto-injection and 0.4 mg Narcan and the study was acceptable. This sNDA plans to introduce an auto injector with 2 mg dose, and its PK profile looks reasonable compared to the 0.4 mg auto-injector.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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WEI QIU  
06/02/2016

YUN XU  
06/02/2016