CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208411Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Addendum to the Primary Clinical Pharmacology Review Dated October 22, 2015

NDA: 208411	Submission Date(s): July 20, 2015
Proposed Brand Name	NARCAN
Generic Name	Naloxone HCl Nasal Spray
Reviewer	Suresh B Naraharisetti, Ph.D.
Team Leader	Yun Xu, Ph.D.
OCP Division	DCPII
OND division	DAAAP
Sponsor	Adapt Pharma
Relevant IND(s)	IND 114704
Submission Type	Original Submission; 505(b)(2)
Formulation; Strength(s)	Solution for Nasal Spray; 40 mg/ mL
Indication	NARCAN nasal spray 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.

This addendum to Primary Clinical Pharmacology review (documented in DARRTS on 10/22/2015) is to address the recommendations made by Office of Study Integrity and Surveillance (OSIS) on the audited pivotal relative bioavailability study, Naloxone-Ph1a-002. At the time of signing-off the primary Clinical Pharmacology review for NDA 208411, OSIS inspection-report for study Naloxone-Ph1a-002 was pending. Subsequently, OSIS finalized their report on October 30, 2015 (see review by Dr. Dasgupta, Arindam, Ph.D. dated 10/30/2015 for details). Overall, the OSIS inspection-report concluded that there were no objectionable conditions observed related to the study Naloxone-Ph1a-002.

For study Naloxone-Ph1a-002, the clinical site where the study was conducted was at Vince Associates Clinical Research, KS 66212, USA; and the bio-analytical facility where the pharmacokinetic samples were analyzed was at (b) (4) , The OSIS inspection-report covered both the observations of Office of Regulatory Affairs (ORA) investigator's findings for clinical site and also the bioanalytical facility inspection.

The ORA investigator had the following two observations related to study Naloxone-Ph1a-002 identified at the clinical site, where a Form FDA 483 was issued to Vince & Associates Clinical Research. The two observations in the Form 483 were:

a) Late to transfer the collected PK samples to -20 °C freezer within 60 minutes of collection (Observation 1B, OSIS Inspection report)
b) Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation (Observation 2A OSIS Inspection report)

The OSIS investigator requested more data to address the two observations mentioned in the Form 483. After reviewing the additional data, it was concluded in the final OSIS report that these two observations are unlikely to impact integrity or outcome of study Naloxone-Ph1a-002. This addendum review focuses on the details of these two observations, and whether the findings impact the study Naloxone-Ph1a-002 data. The details are as follows.

a) Late to transfer the collected PK samples to -20 °C freezer within 60 minutes of collection (Observation 1B, OSIS Inspection report)

At the clinical site, the collected PK samples were not transferred to the -20 °C freezer within 60 minutes after the collection. To address this issue, the OSIS inspectors during their inspection at the bioanalytical facility requested the (b) (4) to design and conduct a benchtop stability study of Naloxone in human whole blood up to 60 minutes at both room temperature and 4 °C.

The detailed description of this aspect (Observation 1B) and the conclusion of the conducted naloxone bench top stability experiment, copied from the OSIS inspection report are as below.

OSIS Evaluation:

The firm failed to transfer a substantial number of PK samples to the -20°C freezer within 60 minutes of sample collection as specified in the study protocol. Additionally, the source data did not document the storage condition (e.g. on ice or at room temperature) of the collected blood samples before they were centrifuged. Although bench top stability was validated for 26 hours during method validation study for naloxone, this data was generated from frozen plasma samples. Stability in fresh plasma or in whole blood for naloxone was not established during method validation.

To assess the integrity of the "Late to Freezer (LTF)" samples, the analytical site for this study, (b) (4) was requested to design and conduct a benchtop stability study of Naloxone in human whole blood up to 60 minutes at both room temperature and 4°C. The plasma was to be transferred to the -20°C freezer after 30 minutes storage in refrigerator. The storage conditions in this experiment would mimic the sample handling procedure at the clinical site and would represent the worst-case scenario for these "Late to Freezer (LTF)" samples.

The results of this study were made available to the FDA investigators during the inspection and revealed that naloxone was

Reviewer Conclusions on Observation 1B:
Based on the conducted naloxone bench top stability experiment and the obtained results, we agree with OSIS conclusion that, Observation 1B is unlikely to impact the integrity of the naloxone concentration data."

b) Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation (Observation 2A OSIS Inspection report)

At the clinical site, discrepancies were observed between the reported protocol deviations and the source documents. Specifically, the protocol deviations submitted to the Agency do not accurately represent the information from the PK Specimen Processing Log.

The detailed description of Observation 2A copied from the OSIS inspection report is as below.

OSIS Evaluation:
Discrepancies were observed between the reported protocol deviations and the source documents. Specifically, the protocol deviations submitted to the Agency (**Please refer to submission**) do not accurately represent the information from the PK Specimen Processing Log (**Attachment 4**).
We compared the data submitted to the Agency in the ADPC Study dataset to the data obtained from the source documents to verify the accuracy of the reported actual dosing and sampling times in the dataset. After comparing the actual dosing times, we conclude that the dosing times were accurately reported for all subjects. When we compared the sampling times for 2.5, 5, 10, 15, 20, 30 and 60 min post-dose for all treatments, we found discrepancies in the sampling times for three subjects (see table below). We request the OCP reviewer to include the actual sampling times in their pharmacokinetic analysis. This observation is unlikely to impact the outcome of the study because all the data except the examples below were accurately reported in the ADPC Study dataset.

Subject	Actual time reported	Actual time from source Data	Time Point	Dose	Period
NALOXONE-PH1A-002-VACR-02031	9:43AM	9:44AM	5 min	0.4mg	3
NALOXONE-PH1A-002-VACR-02033	9:44AM	9:49AM	5 min	2 mg	3
NALOXONE-PH1A-002-VACR-02045	10:57AM	10:55AM	60 min	2 mg	3

Reviewer Conclusions on Observation 2A:
In study Naloxone-Ph1a-002, at total of 29 subjects completed the study in an open-label, randomized, 5-period, 5-treatment, 5-sequence, crossover design. Each participant received following 5 naloxone treatments during the 5 dosing periods:

- Treatment A: 2 mg IN (one 0.1 mL spray of a 20 mg/mL solution in one nostril)
- Treatment B: 4 mg IN (one 0.1 mL spray of a 20 mg/mL solution in each nostril)

- Treatment C: 4 mg IN (one 0.1 mL spray of a 40 mg/mL solution in one nostril)
- Treatment D: 8 mg IN (one 0.1 mL spray of a 40 mg/mL solution in each nostril) and
- Treatment E: 0.4 mg IM (1 mL of a 0.4 mg/mL commercial formulation, as reference)

In this study, two strengths of naloxone nasal spray, 20 mg/mL and 40 mg/mL were used. However, sponsor plans to market only 40 mg/mL strength (4 mg in 0.1 mL). Hence the clinical pharmacology review for study Naloxone-Ph1a-002 focused only on the 40 mg/mL strength and the reference IM injection treatments (Treatments C, D and E).

As per OSIS review with regards to the deviations in actual sampling times, there is one deviation in one time point for each of the three different subjects, #2031, #2033 and #2045 in period 3.

Out of these three deviations, two deviations, in subject #2033 and subject #2045 were from 20 mg/strength (2 mg dose, Treatment A), which the sponsor is not planning to market. Hence these two deviations need not to be considered.

Subject # 2031 had a one-minute deviation at the 5 minute time point, which is from the reference treatment group of IM injection. A total of 29 subjects completed the study, and 16 samples per subject were taken for each treatment up to 720 minutes post dose. Therefore, this one minute deviation at 5 minute time point in one subject, would not affect the calculated PK parameters and conclusion for the study.

Conclusions:

Overall, the conclusions made in the primary clinical pharmacology review dated October 22, 2015, will remain the same.

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/s/

SURESH B NARAHARISETTI
11/02/2015

YUN XU
11/02/2015

CLINICAL PHARMACOLOGY REVIEW

NDA: 208411	Submission Date(s): July 20, 2015
Proposed Brand Name	NARCAN
Generic Name	Naloxone HCl Nasal Spray
Reviewer	Suresh B Naraharisetti, Ph.D.
Team Leader	Yun Xu, Ph.D.
OCP Division	DCPII
OND division	DAAAP
Sponsor	Adapt Pharma
Relevant IND(s)	IND 114704
Submission Type	Original Submission; 505(b)(2)
Formulation; Strength(s)	Solution for Nasal Spray; 40 mg/ mL
Indication	NARCAN nasal spray 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.

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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 NDA 208411 submitted on July 20, 2015 and found it acceptable from clinical pharmacology perspective, pending the Office of Scientific Investigation (OSI) inspection result. While finalizing this review, the OSI inspection report for pivotal comparative bioavailability study Naloxone-Ph1a-002 is still pending. An addendum will be added to the clinical pharmacology review based on the OSI inspection report, if necessary.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology Findings

Key clinical pharmacology findings:

The clinical/clinical pharmacology database for this NDA consists of one pivotal comparative bioavailability study (Naloxone-Ph1a-002) conducted in 29 healthy volunteers. In this study (Naloxone-Ph1a-002), the relative bioavailability from one IN[1] spray in one nostril (4 mg, 0.1 mL of 40 mg/mL) and one IN spray in each nostril (8 mg, 0.1 mL of 40 mg/mL in each nostril) was compared to the reference 0.4 mg of naloxone IM[2] injection. The final to be marketed product was used in the study.

The NARCAN (naloxone hydrochloride) nasal spray exhibited 5.5 -fold higher Cmax and 4.7 -fold higher AUCt from one IN spray in one nostril (4 mg total dose, 0.1 mL of 40 mg/mL naloxone hydrochloride solution), and 11 -fold higher Cmax and 8.9 -fold higher AUCt from one IN spray in each nostril (8 mg total dose, 0.1 mL of 40 mg/mL naloxone hydrochloride solution) compared to the reference, a single dose of 0.4 mg naloxone IM injection.

After 0.4 mg of naloxone HCl IM injection, a Cmax of 880 pg/mL was observed at Tmax of ~23 minutes (n= 29 subjects). With IN NARCAN spray, the concentrations greater than 880 pg/mL were maintained for longer duration, up to 120 minutes from one IN spray in one nostril and up to 180 minutes from one IN spray in each nostril.

Relative Bioavailability of NARCAN (naloxone hydrochloride) Nasal Spray in Comparison to the Reference Product:

The one NARCAN nasal spray in one nostril or one NARCAN spray in each nostril exhibited much higher systemic exposure of naloxone in terms of both AUC and Cmax values in comparison to the reference drug product, 0.4 mg naloxone IM injection **(Figure 1.3).** The administration of one NARCAN nasal spray (4 mg total dose, 0.1 mL of 40 mg/mL naloxone hydrochloride solution) in one nostril exhibited 555%, 469% and 462% higher geometric mean ratios (IN/IM) for Cmax, AUCt and AUCinf, respectively compared to the reference 0.4 mg IM injection. The corresponding 90% CIs for geometric mean ratios for one IN spray in comparison to IM treatment were 464-665%, 418-527% and 412-519%, for Cmax, AUCt and AUCinf, respectively **(Table 1.3a).** The administration of one NARCAN nasal spray in each nostril (8 mg total dose, 0.1 mL of 40 mg/mL naloxone hydrochloride solution) exhibited 1110%, 890% and 878% higher geometric mean ratios (IN/IM) for Cmax, AUCt and AUCinf, respectively compared to the reference 0.4 mg IM injection. The

[1] IN- Intranasal

[2] IM- Intramuscular

corresponding 90% CIs for geometric mean ratios for one IN spray in each nostril in comparison to IM treatment were 925-1320%, 793-999% and 783-985%, for Cmax, AUCt and AUCinf, respectively **(Table 1.3a)**.

Figure 1.3 Mean plasma concentration time profiles of naloxone from 0 to 4 hours following intranasal and intramuscular naloxone administration to healthy subjects (N = 29)

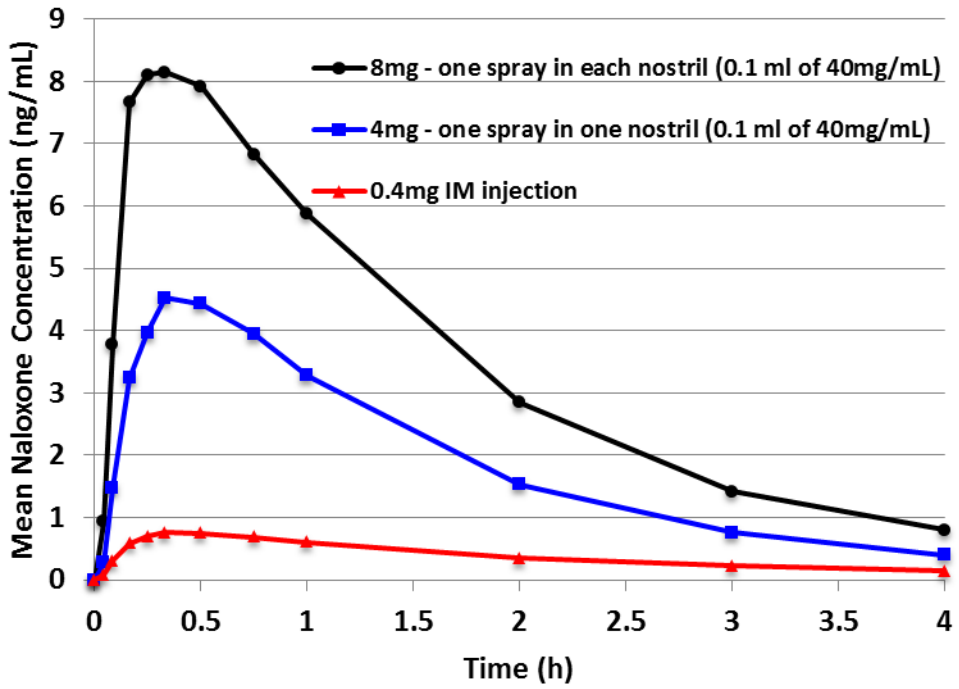


Table: 1.3a. Geometric mean ratios and 90% CIs for plasma naloxone pharmacokinetic parameters following intranasal and intramuscular administration.

Parameter	**Test Vs Reference**	**Adjusted Geometric LS mean**		**Ratio %[Test/Reference] (lower , upper 90% CI of ratio)**
		Test (n=29)	**Reference (n=29)**	
Cmax (ng/mL)	4 mg -one IN Spray in one nostril (Test)	4.83	0.870	555 (464, 665)
AUC0-t (h*ng/mL)	Vs	7.90	1.68	469 (418, 527)
AUC0-inf (h*ng/mL)	0.4 mg IM (Reference)	7.99	1.73	462 (412, 519)
Cmax (ng/mL)	8 mg -one IN Spray in each nostril (Test)	9.62	0.870	1110 (925, 1320)
AUC0-t (h*ng/mL)	Vs	15.0	1.68	890 (793, 999)
AUC0-inf (h*ng/mL)	0.4 mg IM (Reference)	15.2	1.73	878 (783, 985)

Since the concentrations of naloxone at early time points after the administration of naloxone products for reversal of opioid overdose is critical, the mean concentrations of naloxone from plasma concentration-time profile after administration of NARCAN (naloxone hydrochloride) nasal spray

and reference IM injection were compared (Table 1.3b). Compared to the reference IM injection, the naloxone concentrations were higher in the range of 3.5 to 6.0 fold after one IN spray in one nostril, and 9.7 to 13.3 fold after one IN spray in each nostril, respectively, from 2.5 minutes to 60 minutes post dose.

Table 1.3b. Comparison of mean naloxone concentrations between IM injection and NARCAN one spray in one nostril or one spray in each nostril from 2.5 to 60 minutes post dose.

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

The median naloxone Tmax after IN administration was not significantly different compared to the IM administration. The median naloxone Tmax after single NARCAN nasal spray (4 mg) in one nostril and one NARCAN nasal spray in each nostril (8 mg) was 0.50 h (range, 0.17 to 1.00 h) and 0.33 h (range, 0.17 to 1.00 h), respectively. The median naloxone Tmax after IM injection was 0.38h and has relatively high variability with the range of 0.08 to 2.05h compared to the IN route. The IN route has slightly longer half-life of 2.1 h compared to 1.2 h for IM route.

2 Question Based Review

2.1 General Attributes of the Drug

2.1.1. *What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of this drug product?*

Naloxone HCl is approved for intravenous (IV), intramuscular (IM), and subcutaneous (SC) administration. According to Narcan's labeling, Narcan may be administered intravenously, intramuscularly, or subcutaneously. In adults with opioid overdose, an initial dose of 0.4 mg to 2 mg of Narcan may be administered intravenously. Intramuscular or subcutaneous administration may be necessary if the intravenous route is not available.

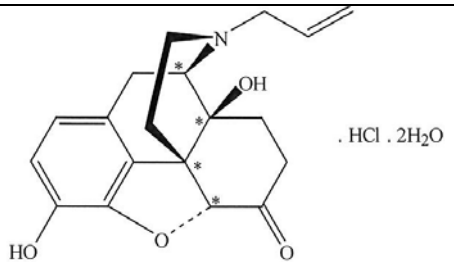
The proposed naloxone hydrochloride nasal spray is an aqueous solution presented in a Type I glass vial closed with a (b) (4) plunger which in turn is mounted into a unit-dose nasal spray device. The device is a non-pressurized dispenser delivering a spray containing a unit dose of the active ingredient. Each delivered dose contains 100 µL.

Adapt Pharma submitted a 505(b)(2) NDA for NARCAN (naloxone hydrochloride) Nasal Spray and proposed to rely on the Agency's previous finding of the safety and efficacy of the listed drug, Narcan (NDA 016636). As indicated in the Agency's comments to regulatory Question #6 at the Pre-IND meeting, for a 505(b)(2) application, the listed drug relied upon for approval must be a product approved under section 505(b) (NDA) of the Food, Drug, and Cosmetic Act. When an ANDA product must be used for a bio-bridging study because the NDA product is no longer available in the market, the Sponsor must identify an NDA product as the listed drug and do a patent certification against that NDA product. Because the NDA product Narcan is not available, in the pivotal comparative bioavailability study Naloxone-Ph1a-002, sponsor used an ANDA product to Narcan NDA (016636), sourced from a commercial supplier and is manufactured by (b) (4) to establish the PK bridge. This approach was deemed acceptable per the Agency's Pre-IND meeting minutes dated May 18, 2012.

After the NDA is submitted, the Sponsor acquired NDA 016636. However, this NDA remains as a 505(b)(2) application since Sponsor still relies on literature data for pediatric assessment to support pediatric labeling. Considering this product is life-saving and will only be used during opioid overdose, no additional clinical pharmacology studies will be required.

2.1.2 *What are the highlights of the chemistry and physico-chemical properties of the drug substances, and the formulation of the drug product?*

Table 2.1.2a Physical-Chemical Properties of Naloxone Hydrochloride

Drug Name	Naloxone Hydrochloride
Chemical Name	17-Allyl-4,5a-epoxy-3,14-dihydroxymorphinan-6 hydrochloride
Structure	 . HCl . $2H_2O$ $C_{19}H_{21}NO_4 \bullet HCl \bullet 2H_2O$
Molecular Weight	(b) (4)
Appearance	White to off-white powder
Solubility	Soluble in water, in dilute acids, and in strong alkali; slightly soluble in alcohol, and practically insoluble in ether and in chloroform

The components and compositions of NARCAN (naloxone hydrochloride) Nasal Spray formulation are listed in **Table 2.1.2b**. The NARCAN (naloxone hydrochloride) nasal spray is an aqueous solution (40 mg/mL) presented in a Type I glass vial closed with a (b) (4) plunger which in turn is mounted into a unit-dose nasal spray device. The device is a non-pressurized dispenser

delivering a spray containing a unit dose of the active ingredient. Each delivered dose contains 100 µL.

Table 2.1.2b Components and Composition of NARCAN (naloxone hydrochloride) Nasal Spray

Component	Grade	Concentration 40 mg/mL	
		Quantity per mL	Quantity per unit dose (100 µL)
Naloxone HCl dihydrate (corresponding to naloxone HCl)	USP/Ph. Eur	44.0 mg (40.0 mg)	4.4 mg (4.0 mg)
Benzalkonium chloride (b) (4)	Ph. Eur/USP/NF	(b) (4)	
Disodium edetate	USP		
Sodium chloride	MULTI-COMPENDIAL; USP, BP, Ph. Eur, JP		
Hydrochloric acid	Ph. Eur/USP		
(b) (4)			

2.1.3. What are the proposed mechanism(s) of action and therapeutic indication(s)?

While the mechanism of action of naloxone is not fully understood, evidence suggests that naloxone antagonizes the opioid effects by competing for the same receptor sites. The NARCAN nasal spray 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.

2.1.4 What are the proposed dosage(s) and route(s) of administration?

A single 4 mg (40 mg/mL) spray of NARCAN nasal spray may be administered nasally into one nostril to adults or pediatric patients. The repeated doses of NARCAN nasal spray may be administered if the patient is not adequately responding or responds and then relapses back into respiratory depression, until emergency medical assistance arrives

2.2 General Clinical Pharmacology

2.2.1. What is known about the PK characteristics of naloxone for the listed drug, Narcan?

Following parenteral administration naloxone hydrochloride is rapidly distributed in the body. It is metabolized in the liver, primarily by glucuronide conjugation, and excreted in urine. In one study the serum half-life in adults ranged from 30 to 81 minutes (mean 64 ± 12 minutes). In a neonatal study the mean plasma half-life was observed to be 3.1 ± 0.5 hours.

2.2.2. What moieties in the plasma appropriately identified and measured to assess the pharmacokinetics?

Naloxone was measured in the pivotal PK study.

2.3 Intrinsic Factors

2.3.1. What is the pediatric plan?

The reference listed product for Naloxone Hydrochloride Intranasal is Narcan, which was approved for use in pediatric patients of all ages experiencing opioid overdose. There have been some clinical studies in pediatric patients with naloxone injection or other dosage forms. Primarily, the safety, efficacy and dose have been extrapolated from adult use or from case studies published in the literature and the Narcan labeling. A literature review and reference to the Narcan labeling has been provided in the NDA.

The Applicant provided a complete literature review and summary of data that is available on the use of naloxone in children by injection (IM or IV), as well as intranasal administration as part of the NDA for Narcan (naloxone hydrochloride) Nasal Spray. The Applicant addressed the following:

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

The Applicant proposed labeling that allows use of a single 4 mg intranasal dose in persons of all ages from infants to adults. The Applicant acknowledged that additional clinical or nonclinical information may be required at a later time to address concerns about the ability to consistently administer the proposed product intranasally to neonates. The Applicant included information that supports the consistent delivery of the proposed product with the proposed intranasal delivery system in neonates with the pediatric assessment in the NDA.

For the proposed product, the Clinical team and PeRC were discussing the pediatric concerns regarding the ability of the product to deliver a consistent dose in neonates who are obligate nasal breathers, and how to address them in the labeling without requiring additional studies.

2.4 General Biopharmaceutics

2.4.1 *What is the relative bioavailability of naloxone following the administration of NARCAN (naloxone hydrochloride) Nasal Spray in comparison to the reference, intramuscular injection via standard syringe?*

The relative bioavailability of naloxone following the administration of NARCAN (naloxone hydrochloride) Nasal Spray in comparison to the reference drug naloxone IM injection were evaluated in an inpatient open-label, randomized, 5-period, 5-treatment, 5-sequence, crossover study involving approximately 29 healthy volunteers. Each participant received 5 naloxone treatments during the 5 dosing periods:

A. 2 mg IN (one 0.1 mL spray of a 20 mg/mL[3] solution in one nostril)
B. 4 mg IN (one 0.1 mL spray of a 20 mg/mL[3] solution in each nostril)
C. 4 mg IN (one 0.1 mL spray of a 40 mg/mL solution in one nostril)
D. 8 mg IN (one 0.1 mL spray of a 40 mg/mL solution in each nostril) and
E. 0.4 mg IM (1 mL of a 0.4 mg/mL commercial formulation)

On the day after clinic admission, participants were administered the study drug in randomized order with a 4-day washout period between doses until all 5 treatments were administered. Blood was collected for naloxone PK prior to dosing and approximately 2.5, 5, 10, 15, 20, 30, 45, 60, 120, 180, 240, 300, 360, 480, and 720 minutes after the start of study drug administration.

Drug Administration:

- IN naloxone was administered using an (b) (4) single dose device (b) (4) with the subject in a fully supine position. The left nostril was used for all single dose IN administrations (Treatments A and C); when two IN sprays were given, one spray was administered into each nostril (Treatments B and D). The participant remained fully supine for approximately one hour postdose. Participants were instructed not to breathe through the nose during administration of the nasal spray into the nose.
- IM naloxone was administered at a dose of 0.4 mg in 1.0 mL with a 23-gauge needle as a single injection in the *gluteus maximus* muscle. For the IM injection, 1 mL of naloxone was withdrawn from one vial (0.4 mg/mL in a 1 mL vial) into a syringe at bedside.

Lot and Formulation Identification:

- Naloxone Nasal Spray: Naloxone hydrochloride for IN administration was provided by (b) (4) at a concentration of either 20 mg/mL or 40 mg/mL.

Naloxone Nasal Spray	Batch Number	Lot Code	Manufacture Date
20 mg/mL	(b) (4)		02 Sep 2014
40 mg/mL			29 Aug 2014

- IM injection: Naloxone hydrochloride for IM injection, an ANDA product to Narcan NDA (016636), was sourced from a commercial supplier and is manufactured by (b) (4) .

The naloxone plasma concentration-time profiles from 0 to 4 h following intranasal and intramuscular naloxone administration to healthy subjects are shown in **Figure 2.4.1a**. The naloxone plasma concentration-time profiles with and without error bars from 0 to 12 h are shown in **Figure 2.4.1b**.

After 0.4 mg of naloxone HCl IM injection, a Cmax of 880 pg/mL was observed at Tmax of ~23 minutes (n= 29 subjects). With IN NARCAN spray, the concentrations greater than 880 pg/mL were maintained for longer duration, up to 120 minutes from one IN spray in one nostril (4 mg) and up to 180 minutes from one IN spray in each nostril (8 mg).

[3] *Although both 20 mg/mL and 40 mg/mL strengths of Naloxone Nasal Spray were used in this study, sponsor plans to market only 40 mg/mL strength (4 mg in 0.1 mL).*

The initial time concentrations of naloxone after the administration of naloxone drug products for reversal of opioid overdose are critical. Hence the mean concentrations of naloxone from plasma concentration time profile after administration of NARCAN (naloxone hydrochloride) nasal spray and IM injection were compared **(Table 2.4.1a).** Compared to the reference IM injection, the naloxone concentrations were higher in the range of 3.5 to 6.0 fold after one IN spray in one nostril and 9.7 to 13.3 fold after one IN spray in each nostril from 2.5 minutes to 60 minutes post-dose.

The PK parameters and statistical analysis for the assessment of relative bioavailability following intranasal and intramuscular naloxone administration to healthy subjects' results are presented in the **Table 2.4.1b and Table 2.4.1c.** The PK parameters of only 40 mg/mL strength of Naloxone Nasal Spray, which the sponsor plans to market, were included in the Tables.

The one NARCAN nasal spray in one nostril or one NARCAN spray in each nostril exhibited much higher systemic exposure of naloxone in terms of both AUC and Cmax values in comparison to the reference drug product, 0.4 mg naloxone IM injection. The administration of one NARCAN nasal spray (4 mg total dose, 0.1 mL of 40 mg/mL naloxone hydrochloride solution) in one nostril exhibited 555%, 469% and 462% higher geometric mean ratios (IN/IM) for Cmax, AUCt and AUCinf, respectively compared to the reference 0.4 mg IM injection. The corresponding 90% CIs for geometric mean ratios for one IN spray in comparison to IM treatment were 464-665%, 418-527% and 412-519%, for Cmax, AUCt and AUCinf, respectively. The administration of one NARCAN nasal spray in each nostril (8 mg total dose, 0.1 mL of 40 mg/mL naloxone hydrochloride solution) exhibited 1110%, 890% and 878% higher geometric mean ratios for Cmax, AUCt and AUCinf, respectively compared to the reference 0.4 mg IM injection. The corresponding 90% CIs for geometric mean ratios for one IN spray in each nostril in comparison to IM treatment were 925-1320%, 793-999% and 783-985%, for Cmax, AUCt and AUCinf, respectively.

The median naloxone Tmax after single NARCAN nasal spray (4 mg) in one nostril and one NARCAN nasal spray in each nostril (8 mg) was 0.50 h (range, 0.17 to 1.00 h) and 0.33 h (range, 0.17 to 1.00 h), respectively. The median naloxone Tmax after IM injection was 0.38h and has relatively high variability with the range of 0.08 to 2.05h compared to the IN route. The IN route has slightly longer half-life of 2.1 h compared to 1.2 h for IM route.

Figure 2.4.1a Mean plasma concentration time profiles from 0 to 4 hours of naloxone following intranasal and intramuscular naloxone administration to healthy subjects (N = 29)

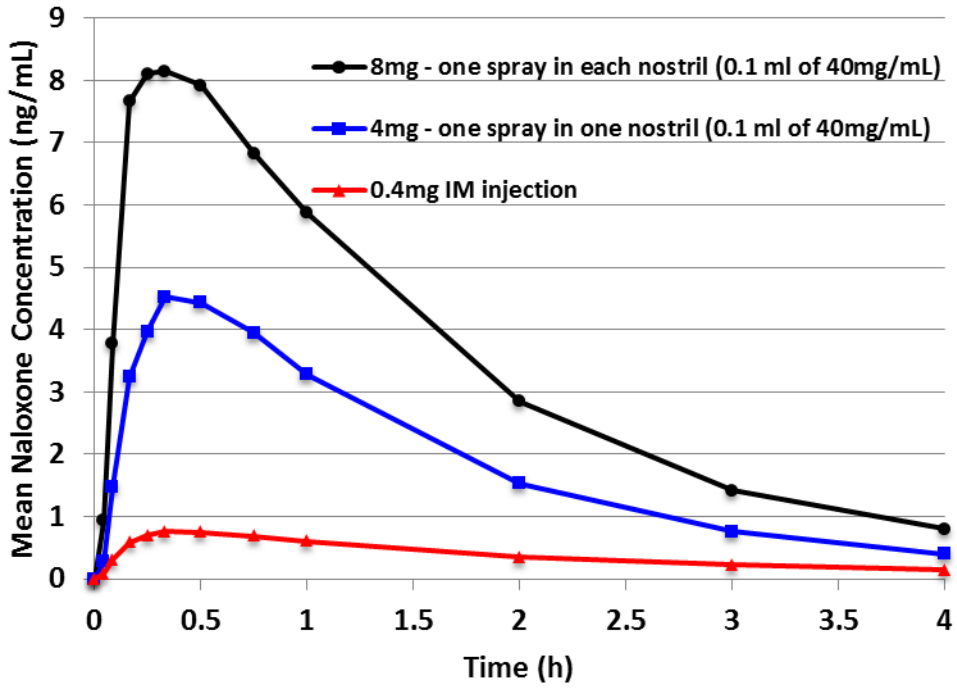


Figure 2.4.1b Mean plasma concentration time profiles of naloxone following intranasal and intramuscular naloxone administration to healthy subjects (N = 29)

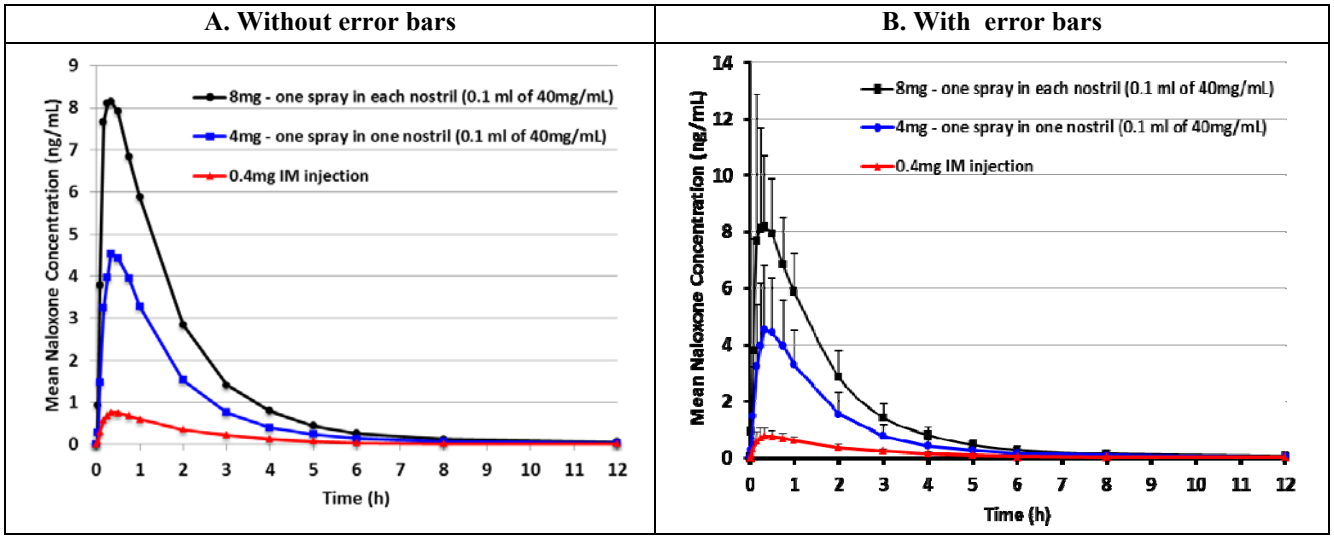


Table: 2.4.1a.The comparison of mean naloxone concentrations between IM injection and NARCAN one or two IN sprays from 2.5 to 60 minutes post dose.

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

Table: 2.4.1b. Geometric mean naloxone PK parameters (CV%) following IN administration and IM injection of Naloxone to healthy subjects (n=29)

Parameter	4 mg – Single nasal spray in one nostril (N=29)	8 mg – One nasal spray in each nostril (N=29)	0.4 mg Intramuscular Injection (N=29)
Cmax (ng/mL)	4.8 (43)	9.7 (36)	0.88 (31)
AUC 0-2h (hr ng/mL)	5.5 (35)	10.5 (21)	1.06 (22)
AUC 0-4h (hr ng/mL)	7.1 (36)	13.5 (22)	1.52 (21)
AUCt (hr ng/mL)	7.9 (37)	15.3 (23)	1.72 (23)
AUCinf (hr.ng/mL)	8.0 (37)	16 (23)	1.8 (23)
Tmax (h)	0.50 (0.17, 1.00)	0.33 (0.17, 1.00)	0.38 (0.08, 2.05)
Cmax(dn) (ng/mL/mg)	1.2 (43)	1.21 (36)	2.2 (31)
AUCt(dn) (hr ng /mL/mg)	2.0 (37)	1.9 (23)	4.3 (23)
AUCinf(dn) (hr ng /mL/mg)	2.0 (37)	1.9 (23)	4.4 (23)
t½, (h)	2.1 (30)	2.1 (32)	1.2 (26)
Dose normalized Relative BA (%) vs. IM	47 (31)	44 (24)	100

Table: 2.4.1c. Geometric mean ratios and 90% CIs for plasma naloxone pharmacokinetic parameters following intranasal and intramuscular administration.

Parameter	Test Vs Reference	Adjusted Geometric LS mean		Ratio %[Test/Reference] (lower , upper 90% CI of ratio)
		Test (n=29)	Reference (n=29)	
Cmax (ng/mL)	4 mg -one IN Spray in one nostril (Test) Vs 0.4 mg IM (Reference)	4.83	0.870	555 (464, 665)
AUC0-t (h*ng/mL)		7.90	1.68	469 (418, 527)
AUC0-inf (h*ng/mL)		7.99	1.73	462 (412, 519)
Cmax (ng/mL)	8 mg -one IN Spray in each nostril (Test) Vs 0.4 mg IM (Reference)	9.62	0.870	1110 (925, 1320)
AUC0-t (h*ng/mL)		15.0	1.68	890 (793, 999)
AUC0-inf (h*ng/mL)		15.2	1.73	878 (783, 985)

While finalizing this review, the Office of Scientific Investigation (OSI) inspection report for thepivotal comparative bioavailability study Naloxone-Ph1a-002 is still pending. Apart from the pending OSI inspection report, the submitted information is acceptable from a clinical pharmacology perspective. An addendum will be added to the clinical pharmacology review, if necessary based on the OSI inspection report.

2.5 Analytical Section

1. ***Do the bioanalytical methods adequately validated for determining plasma concentrations of naloxone and total naloxone?***

- Clinical Center: Vince Associates Clinical Research, KS 66212
  - Study Activation Date: 16 Oct 2014
  - Study Completion Date: 02 Jan 2015
  - Total samples: 2317

- Bio-analytical Facility: (b) (4)
  - Analytical Start Date: (b) (4)
  - Analytical Completion Date: (b) (4)

- Naloxone Bioanalytical Assay:
  - HPLC-MS/MS assay
  - Calibrators: 0.01, 0.02, 0.1, 0.5, 2, 5, 9, 10 ng/mL
  - Quality controls: 0.03 , 0.3, 4, and 8 ng/mL
  - Internal standard: Naloxone-d5
  - Accuracy and Precision over the range:
    - Accuracy (expressed as % bias) : < ± 15%
    - Precision (expressed as % CV) : < 15%

- Stability:
  - Storage stability: Naloxone: 54 days at -70°C and 70 days at - 20°C
  - All samples were analyzed within sample storage stability. The longest sample storage time prior to analysis is 50 days at -20°C.

- Incurred sample reproducibility: 168 out of 168 samples met the acceptance criteria

3 Labeling Recommendations

The labelling comments have been made to the following sections in the Label:

Section 12.3

4 Appendix

4.1 Clinical Pharmacology Filing Memo

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	***NDA-208411***	**Brand Name**	***Narcan***
OCP Division (I, II, III, IV, V)	***II***	**Generic Name**	***Naloxone HCL***
Medical Division	***DAAAP***	**Drug Class**	***Opioid antagonist***
OCP Reviewer	***Suresh B Naraharisetti***	**Indication(s)**	***Reversal of opioid depression***
OCP Team Leader	***Yun Xu***	**Dosage Form**	***Nasal spray, 4 mg***
Pharmacometrics Reviewer		**Dosing Regimen**	***Single spray of NARCAN nasal spray; Second spray if required***
Date of Submission	***July 20, 2015***	**Route of Administration**	***Nasal***
Estimated Due Date of OCP Review		**Sponsor**	***Adapt Pharma***
Medical Division Due Date		**Priority Classification**	***Priority***
PDUFA Due Date	***January 20, 2016***		

Clin. Pharm. and Biopharm. Information

	"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.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods	**X**	**1**		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
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 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:				
alternate formulation as reference:	**X**	**2**		Narcan (016636) as reference in R BA study
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	**X**			
Bio-waiver request based on BCS				
BCS class				
In vivo alcohol induced dose-dumping	**X**			
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				**Yes**
Literature References				
Total Number of Studies		**3**		

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

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			

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)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
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?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
Yes

BACKGROUND
Adapt Pharma submitted a 505 (b) (2) NDA (208411) for Naloxone HCL nasal spray for the indication 'emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression'. As a 505(b) (2) NDA, Sponsor is relying on the Agency's findings on the safety and efficacy of Narcan (NDA 016636), naloxone HCL injectable injection and literature. The Applicant is relying upon literature to support the use of their product in all pediatric age ranges. In support of this NDA, sponsor conducted the following Clinical Pharmacology/Clinical studies:

Clinical Pharmacology Studies with final formulation:
Phase 1 Naloxone-Ph1a-002: Relative BA to Narcan Injection

Naloxone-Ph1a-002: Phase 1, Pharmacokinetic Evaluation of Intranasal and Intramuscular Naloxone in Healthy Volunteers

Suresh Babu Naraharisetti	September 11, 2015
Reviewing Clinical Pharmacologist	Date
Xu Yun	September 11, 2015
Team Leader/Supervisor	Date

4.2 Individual Study Synopsis

SYNOPSIS

Study Number	Naloxone-Ph1a-002
Title	Phase 1, Pharmacokinetic Evaluation of Intranasal and Intramuscular Naloxone in Healthy Volunteers
Phase	I
Sponsor	Adapt Pharma Operations, Dublin, Ireland
Study Drug Substance	Naloxone hydrochloride (naloxone)
Investigator	Martin Kankam, M.D., Ph.D., M.P.H., Vince & Associates Clinical Research
Site	Vince & Associates Clinical Research, Inc., Overland Park, KS
Study Period	**Date of First Screening Visit:** 17 Nov 2014 **Date of Last Visit:** 02 Jan 2015
Participants Randomized	**Planned:** 30 **Actual:** 30
Objectives 1. To determine the pharmacokinetics (PK) of 4 intranasal (IN) doses [2 mg, 4 mg (2 nostrils), 4 mg (1 nostril), and 8 mg (2 nostrils)] of naloxone compared to a 0.4 mg dose of naloxone administrated intramuscularly (IM) and to identify an appropriate IN dose that could achieve systemic exposure comparable to an approved parenteral dose. 2. To determine the PK of two different concentrations (20 mg/mL and 40 mg/mL) of IN naloxone. 3. To determine the safety of IN naloxone, particularly with respect to nasal irritation (erythema, edema, and erosion).	
Study Design: Inpatient, open-label, randomized, 5-period, 5-treatment, 5-sequence, crossover study involving approximately 30 healthy volunteers. Participants were assigned to one of 5 sequences, with 6 participants planned in each sequence. On the day after clinic admission, participants were administered study drug in randomized order with a 4-day washout period between doses until all 5 treatments had been administered. Blood was collected for PK analysis prior to administration and up to 12 hours after each dose; electrocardiogram (ECG), vital signs, and other adverse event (AE) assessments were performed. The total inpatient stay was 18 days, with a follow-up visit 3-5 days after discharge.	
Main Criteria for Inclusion: Healthy male and female volunteers, 18 to 55 years of age.	

Study Product: Naloxone hydrochloride; (1*S*,5*R*,13*R*,17*S*)- 10,17-dihydroxy- 4-(prop-2-en-1-yl)- 12-oxa- 4-azapentacyclo [9.6.1.$0^{1,13}$.$0^{5,17}$.$0^{7,18}$] octadeca-7(18),8,10-trien-14-one.

Naloxone hydrochloride for IN administration (20 mg/mL or 40 mg/mL) was provided by (b) (4)

Naloxone hydrochloride for IM injection (0.4 mg/mL) was manufactured by (b) (4) , and obtained from a commercial supplier.

Mode and Duration of Treatment: Naloxone given IM was administered with a 23-gauge needle as a single injection in the *gluteus maximus* muscle.

Naloxone given IN was administered using an (b) (4) single dose device with the participant in a fully supine position. The participant was instructed to not breathe through the nose when the IN dose of naloxone was administered.

Participants received a total of 5 doses (4 IN and 1 IM), in a randomized order (5 potential sequences):

A = 2 mg IN Naloxone (one 0.1 mL spray of the 20 mg/mL formulation in one nostril)

B = 4 mg IN Naloxone (one 0.1 mL spray of the 20 mg/mL formulation in each nostril)

C = 4 mg IN Naloxone (one 0.1 mL spray of the 40 mg/mL formulation in one nostril)

D = 8 mg IN Naloxone (one 0.1 mL spray of the 40 mg/mL formulation in each nostril)

E = 0.4 mg IM Naloxone (1 mL of a 0.4 mg/mL commercial formulation)

There was a 4-day washout period between doses for a total inpatient stay of 18 days.

Criteria for Evaluation: The primary endpoint was to compare the PK parameters (maximum plasma concentration [C_{max}], time to reach C_{max} [t_{max}], area under the plasma concentration-time curve from time 0 to the time of last measurable concentration [AUC_{0-t}], and AUC from time 0 extrapolated to infinity [AUC_{0-inf}]) of the four IN naloxone treatments (2 mg [1 nostril], 4 mg [in 2 nostrils], 4 mg (1 nostril), and 8 mg [in 2 nostrils]) with an IM dose of 0.4 mg of naloxone.

Secondary endpoints were evaluations of AEs, vital signs (heart rate, sitting blood pressure, and respiration rate), ECG, clinical laboratory changes, and nasal irritation (erythema, edema, and erosion).

Statistical Methods: Non-compartmental PK parameters including C_{max}, t_{max}, AUC_{0-t}, AUC_{0-inf}, apparent half-life ($t_{½}$), terminal-phase exponential rate constant (λ_z), and apparent clearance (CL/F) were determined. PK parameters (C_{max}, t_{max}, and AUCs) for IN naloxone were compared with those for IM naloxone. T_{max} was determined starting from the time of administration (spraying into the nasal cavity or IM injection). Dose adjusted values for AUCs and C_{max} were calculated. The relative extent of intranasal absorption (IN versus IM) was estimated from the dose-corrected AUCs. Within an ANOVA framework, comparisons of ln-transformed PK parameters (C_{max} and AUCs) for IN versus IM naloxone treatments were performed. The 90% confidence interval (CI) for the ratio (IN/IM) of the geometric least squares means of AUC and C_{max} parameters were constructed for comparison of each treatment with IM naloxone. These 90% CIs were obtained by exponentiation of the 90% CIs for the difference between the least squares means based upon an ln scale.

Additional exploratory analyses include:

1) 90% CI for dose corrected AUC and C_{max} between the 20 mg/mL formulation treatment and 40 mg/mL formulation for both a single administration and two dose administrations (once in each nostril).
2) 90% CI adjusted for dose for geometric ratios of one 0.1 mL spray (in one nostril) vs. two 0.1 mL sprays (one spray in each nostril) from a 20 mg/mL formulation.
3) 90% CI adjusted for dose for geometric ratios of one 0.1 mL spray (in one nostril) vs. two 0.1 mL sprays (one spray in each nostril) from a 40 mg/mL formulation.

AEs were coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and grouped by system, organ, class (SOC) designation. The severity, frequency, and relationship of AEs to study drug are presented by preferred term by SOC grouping. Separate summaries are provided for the 5 study periods: after the administration of each dose of study drug up until the time of the next dose of study drug or clinic discharge.

Vital signs, ECG, and clinical laboratory parameters are presented as summary statistics and changes from baseline (with baseline being the measurement prior to each dose).

Results: Thirty healthy male (n=18) and female (n=12) participants were randomized and received at least one dose of naloxone; 28 (93%) completed the study. The participants had a mean (range) age of 36 (22 to 55) years and mean (range) BMI of 27.1 (19.6 to 29.8) kg/m^2. One male participant was discharged on Day 5 prior to receiving the second administration due to a predose systolic blood pressure (BP) reading greater than 140 mmHg, a condition for continued inclusion in the study. Another male participant requested to withdraw from the study on Study Day 17 before the fifth administration of naloxone.

Naloxone plasma concentrations were at measurable concentrations 2.5 minutes after IN administration, the first collection time point, in all but 2 samples. The median t_{max} values after IN and IM dosing ranged from 20 to 30 minutes, indicating that naloxone was absorbed quickly following either route of administration.

The mean C_{max} increased from 2.92 to 9.70 ng/mL as the dose increased from 2 to 8 mg; the mean C_{max} for the IM treatment (0.4 mg) was 0.877 ng/mL (**Table 2-1**). The mean dose-normalized C_{max} ranged from 1.21 to 1.55 ng/mL/mg for the 4 IN treatments; it was 2.19 ng/mL/mg for the IM treatment.

The mean $AUC_{0\text{-}inf}$ values increased from 4.56 to 15.5 h*ng/mL as the IN dose increased from 2 to 8 mg; the value for the IM dose was 1.76 h*ng/mL. The dose-normalized $AUC_{0\text{-}inf}$ values for the IN treatments were between 1.93 and 2.36 h*ng/mL/mg; it was 4.40 h*ng/mL/mg for the IM treatment. Based on the dose-normalized values, the relative bioavailability of the IN-administered naloxone compared to the IM treatment ranged from 43.9% to 53.6% across IN treatments.

The mean terminal phase half-life ranged between 1.81 and 2.23 hours for the 4 IN treatments; it was 1.24 hours after the IM injection.

Dose proportionality for the 4 IN doses of naloxone was assessed using the ratio of the dose-normalized geometric mean values (R_{dnm}) of C_{max} and $AUC_{0\text{-}inf}$. The R_{dnm} value (90% CI) value for C_{max} was 0.831 (0.744-0.927); for $AUC_{0\text{-}inf}$, the R_{dnm} value was 0.847 (0.786-0.912). Both C_{max} and $AUC_{0\text{-}inf}$ increased slightly less than dose proportionally, as indicated by R_{dnm} values and confidence intervals that were less than 1.

The geometric mean ratios (GMR) of the dose-normalized C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$ were approximately 12 to 20% higher when one spray of the 20 mg/mL formulation was compared to one spray of the 40 mg/mL IN formulation (2 mg versus 4 mg). The GMRs of the 3 parameters were 22 to 28% higher when 4 mg of naloxone delivered with 2 sprays of the 20 mg/mL formulation was compared to 8 mg delivered with 2 sprays of the 40 mg/mL formulation. The upper limit of the 90% CI of the GMR was above 125% for all of the comparisons.

Evaluations were also done to compare dose-normalized PK parameters for one spray versus 2 sprays of the 20 mg/mL formulation; similar comparisons were done for the 40 mg/mL formulation. The geometric least-squares mean ratios (GMRs) for the PK parameters were between 94% and 97% when comparing 2 mg (one spray) and 4 mg (2 sprays) delivered using the 20 mg/mL formulation. The 90% CIs of the GMR for both dose-normalized $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ were within 80-125% while the values for dose-normalized C_{max} were 78.7 to113%. For the 40 mg/mL formulation, the GMRs and 90% CIs for all 3 PK parameters ($AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max}) were within the 80-125% range when comparing one spray (4 mg) and two

sprays (8 mg).

Table 2-1. Geometric Mean Pharmacokinetic Parameters (CV%) of Naloxone Following Single Intranasal Administration and Intramuscular Injection of Naloxone to Healthy Subjects, Study Naloxone-Ph1a-002

Parameter	Treatment A 2 mg - One Spray 20 mg/mL IN (N = 29)	Treatment B 4 mg - Two Sprays 20 mg/mL IN (N = 29)	Treatment C 4 mg - One Spray 40 mg/mL IN (N = 29)	Treatment D 8 mg - Two Sprays 40 mg/mL IN (N = 29)	Treatment E 0.4 mg IM (N = 29)
λz (1/h)	0.382 (34.9)	0.310 (34.5)	0.334 (29.5)	0.330 (32.4)	0.557 (25.9)
t½ (h)	1.81 (34.9)	2.23 (34.5)	2.08 (29.5)	2.10 (32.4)	1.24 (25.9)
t_{max} (h) [a]	0.33 (0.25, 1.00)	0.33 (0.17,0.57)	0.50 (0.17, 1.00)	0.33 (0.17, 1.00)	0.38 (0.08, 2.05)
C_{max} (ng/mL)	2.92 (34.3)	6.20 (31.9)	4.83 (43.1)	9.70 (36.0)	0.877 (30.5)
C_{max}/Dose (ng/mL/mg)	1.46 (34.3)	1.55 (31.9)	1.21 (43.1)	1.21 (36.0)	2.19 (30.5)
AUC_{0-t} (h*ng/mL)	4.51 (27.2)	9.32 (24.0)	7.87 (37.4)	15.3 (23.0)	1.72 (22.9)
AUC_{0-t}/Dose (h*ng/mL/mg)	2.25 (27.2)	2.33 (24.0)	1.97 (37.4)	1.91 (23.0)	4.29 (22.9)
AUC_{0-inf} (h*ng/mL)	4.56 (26.9)	9.43 (24.0)	7.95 (37.3)	15.5 (22.7)	1.76 (22.6)
AUC_{0-inf}/Dose (h*ng/mL/mg)	2.28 (26.9)	2.36 (24.0)	1.99 (37.3)	1.93 (22.7)	4.40 (22.6)
AUC% Extrapolated (%)	1.06 (56.5)	0.935 (60.1)	0.965 (53.5)	0.963 (69.3)	2.18 (57.5)
CL/F (L/h)	438 (26.9)	424 (24.0)	503 (37.3)	518 (22.7)	227 (22.6)
Relative BA (%) vs. IM	51.9 (21.7)	53.6 (22.5)	46.7 (31.4) [b]	43.9 (23.8)	100
C_{max}/Dose Ratio (IN vs. IM) (%)	66.6 (41.4)	70.7 (37.7)	56.6 (47.5) [b]	55.3 (41.4)	100

a: Median (minimum, maximum)

b: N=28 for Relative Bioavailability (BA) and C_{max}/Dose ratio of Treatment C

There were no apparent gender-related differences observed for the PK parameters for any of the naloxone IN and IM treatments.

Safety Results: In general, IN doses of 2 to 8 mg naloxone were safe and well tolerated. A total of 17 participants experienced at least one AE, of whom 12 experienced at least one AE thought to be at least possibly related to naloxone. The most frequent naloxone-related AEs experienced over all doses/routes were nasal inflammation (erythema) (n=5 participants, 16.7%), nasal edema (n=4, 13.3%), and headache (n=2, 6.7%).

Conclusions:

- The median t_{max} values after IN and IM dosing ranged from 20 to 30 minutes, indicating that naloxone was absorbed quickly following either route of administration.
- C_{max} increased from 2.92 to 9.70 ng/mL as the IN dose increased from 2 to 8 mg. The dose- normalized C_{max} ranged from 1.21 to 1.55 ng/mL/mg for the four IN treatments and was
  2.19 ng/mL/mg for the IM treatment.
- $AUC_{0\text{-}inf}$ increased from 4.56 to 15.5 h*ng/mL as the IN dose increased from 2 to 8 mg. The dose-normalized $AUC_{0\text{-}inf}$ ranged from 1.93 to 2.36 h*ng/mL/mg and was 4.40 h*ng/mL/mg for the IM treatment. The relative bioavailability of IN-administered naloxone compared to the IM treatment ranged from 43.9 to 53.6%.
- There were no apparent gender-related differences observed for the PK parameters for any of the naloxone IN and IM treatments.
- Naloxone treatments were generally safe and well-tolerated with few treatment-related AEs (all mild in severity). The most frequent AEs across all dose level/routes were nasal inflammation (erythema) and nasal edema.

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/s/

SURESH B NARAHARISETTI
10/22/2015

YUN XU
10/22/2015

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	***NDA-208411***	**Brand Name**	***Narcan***
OCP Division (I, II, III, IV, V)	***II***	**Generic Name**	***Naloxone HCL***
Medical Division	***DAAAP***	**Drug Class**	***Opioid antagonist***
OCP Reviewer	***Suresh B Naraharisetti***	**Indication(s)**	***Reversal of opioid depression***
OCP Team Leader	***Yun Xu***	**Dosage Form**	***Nasal spray, 4 mg***
Pharmacometrics Reviewer		**Dosing Regimen**	***Single spray of NARCAN nasal spray; Second spray if required***
Date of Submission	***July 20, 2015***	**Route of Administration**	***Nasal***
Estimated Due Date of OCP Review		**Sponsor**	***Adapt Pharma***
Medical Division Due Date		**Priority Classification**	***Priority***
PDUFA Due Date	***January 20, 2016***		

Clin. Pharm. and Biopharm. Information

	"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.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods	**X**	**1**		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
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:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
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:				
alternate formulation as reference:	**X**	**2**		Narcan (016636) as reference in R BA study
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	**X**			
Bio-waiver request based on BCS				
BCS class				
In vivo alcohol induced dose-dumping	**X**			
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				**Yes**
Literature References				
Total Number of Studies		**3**		

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

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
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)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
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?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
Yes

BACKGROUND

Adapt Pharma submitted a 505 (b) (2) NDA (208411) for Naloxone HCL nasal spray for the indication 'emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression'. As a 505(b) (2) NDA, Sponsor is relying on the Agency's findings on the safety and efficacy of Narcan (NDA 016636), naloxone HCL injectable injection and literature. The Applicant is relying upon literature to support the use of their product in all pediatric age ranges. In support of this NDA, sponsor conducted the following Clinical Pharmacology/Clinical studies:

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Clinical Pharmacology Studies with final formulation:

Phase 1 Naloxone-Ph1a-002: Relative BA to Narcan Injection

Naloxone-Ph1a-002: Phase 1, Pharmacokinetic Evaluation of Intranasal and Intramuscular Naloxone in Healthy Volunteers

Suresh Babu Naraharisetti	September 11, 2015
Reviewing Clinical Pharmacologist	Date
Xu Yun	September 11, 2015
Team Leader/Supervisor	Date

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/s/

SURESH B NARAHARISETTI
09/11/2015

YUN XU
09/11/2015