FDA ADVISORY COMMITTEE BRIEFING MATERIALS

Intranasal Naloxone Intended for Use in the Community

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee
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ABBREVIATIONS

IN NALOXONE

ADE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AST	Aspartase Transaminase
AUC	Area Under the Curve (pharmacokinetics)
BLSA	Basic Life Support Action
BUN	Blood Urea Nitrogen
CI	Confidence Interval
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
EMS	Emergency Medical Services
EP	Evaluable Population
HR	Heart Rate
ES	Extremely Severe
HCl	Hydrochloride
IAF	Investigator Assessment Findings
IFU	Instructions for Use
IM	Intramuscular
IN	Intranasal
IR	Incidence Rate
IV	Intravenous
LCI	Lower limit of Confidence Interval
MedDRA	Medical Dictionary for Regulatory Activities
NOME	Nasal and Oropharyngeal Mucosa Exam
OOP	Opioid Overdose Population
PK	Pharmacokinetics
p-value	The probability of obtaining a test statistic at least as extreme as the one that was actually observed, assuming that the null hypothesis is true
RP	Reported Population
S	Severe
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SC	Subcutaneous
SOC	System Organ Class (for ADE symptom)

SR	Survival Rate
SSA	Subject Symptom Self-Assessment
TP	Treated Population
UCI	Upper Limit of Confidence Interval
VS	Very Severe

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1. EXECUTIVE SUMMARY

1.1. Unmet Medical Need

Opioid overdose and mortality have increased at an alarming rate over the last few decades. Opioids, including prescription opioid medications and heroin, are the major causes of drug overdose deaths in the United States [1, 2]. Naloxone hydrochloride (Naloxone HCl), a narcotic antagonist, is the standard of care for opioid overdose.

As naloxone injection is primarily delivered through IV, IM or SC administration, it can be difficult to use for most lay people. There has been concern about the potential for accidental needle stick injury and transmission of hepatitis or HIV infection. Therefore, based on the limited availability of alternatives to naloxone injection, an unmet medical need has been identified to have greater availability of user-friendly, needle-free naloxone delivery systems for medical professionals, first responders and at home family member use. The addition of an easy to use product that can meet the public health demand in the context of an opioid abuse epidemic, with little to no associated risk, and with product characteristics ensuring performance reliability would be of great public health benefit.

1.2. Overview of Pharmacology Profile and Clinical Studies

This briefing document is prepared for discussion of Intranasal Naloxone HCl (referred to as IN naloxone throughout this report). This document is intended to summarize Amphastar's efforts at developing an injection free, naloxone product that can be made available for use in the community setting. The primary purpose for our clinical studies was to provide a scientific bridge from the Agency's previous findings of efficacy and safety for Narcan (NDA 016636) to a new formulation of naloxone. Two (2) generic products for naloxone injection, Hospira's Naloxone HCl 0.4mg IM/SC and Amphastar/IMS' Naloxone 2.0mg IM/SC were both used as the reference product for comparison of efficacy and safety, respectively, as Narcan for injection is no longer marketed.

1.3. Summary of Efficacy Via Evaluation of Pharmacokinetics (PK)

The efficacy of an IN naloxone can be demonstrated clinically as follows:

(1) PK studies to provide an adequate scientific bridge from FDA's previous findings of efficacy and safety of Naloxone IM treatment (**Narcan 016636**) to the final to-be-marketed IN naloxone.

(2) Efficacy can be assessed by using the area under curve (AUC) for partial time, which we defined as (i) the tmax for IM (0.4mg) and (ii) comparative serum concentrations taken for 30 minutes at 5 minute intervals. A range of proposed doses should be evaluated.

(3) Bioequivalence statistical analysis methods can be used for the comparative efficacy assessment.

(4) Onset time is an important efficacy parameter since IN Naloxone is used under emergency conditions.

(5) In a retrospective study, it has been demonstrated that the IMS' naloxone (2mg/2mL) off-label use via IN administration was highly effective with a survival rate statistically significantly greater than 90% ($p<0.001$). These results, obtained from "actual use" conditions, demonstrate that IN delivery with the currently marketed IMS' Naloxone formulation was highly effective for reversal of opioid overdose when administered by first responders.

(6) Results from the analysis of the retrospective study combined with data obtained from prospective PK studies provide strong evidence of the proposed dose of 2 mg being highly effective in "**the complete or partial reversal of opioid depression, including respiratory depression**", the current indication for the reference products.

(7) An appropriate dose of IN Naloxone should be determined in a PK study that demonstrates the following results, characterized by partial time AUC as described above:

"Partial AUC of Proposed dose IN Naloxone $\geq$ IMS Naloxone 2mg/2mL by IN
$\geq$ Naloxone 0.4 mg by IM "

where " $\geq$ " means that the lower 90% confidence interval should be greater than 80%.

(8) Naloxone should be packaged as a kit with two (2) units of individual doses for IN administration. This is supported by the retrospective study discussed above where 98% of victims received one or two vials.

1.4. Summary of Safety

1.4.1 Safety Evaluation Based on Systematic Exposure

In lieu of extensive safety studies, the PK parameter $AUC_{0-\infty}$, characterizing total exposure, can be used to demonstrate comparative safety to the IM injection of RLD (Naloxone 2.0 mg), the maximum marketed injectable dose. The Upper Confidence Limit (UCL) of all geometric mean ratios should not exceed 125%.

1.4.2 Adverse Drug Events (ADE) Evaluation in Clinical Trials

ADEs, including major ADE (occurrence rate >2%), severe and serious ADE should be assessed in the clinical trials and compared with the IM treatment.

1.4.3 Local Tolerability Evaluation

Local tolerability, including a nasal and oropharyngeal mucosa exam should be conducted in the clinical trials, especially if the concentration of the proposed IN naloxone is more than 10 mg/mL, which is 10 times or more of the highest concentration for the currently distributed naloxone injection (1mg/mL).

In the examination, the nostril, septum, turbinates, and nasal floor should be evaluated; and for oropharyngeal, soft palate, tonsil/tonsilar fossa, base of tongue and posterior pharyngeal wall should be evaluated. The exam may also evaluate for edema, erythema and appearance of lesions.

1.4.4 Assessment of acute withdrawal syndrome

If the proposed single dose of IN Naloxone is greater than the highest single dose of the currently marketed naloxone injection (2mg), an acute withdrawal syndrome evaluation should be performed.

1.5 OVERVIEW OF THE LABEL AND INSTRUCTION FOR USE

The rescue kit should be presented in outer packaging that contains 2 individually packaged units sealed in blister cartons or other protective, printable packaging material. Each unit should contain the required medication to administer a single dose. The outer packaging should be durable and include a "Quick Guide" or abbreviated version of the instructions for use (IFU). A set of written instructions providing more specific information, such as a user leaflet (or IFU) and prescribing information should be easily accessible. The IFU should be presented as a single-sided document and the same Quick Guide should be printed on each blister carton.

Human factors studies should be performed on the instructions for use to ensure competency in administering the product.

1.6 RISK BENEFIT DISCUSSION

The totality of data from studies should demonstrate the efficacy of proposed IN naloxone in "**the complete or partial reversal of opioid depression, including respiratory depression**". In addition, it should be concluded that IN naloxone is generally safe and well-tolerated at multiple dose levels. In the absence of significant safety concerns, the life-saving benefit of Naloxone far outweighs its risk in patients suffering from opioid overdose.

The expected advantages of IN naloxone, compared to 0.4 mg Naloxone injection are:

- Intranasal administration of IN naloxone should demonstrate quicker onset of action and higher systemic exposure than the reference product. This is likely due to the rich vascular plexus of the nasal cavity provides a direct route into the blood stream for IN naloxone that easily cross the mucous membranes;
- Intranasal administration of naloxone is intrinsically easier to use. There is no need to learn 1) how to administer an injection, 2) aseptic technique, or 3) intravenous cannulation or injection techniques. It provide first responders and caregivers who may have little medical training a simpler solution than injection;
- Intranasal administration allows individuals to safely administer the medication. It does not require any invasive device. It eliminates the risk of needle-sticks resulting in the possible transmission of blood borne pathogens and the infection risk of patients and user.

The major improvements for the IN naloxone over currently off-label use 2 mg/2mL Naloxone injection are:

- a volume that is significantly lower than that of the current formulation, minimizing medication loss during administration;
- a concentration that is higher than the current formulation achieving optimal systemic exposure in the first thirty (30) minutes after administration;
- allows for effective delivery into one nostril for IN naloxone in comparison to 2 nostrils used in off-label delivery;
- configure in a two pack kit to eliminate the need to have multiple individual units on hand.

2. BACKGROUND INFORMATION

2.1 NALOXONE INJECTION, INDICATION AND DOSE

Opioid overdose and mortality have increased at an alarming rate over the last few decades. Opioids, including prescription opioid medications and heroin, are the major causes of drug overdose deaths in the United States [1, 2]. Naloxone hydrochloride (Naloxone HCl), a narcotic antagonist, is standard of care for opioid overdose.

Naloxone is the N-allyl derivative of oxymorphone. It acts by competitively binding at opiate receptors. Naloxone binds most strongly to the mu receptor but displays antagonistic activity at kappa and sigma receptors as well. However, naloxone has little or no agonist activity and does not cause apnea. Therefore, it could be used safely to treat patients with respiratory depression.

Naloxone HCl was first approved in 1971 to reverse opioid intoxication or overdose (**Narcan NDA 016636**). According to its labeling, **Narcan** may be administered intravenously (IV), intramuscularly (IM), or subcutaneously (SC). IM or SC administration may be necessary if the IV route is not available.

The currently approved label for naloxone injection indicates [3]:

"An initial dose of **0.4 mg to 2 mg** of naloxone hydrochloride may be administered intravenously. If the desired degree of counteraction and improvement in respiratory functions is not obtained, it may be repeated at 2 to 3 minute intervals. If no response is observed after 10 mg of naloxone hydrochloride have been administered, the diagnosis of narcotic-induced or partial narcotic-induced toxicity should be questioned." (Emphasis added)

2.2 NALOXONE IN USE RATIONAL

As naloxone injection is primarily delivered through IV, IM or SC administration, it can be difficult to use for most lay people. There has been concern about the potential for accidental needle stick injury and transmission of hepatitis or HIV infection. Therefore, based on the limited availability of alternatives to naloxone injection, an unmet medical need has been identified to have greater availability of user-friendly, needle-free naloxone delivery systems for medical professionals, first responders and at home family member use. The addition of

an easy to use product that can meet the public health demand in the context of an opioid abuse epidemic, with little to no associated risk, and with product characteristics ensuring performance reliability would be of great public health benefit.

Intranasal (IN) naloxone is an excellent method of safely administering an opioid antagonist to a person suffering a severe opioid overdose. The expected advantages Intranasal Naloxone, compared to Naloxone HCl injection are:

- Intranasal administration of naloxone showed a quicker onset of action and higher efficacy. It could be due to the rich vascular plexus of the nasal cavity provides a direct route into the blood stream for naloxone that easily cross mucous membranes;

- Intranasal administration of naloxone is easier to use. There is no need to learn 1) how to administer an injection, 2) aseptic technique, or 3) intravenous cannulation or injection techniques. It provide first responders and caregivers who may have little medical training a simpler solution than injection;

- Intranasal administration of naloxone allows individuals to safely administer the medication. It does not require any invasive device. It eliminates the risk of needle-sticks resulting in the possible transmission of blood borne pathogens and the infection risk of victims and users;

2.3 OFF-LABEL USE OF IMS' NALOXONE INJECTION 2MG/2ML

The past few years have seen the rapid rise of off-label IN naloxone administration for opioid overdose in community settings. Generic naloxone HCl injection product 2mg/2mL in pre-filled syringes, manufactured by International Medication Systems, Limited (IMS), a wholly-owned subsidiary of Amphastar Pharmaceuticals, Inc., are currently being used widely off-label by emergency medical service (EMS) providers and non-medical personnel, including police officers and civilian bystanders in the US.

2.4 SUGGESTED IN PRODUCT CONFIGURATION, 2 UNITS PER KIT

The major improvements for the IN naloxone over currently off-label use 2 mg/2mL Naloxone injection are:

- a volume that is significantly lower than that of the current formulation, minimizing medication loss during administration;

- a concentration that is higher than the current formulation achieving optimal systemic exposure in the first thirty (30) minutes after administration;
- allows for effective delivery into one nostril for IN naloxone in comparison to 2 nostrils used in off-label delivery;
- configure in a two pack kit to eliminate the need to have multiple individual units on hand.

3. EFFICACY EVALUATION

3.1 OPTIMAL EFFECTIVE INITIAL DOSE CONSIDERATIONS

3.1.1 505(b)(2) Application

A 505(b)(2) regulatory pathway referencing the Agency's previous findings of safety and effectiveness for Narcan (NDA 016636) is appropriate for a IN naloxone application. As Narcan is no longer marketed, the approved generic products to Narcan listed in the Orange Book could be used as the comparator.

3.1.2 Pharmacokinetics Standard

Studying naloxone products poses significant ethical challenges. It is not ethical to conduct an efficacy study in the setting of opioid overdose using an unapproved route of administration for naloxone when life-saving, already-approved products are available. Nor would it be ethical to intentionally overdose subjects with opioids in a controlled setting. Therefore, a pharmacokinetic standard in healthy volunteers need to be met to demonstrate the safety and effectiveness of their product.

This standard set forth by FDA is based on the life-saving nature of the therapy in the setting of an opioid overdose in the community, the known efficacy of naloxone by the intramuscular and subcutaneous routes of administration, and the relatively wide safety margin for naloxone.

A pivotal comparative bioavailability study should be required for the approval. The bioequivalence method should be used to analyze the pharmacokinetic data between the final to-be-marketed product and the comparator in the proposed PK study.

3.2 FACTORS FOR CONSIDERATION FOR STUDY DESIGN OF CLINICAL TRIALS

The primary purpose for clinical studies designed in any IN naloxone application is to provide a scientific bridge from the Agency's previous findings of efficacy and safety for Narcan (NDA 016636) to the proposed formulation.

Pharmacokinetic (PK) studies should be conducted to establish the pharmacokinetic and safety/tolerability of the proposed intranasal product. The PK studies should be randomized, evaluator or double-blinded, crossover studies conducted in healthy adult volunteers.

The PK parameters which characterize the IN naloxone efficacy and safety must be compared between IN deliveries of IN naloxone and IM injection of Naloxone HCl as a "comparator".

Two (2) approved generic products for naloxone injection:

- Hospira's Naloxone HCl 0.4mg IM; and
- Amphastar/IMS' Naloxone 2.0mg IM

are recommended to be used in these studies as the reference product for efficacy and safety, respectively.

A wide range of doses and volumes of intranasal naloxone should be investigated.

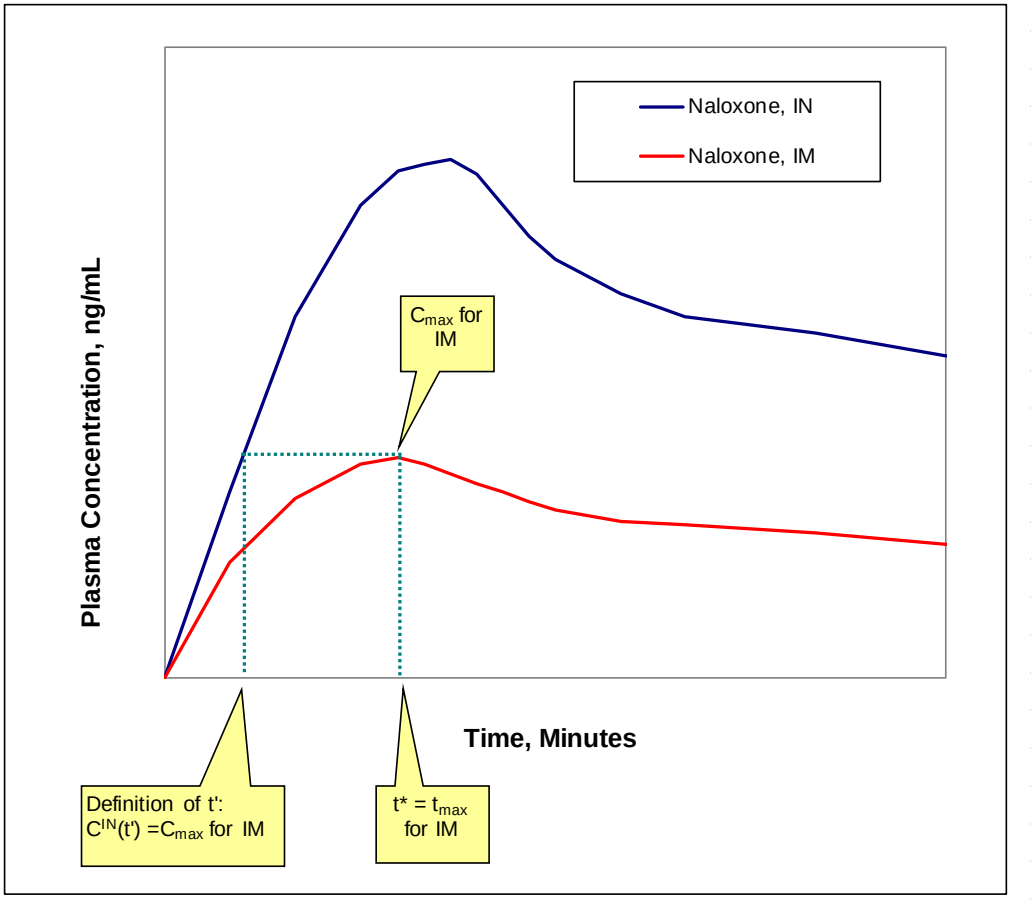
3.2.1 The Definition of *t** and *t'*

FDA has set forth the pharmacokinetic approach as a path to develop naloxone products intended for use in the community settings.

The proposed product must achieve comparable or higher naloxone concentration as the reference product, naloxone 0.4 mg by IM, at the t_{max} of the reference product. In addition, it was advised by the FDA that there should not be a delay in onset of action of the proposed product as compared to the reference product.

In light of these considerations, the concept of ***t**** and ***t'*** were defined (see **Figure 1**) to compare the efficacy and onset of action between a proposed IN naloxone product and the IM reference.

Figure 1 Definition of t* and t' Used for IN Naloxone Efficacy Evaluation



3.2.2 Efficacy Endpoints

The efficacy endpoints of the clinical studies should include:

- ***AUC*$_{0\text{-}t^*}$**, (where $t^* = t_{max}^{IM}$ for IM treatment, 0.4mg), defined as the area under the curve (AUC) in the plot of plasma Naloxone concentrations versus time from time 0 to the ***t_{max}*** of 0.4 mg of Naloxone delivered by IM;

- ***t'***, defined as the time when the plasma Naloxone concentration of a given IN treatment first reaches the peak plasma Naloxone concentration (***C_{max}***) of the IM treatment of 0.4 mg.

AUC_{0-t^*} and ***t'*** which characterize the efficacy and the time of onset of efficacy for IN naloxone, respectively.

3.2.3 Statistical Analysis for Efficacy in Studies

Based on the FDA Bioequivalence guidance, for endpoints AUC 0-t*, the statistical hypothesis to be tested should be:

$$H_{01}: \mu_T - \mu_{C1} \leq \theta_1 \quad (1a)$$

vs.

$$Ha1: \theta 1 < \mu T - \mu C1 \quad (1b)$$

where μT is mean of logarithms of PK endpoints for IN treatment, and μC1 is mean of logarithms of PK endpoints for IM treatment (0.4 mg) and θ1 = -0.223

For endpoints t', the following hypotheses should be tested:

$$H02: \mu T - \mu C1 \geq \theta 2 \quad (2a)$$

vs.

$$Ha2: \mu T - \mu C1 < \theta 2 \quad (2b)$$

where μT is mean of logarithms of PK endpoints for IN treatment, and μC1 is mean of logarithms of PK endpoints for IM treatment, and θ2=0.223

For each 2 × 2 crossover IN/IM treatment pair, the geometric mean ratio of the PK parameters (T/C, i.e. IN/IM) and its 90% confidence intervals (CI) should be computed.

For the purpose of evaluation of efficacy endpoints, for any IN treatment, if:

(i) the lower bound of 90% confidence interval (LCI) of the ratio of geometric mean of IN naloxone to IM (0.4mg) for ***AUC_{0-t^*}*** are greater than 80%, which indicates that the null hypothesis H_{01} is rejected; and

(ii) the upper bound of 90% confidence interval (UCI) of the ratio of geometric mean of IN naloxone to IM (0.4 mg) for ***t'*** is less than 125%, which indicates that the null hypothesis H_{02} is rejected.

The criteria for efficacy evaluation of the PK endpoints are summarized in **Table 1**.

Table 1 Criteria to Reject the Null Hypothesis

PK Endpoints			Hypothesis	
#	Parameters	Evaluation for	Null	Alternative
1	$AUC_{0\text{-}t^*}$	Efficacy	H_{01} : LCI ≤80%	H_{a1} : LCI >80%
2	t'	Onset Time of Efficacy	H_{02} : UCI ≥125%	H_{a2} : UCI <125%

3.2.4 Partial AUC

It is anticipated that during actual use of IN naloxone, most of the opioid overdose victims will be at a severe and critical state. The more naloxone delivered into the blood system in a short time period after administration, the greater possibility that the victims can be reversed and survive the overdose.

The $AUC_{0\text{-}t}$ at a series of time points (with intervals of 5 minutes or less) within the first 30 mins should be calculated. The 90% confidence intervals (CI) of ratios of geometric mean of IN treatments to the efficacy reference (0.4 mg by IM) at each time point should be statistically evaluated.

There should be higher systemic exposure, measured by $AUC_{0\text{-}t}$, achieved during the first 30 minutes after IN delivery for ≥2.0 mg than IM administration 0.4 mg, the efficacy RLD.

3.3 EFFICACY RESULTS AND OPTIMAL DOSE CONSIDERATIONS

The PK studies should demonstrate that:

(i) The proposed IN naloxone treatment delivers a dose that meets the efficacy criteria (90% LCI of geometric mean ratio for $AUC_{0\text{-}t^*}$ >80% and 90% UCI of geometric mean ratio for t' <125%, IN naloxone vs. IM Naloxone 0.4mg);

(ii) The proposed IN naloxone treatment delivers a dose that meets the safety criteria (90% UCI of geometric mean ratio for $AUC_{0\text{-}\infty}$ <125%, IN naloxone vs. IM Naloxone 2.0mg).

3.4 FACTORS INVESTIGATED IN THE PK STUDIES

3.4.1 Dose Range Response

Multiple doses using the same delivery condition should be conducted to determine the dose range response.

3.4.2 Influence of Concentration

Multiple concentrations using the same delivery condition should be conducted to determine the influence of concentration on the delivery and efficacy evaluation.

3.4.3 Bridging Study Comparing to the IMS Naloxone Injection (2mg/2mL)

The IMS naloxone injection (2mg/2mL) has been used off-label for several years. Various state agencies have reported positive feedback from first responders using this product. To assure any proposed IN naloxone is safe and effective, a bridging study should be performed comparing the proposed product with IMS naloxone injection (2mg/2mL).

The appropriate dose of IN Naloxone should be determined in a PK study that demonstrates the following results, characterized by partial time AUC as described above:

"Partial AUC of Proposed dose IN Naloxone $\geq$ IMS Naloxone 2mg/2mL by IN
$\geq$ Naloxone 0.4 mg by IM "

where " $\geq$ " means that the lower 90% confidence interval should be greater than 80%.

3.4.4 Subject Head/Neck Position during IN naloxone Delivery

The effect of head/neck position of IN naloxone administration should be evaluated in at least one PK Study. Treatments should incorporate the same formulation/concentration, administered at the same volume, in the same supine body position and same dose in one

nostril, but at different head/neck positions: one dosed with the head tipped back at an approximate 45° angle, and the other administered in a horizontal neck position.

The PK data should demonstrate that both head/neck position delivers a dose that meets the efficacy criteria (90% LCI of geometric mean ratio for AUC0-t* >80% and 90% UCI of geometric mean ratio for t' <125%, IN naloxone vs. IM Naloxone 0.4mg);

3.4.5 Delivery Volume

There is a concern that administering a large volume of liquid into the nostrils may result in dripping out or oral ingestion, both of which would lead to reduced absorption. A wide range of different volumes of the proposed IN naloxone at (i) same dose, (ii) same delivery positions, and (iii) same number of nostril should be examined for the effect of delivered volume on efficacy per $AUC_{0\text{-}t^*}$.

3.4.6 Number of Nostrils Used During Administration

The effect of administering the same total dose and volume through 1 or 2 nostrils is recommended for evaluation.

IN delivery of the same dose with the same total volume, but under two different delivery conditions: (i) through two nostrils, and (ii) through one nostril, should result in comparable plasma naloxone exposure, represented by $AUC_{0\text{-}t^*}$.

4. SAFETY EVALUATION

4.1 SAFETY EVALUATION PLAN

The overall safety evaluation plan for the proposed IN naloxone should include evaluating data regarding:

(i) drug exposure evaluation;
(ii) safety evaluation of the total systemic exposure through PK parameters;
(iii) adverse drug events (ADE) summary and analysis;
(iv) tolerability evaluations including scores of Nasal and Oropharyngeal Mucosa Exam, Subject Symptom Self-Assessment and Investigator Assessment Findings;
(v) safety parameters, including vital signs with systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR), and 12-lead ECG;
(vi) clinical lab tests for hematology, clinical chemistry, and urinalysis;
(vii) if the proposed single dose of IN Naloxone is greater than the highest single dose of the currently marketed naloxone injection (2mg), acute withdrawal syndrome should be assessed.

in clinical studies conducted for the proposed IN naloxone.

4.2 TOTAL SYSTEM EXPOSURE

The safety evaluation of the total systemic exposure per PK parameters should be conducted. IMS Naloxone 2mg IM, the highest single dose among the currently marketed naloxone injection, should be used as the reference product for safety.

The safety endpoints to be evaluated should be:

- $AUC_{0-\infty}$, defined as AUC in the plot of plasma naloxone concentrations versus time from time 0 to infinity;
- AUC_{0-6hrs}, defined as AUC in the plot of plasma naloxone concentrations versus time from time 0 to the last sampling point.

The geometric mean ratio of $AUC_{0-\infty}$ and AUC_{0-6hrs} for IN versus IM and its 90% confidence intervals (CI) should be computed. A reduced total systemic exposure of the proposed IN naloxone compared to the IM injection of safety RLD (Naloxone 2.0 mg) should be demonstrated. The proposed IN naloxone treatment should deliver a dose that meets the

safety criteria (90% UCI of geometric mean ratio for AUC0-∞ <125%, IN naloxone vs. IM Naloxone 2.0mg), indicating the lower total systemic exposure.

4.3 ADVERSE EVENTS

Overall, it should be demonstrated that the IN naloxone treatment has a similar AE profile with that for the naloxone IM. The IN naloxone treatments may demonstrate a higher incidence rate of respiratory system related events as compared to that for the naloxone Injection IM; this observed difference would be likely due to IN route of administration used for IN naloxone.

4.4 LOCAL TOLERABILITY

Local tolerability, including a nasal and oropharyngeal mucosa exam should be conducted in the clinical trials, especially if the concentration of the proposed IN naloxone is more than 10 mg/mL, which is 10 times or more of the highest concentration for the currently distributed naloxone injection (1mg/mL).

4.4.1 Nasal and oropharyngeal mucosa exam

The nasal and oropharyngeal mucosa exam results should be used to support an application, which should include several evaluations.

At each study visit, the data points of local tolerability in each nostril (left and right) should be collected:

- for three (3) nasal regions,
- for each region, three (3) assessments,
- at three (3) time points (baseline, two post-dose).

In addition, data points of local tolerability in the oropharyngeal region should also be collected:

- for four (4) oropharyngeal sub-regions,
- for each region, three (3) assessments
- at three (3) time points (baseline, two post-dose).

4.4.2 Subject Symptom Self-Assessment (SSA) Rate:

The SSA of each study visit should be grade the following three (3) symptoms on a multi-point scale:

- nasal burning or pain,
- the need to blow nose,
- facial pain/pressure.

4.5 VITAL SIGNS AND ECGS

The vital sign and ECG data, including mean, standard deviation and ranges, for each parameter (SBP, DBP and HR for Vital Sign, and QT and QTc for ECG), at each time point for each treatment should be evaluated**.**

Additionally, the changes from the same day baseline, including mean, standard deviation and ranges, for each parameter (ΔSBP, ΔDBP and ΔHR for Vital Sign, and ΔQT and ΔQTc for ECG), at each time point for each treatment should also be evaluated**.**

There should be no significant change of SBP, DBP, HR or QTc prolongation indicating any safety concern in any studies performed.

4.6 CLINICAL LABORATORY DATA

Hematology, clinical chemistry, and urinalysis parameters should be analyzed at the screening visit and at the end of study.

Complete blood count with differential, comprehensive metabolic panel, and urine analysis, including RBC, hemoglobin, hematocrit, and WBC with differential, total proteins, sodium, potassium, chloride, glucose, calcium, CO2, BUN, creatinine, ALP, ALT, AST, bilirubin, etc. should be collected at screening and end of the study for each subject as part of the clinical safety evaluations.

No clinical significant changes from baseline in clinical laboratory parameters (hematology, clinical chemistry, and urinalysis) should be observed.

4.7 ASSESSMENT OF ACUTE WITHDRAWAL SYNDROME

Abrupt reversal of the opioid effects in persons who are physically dependent on opioids can precipitate acute withdrawal syndrome [6].

If the proposed single dose of IN Naloxone is greater than the highest single dose of the currently marketed naloxone injection (2mg), an acute withdrawal syndrome evaluation should be performed.

According to the prescribing information for the FDA approved product of naloxone (Evzio) [6],

> "excessive doses of naloxone hydrochloride in post-operative patients have resulted in significant reversal of analgesia and have caused agitation. Abrupt reversal of opioid effects in persons who were physically dependent on opioids has precipitated an acute withdrawal syndrome. Signs and symptoms have included: body aches, fever, sweating, runny nose, sneezing, piloerection, yawning, weakness, shivering or trembling, nervousness, restlessness or irritability, diarrhea, nausea or vomiting, abdominal cramps, increased blood pressure, tachycardia. In the neonate, opioid withdrawal signs and symptoms also included: convulsions, excessive crying, hyperactive reflexes."

> It has also been reported that following the use of opiates during surgery, excessive dosage of naloxone hydrochloride should be avoided [7]. It may result in excitement, agitation, an increase in blood pressure, and clinically important reversal of analgesia. A reversal of opiate effects achieved too rapidly may induce nausea, vomiting, sweating, tremor, tachycardia, increased blood pressure, seizures, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest, which may result in death [7].

5. RETROSPECTIVE ANALYSIS OF DATA FROM NY AND NJ

5.1 DATA SOURCE: OFF-LABEL USE OF IMS NALOXONE BY FIRST RESPONDERS IN NY/NJ

Naloxone injection (2mg/2mL) is currently being used off-label for intranasal administration by first responders including Emergency Medical Services (EMS) personnel and police officers to reverse opioid overdose in out of hospital or community settings.

A retrospective study evaluating the efficacy and safety of real-world off-label use of naloxone 2mg/2mL (Amphastar/IMS) by first responders in adolescent and adult opioid overdose victims was conducted by Amphastar based on data provided by state agencies in New York (NY) and new Jersey (NJ).

First responders that participated in overdose prevention programs in NY and NJ provided naloxone intranasal usage information using standardized questionnaire forms generated by the state agencies:

- "New York State Public Safety Naloxone Quality Improvement Usage Reports" and
- "NJ Attorney General's Heroin & Opiates Task Force: Naloxone Deployment Reporting Form".

Amphastar is authorized to use these data from NY and NJ to support development of a proposed IN naloxone. These data were obtained from state agencies with oversight from community based overdose prevention programs.

5.2 POPULATIONS: OPIOID OVERAGE POPULATION (OOP)

A total of 1,979 cases were reported during 2014-2015, which comprises the Reported Population (RP).

The number of cases in the treated (TP), evaluable (EP), and opioid overdose (OOP) populations were 1,765, 1,691, and 1,390, respectively, as shown in **Figure 2**.

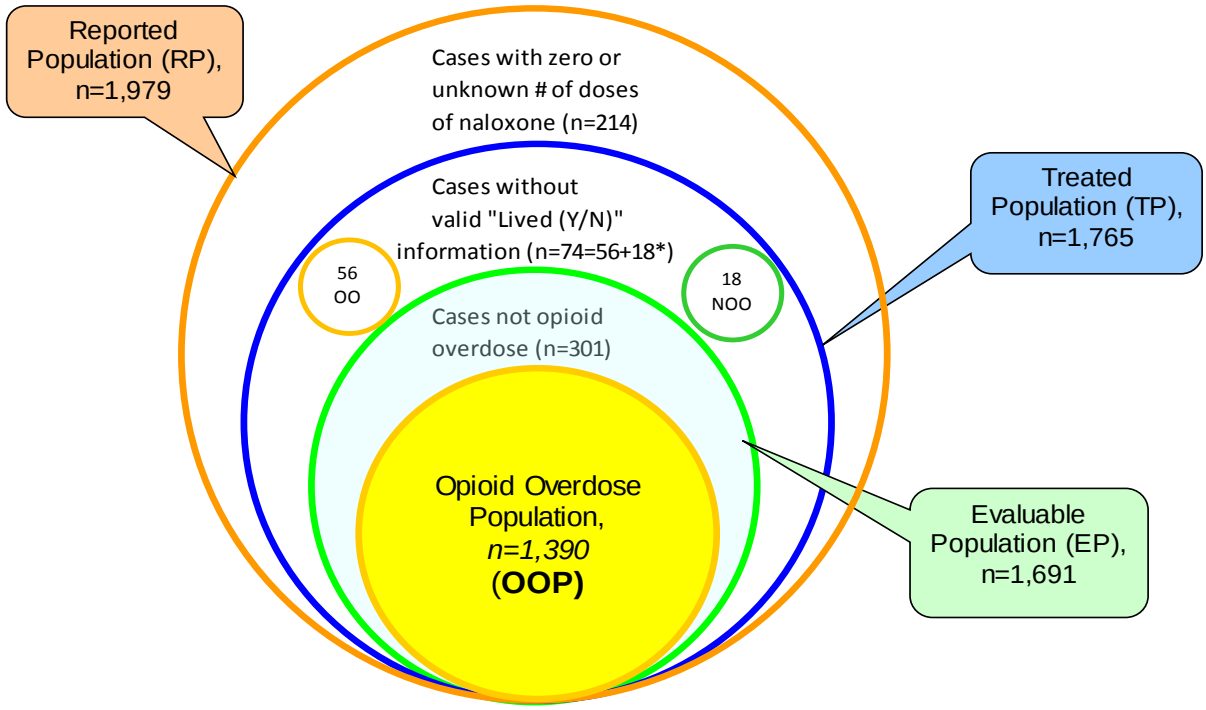
The general information (approximately, depending on populations of RP, TP, EP, and OOP) are as follows,

(1) Gender: 69% of the victims were male and 31% were female;
(2) Age: average age was 31 years old;
    - 80 – 85% were 18 – 64 years;

- 14 – 19% were age unknown or not reported;
- 0.4 – 0.7% were adolescent (i.e., 11-18 years old); and
- 0.3 – 0.7% were ≥65 years.
- In the RP 13 victims were under 18 years.

(3) Race: Most of the overdose victims were Caucasian (58 – 65%). The race for 27-33% victims was unknown.

Figure 2 Populations: RP, TP, EP and OOP



* In TP, 74 cases had no information of "Lived (Y/N)" and were excluded out of EP.
Among these 74 cases, 56 were opioid overdose victims ("OO") and 18 are non-OO ("NOO")

5.3 EFFICACY ASSESSMENT: SURVIVAL RATE AFTER USE IMS NALOXONE BY IN

The efficacy results are summarized in **Table 2**. The data reported by first responders of both NY and NJ States shows that IN administration of IMS' Naloxone (2mg/2mL) for overdose reversal was highly effective with a survival rate of 93.9% for OOP, which was statistically significantly greater than a 90% survival rate with a p-value <0.0001. The efficacy analysis for the two states is shown in **Figure 3**.

Table 2 Efficacy Parameter Analysis

Populations	Treated Population (TP)	Evaluable Population (EP)	Opioid Overdose Population (OOP)
Population Size, (# of Cases)	1,765	1,691	1,390
Primary Endpoint: Survival rate			
Yes (Lived)	1577 (89.3%)	1577 (93.3%)	1305 (93.9%)
No (Died)	114 (6.5%)	114 (6.7%)	85 (6.1%)
Unknown	74 (4.2%)	0 (0.0%)	0 (0.0%)
p-value, SR% > 90% for OOP?	-	-	< 0.0001
Secondary Endpoint: Response Time			
RT ≤ 5min	1115 (63.2%)	1078 (63.7%)	984 (70.8%)
RT > 5min	209 (11.8%)	206 (12.2%)	184 (13.2%)
Not Recorded	192 (10.9%)	177 (10.5%)	119 (8.6%)
Not Applicable	249 (14.1%)	230 (13.6%)	103 (7.4%)
Response Time (data available)			
RT ≤ 5min	1115 (84.2%)	1078 (84.0%)	984 (84.2%)
RT > 5min	209 (15.8%)	206 (16.0%)	184 (15.8%)
# of Doses of Rescue Medication			
mean ± S.D.	1.4 ± 0.6	1.4 ± 0.6	1.4 ± 0.6
# of cases used 1 vial	1180 (66.9%)	1135 (67.1%)	909 (65.4%)
# of cases used 2 vials	551 (31.2%)	524 (31.0%)	452 (32.5%)
# of cases used ≥ 3 vials	34 (1.9%)	32 (1.9%)	29 (2.1%)

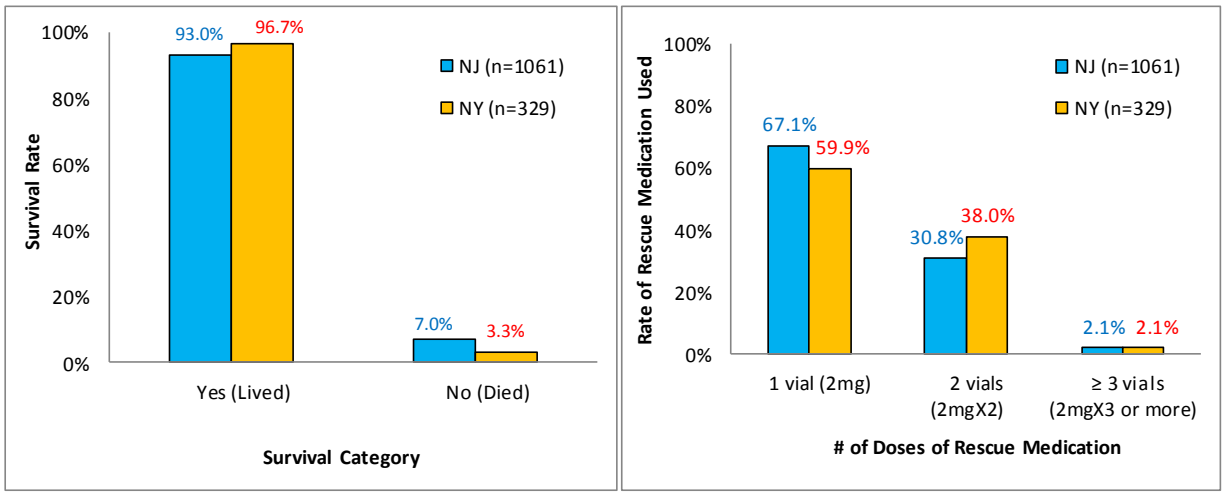
5.4 AVERAGE DOSE USED

It was noted that for all TP, EP and OOP cases, the mean number of units of naloxone administered by IN was 1.4 units (~2.8 mg). Specifically:

- 65 – 67% (approximately two-thirds) of the cases were given one (1) unit (2 mg),
- 31 – 32% (about one-third) of the cases were given two (2) units (4 mg), and
- only about 2% of the cases were given three (3) or more units (≥ 6 mg).

These results, obtained from "actual use" conditions, show that IN delivery with the current IMS' naloxone formulation can be used effectively and safety on opioid overdose victims when administered by first responders, with mostly basic medical training.

Figure 3 Subgroup Efficacy Analysis per State (based on OOP)



5.5 SUBGROUP ANALYSIS

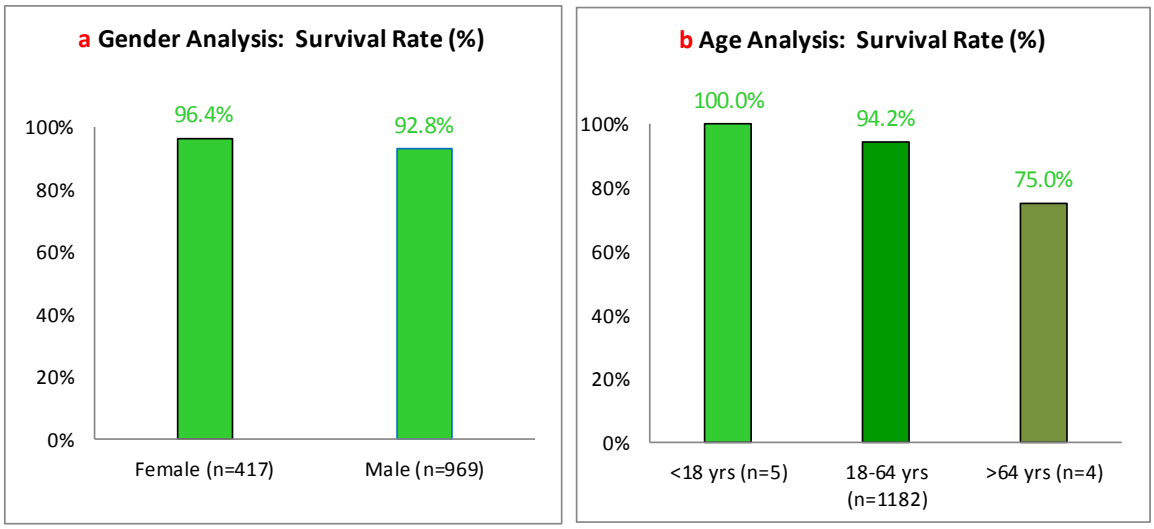
Multiple subgroup analyses were conducted.

5.5.1 Gender

As shown in **Figure 4a**, the survival rate (SR%) for IN administration of IMS' Naloxone for the opioid overdose population (OOP) for both female and male cases were 96.4% and 92.8%, respectively. It was shown that the survival rate of OOP after IN administration is statistically significantly greater than 90% SR for both female and male subgroups, with $p<0.001$ and $p=0.002$, respectively.

Further, the result that the SR% for female subgroup (96.4%, n=417) is greater than that for male subgroup (92.8%, n=969) is statistically significant with a p-value=0.005 for OOP. The reason for this significant result is unknown. It may be due to (i) the gender different reaction to naloxone, or (ii) the actual opioid overdose difference for male and female victims, or (iii) a combination of (i) and (ii), or (iv) other reasons.

Figure 4 Subgroup Analysis of Efficacy: Survival Rate for OOP (Gender & Age)
a. Gender subgroup Analysis; b. Age Subgroup Analysis



5.5.2 Age

As shown in **Figure 4b**, the survival rates (SRs) after IN administration for the opioid overdose (OOP population) for different age subgroups were as follows:

- For age <18 years, the SR was 100% (n=5). However, due to the small sample size, it cannot be concluded that the SR% is statistically significantly greater than 90%.
- For age of 18 – 64 years, the SR was 94.2%. The opioid overdose SR% was statistically significantly greater than 90% for the 18 – 64 year subgroup (n=1,182) with p-value <0.001.
- For age of ≥65 year, the SR was 75.0% (n=4), which is less than 90%.

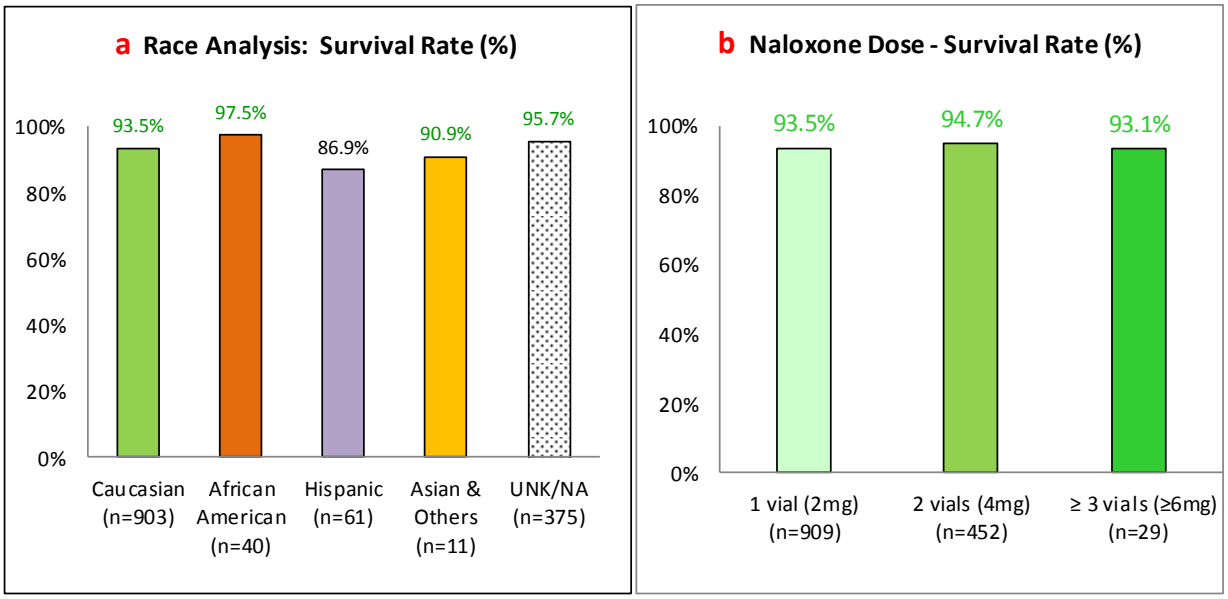
The SR% showed an age-dependent trend, although it cannot be concluded as statistically significant.

5.5.3 Race

As shown in **Figure 5a**, the survival rate after IN administration for the opioid overdose population (OOP) for race subgroups, Caucasian, African American, Hispanic, Asian and Others, and Unknown/NA, were 93.5%, 97.5%, 86.9%, 90.9%, and 95.7%, respectively.

The survival rates after IN administration were statistically significantly greater than 90% for Caucasian and Unknown/NA race groups (p=0.0003 and p=0.0001, respectively).

Figure 5 Subgroup Analysis of Efficacy: Survival Rate for OOP (Race & Dose)
a – Race subgroup Analysis; b. Naloxone Dose Subgroup Analysis



5.5.4 Dose Used

As shown in **Figure 5b**, the survival rate after IN administration for the opioid overdose population (OOP) for subgroups of number of doses, one unit (2 mg), two units (4 mg), or three or more units (≥ 6mg), were 93.5%, 94.7%, and 93.1%, respectively. **Figure 5b** shows that SR% was not sensitive to the number of units used.

5.5.5 Initial Severity Status

Only the case reports received from NY State have the details for the initial overdose severity. Based on the information provided on the reporting document, the initial overdose severity was classified as follows:

- ES = "Extremely severe", if "no breathing" **AND** "no pulse" was observed at the initial scene;
- VS = "Very severe" if "no breathing" **OR** "no pulse" was observed at the initial scene; and
- S = "Severe" if "slow breathing" and/or "slow pulse" or "unresponsive" was observed at the initial scene.

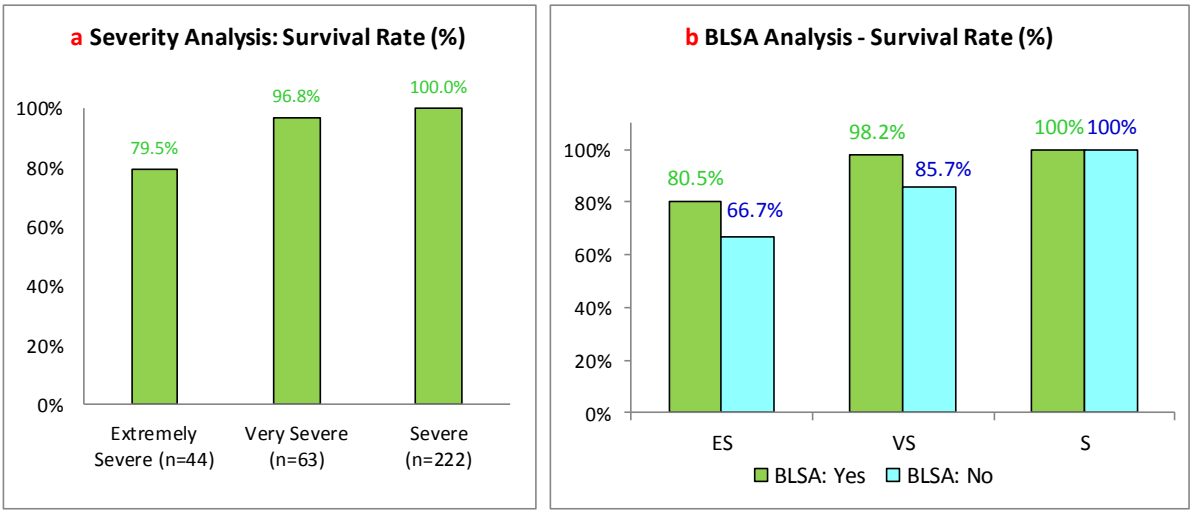
As shown in **Figure 6a**, the survival rate after IN administration for the opioid overdose population (OOP) for subgroups of different initial overdose severities, i.e. extremely

severe (ES), very severe (VS), and severe (S), were 79.5%, 96.8%, and 100.0%, respectively. Except for the extremely severe initial overdose subgroup, the survival rate was statistically significantly greater than 90% for other subgroups with different initial overdose severities. As shown in **Figure 6a**, the SR% was dependent on the initial status of the victims.

5.5.6 Basic Life Support Action (BLSA)

The survival rate after IN administration of IMS' Naloxone for opioid overdose population (OOP) for subgroups without or with BLSA were 90.9% and 97.1%, respectively. As shown in **Figure 6b**, the SR% correlates with the initial severity status of the overdose victims.

Figure 6 Subgroup Analysis of Efficacy: Survival Rate for OOP (Age & BLSA)
a – Severity subgroup Analysis; b. BLSA Subgroup Analysis



A further dual-subgroup analysis, BLSA and initial status, was conducted. Since the initial status data was only available from NY, the sample size for this subgroup analysis is relatively small, 307 – for BLSA "yes" and 22 for BLSA "no", in total 329 subjects (i.e., OOP for the State of NY). The results are summarized in **Figure 6b**.

The subgroup analysis indicated:

- For victims with "ES" initial status, cases with the BLSA showed an increased SR% of 80.5% (n=41) vs.66.7% (n=3) for no BLSA provided;
- For victims with "VS" initial status, cases with the BLSA showed an increased SR% of 98.2% (n=56) vs. 85.7% (n=7) for no BLSA provided; and

- For victims with "S" initial status, with or without BSLA, the SR% was always 100%.

The above increase of SR% due to use of BSLA was not statistically significant, likely due to the limited sample size. However, the results of the subgroup analysis showed a beneficial trend of use of BLSA in the opioid overdose victims with the initial status of "extremely severe" (no pulse and no breathing) and "very severe" (no pulse or no breathing).

5.5.7 Fentanyl Overdose

Fentanyl is used as part of anesthesia to help prevent pain after surgery or other medical procedures. It is one of the strongest opioid drugs on the market.

Fentanyl (or suspected fentanyl) overdoses were identified in eight (8) cases in the analysis. It is noteworthy that all eight victims (i.e. 100%) survived after the naloxone treatment with IMS naloxone (2mg/2mL) through IN delivery.

5.5.8 Profile of Subgroup Analyses

The above subgroup analyses for survival rates provide the following profile:

(1) Un-sensitive Factors:

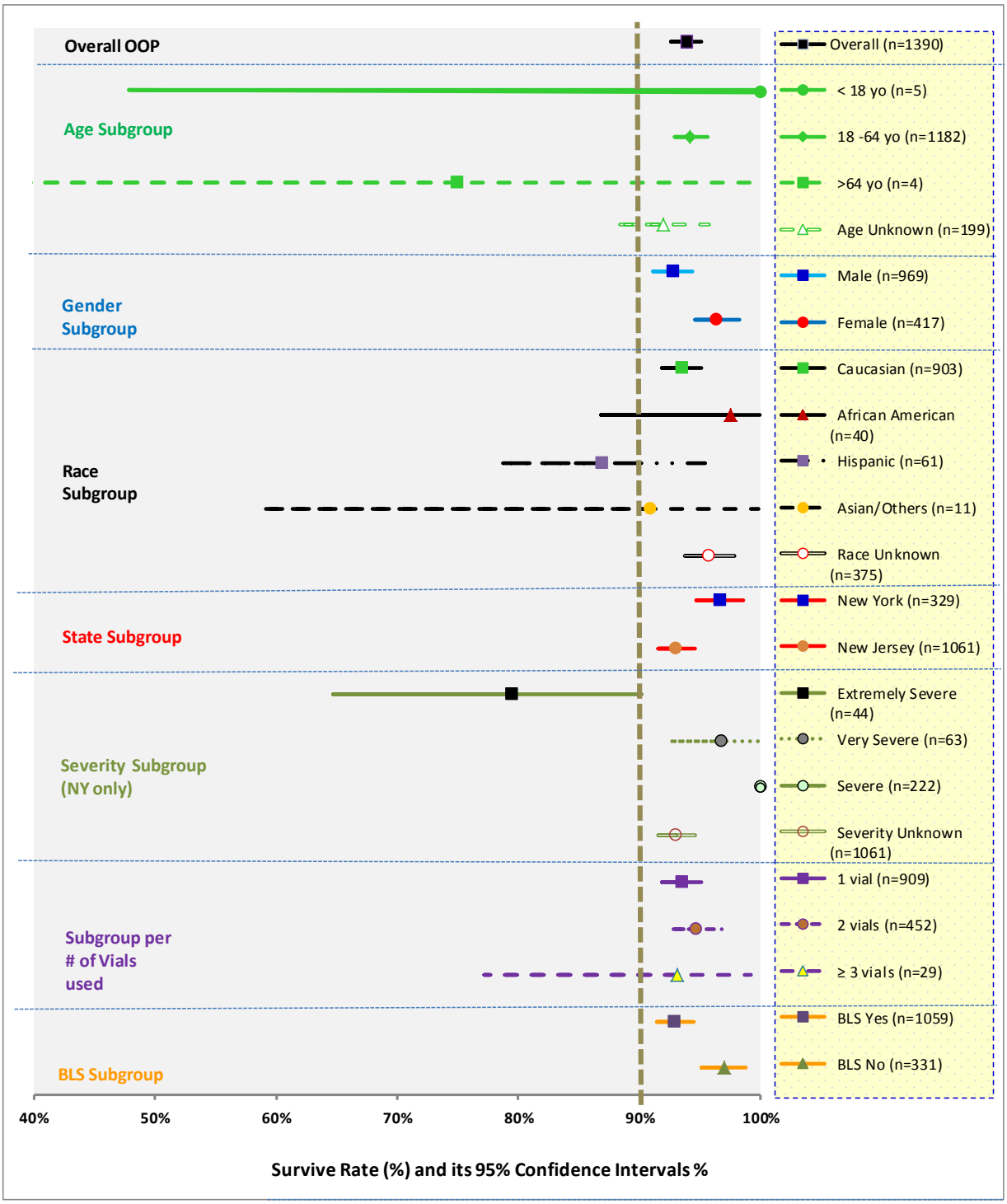
These factors include (i) gender, (ii) race and (iii) units used.

(2) Sensitive Factors:

- Age: a lower survival rate was observed in older victims, however, due to the limited number of cases, no meaningful conclusions can be drawn;
- Initial Severity status: this appears to be an important factor for determining survival rates (see **Section 5.5.5** and **Figure 6a**);
- Use of Basic Life Support Action (BLSA) may be helpful to increase the survival rates.

Figure 7 displays the survival rates and their lower and upper 95% Confidence Intervals of subgroups.

Figure 7 Survival Rates and 95% CIs in Subgroups (based on OOP)



5.6 MORTALITY EVALUATION

Among the 1,765 victims in the treated population (TP), 1,691 had their survival status available (Evaluable Population, EP). There were 114 deaths reported (i.e., 6.7%).

The majority of victims (98%) received one or two vials of naloxone via IN administration. Due to the large safety margin of naloxone established from extensive clinical experience, these deaths were unlikely attributable to the treatment.

The mortality in those identified as "Non-Opioid" Overdose victims was significantly higher than that in the OOP group (9.6% vs 6.1%). Importantly, no one with signs of heartbeat and breathing at the initial scene died in the OOP population.

6. LABELING/HUMAN FACTORS VALIDATION

6.1 LABEL AND INSTRUCTION FOR USE (IFU)

The product is intended to be used in various non-healthcare settings. In interviews with police officers experienced in off-label use of an inhaled nasal product, these applications include inside of a house (such as bedrooms or bathrooms), outside (alleys, parking lots) and numerous other "field settings", such as inside of a car. Therefore the product design and Instructions for Use (IFU) should be targeted for use in emergency situations.

There are two main intended user populations for this combination product. The first population includes Lay Responders (e.g. a parent, friend, or other family member of a known or suspected opioid overdose victim) who would be the person responsible for administering the dose to the patient. The second population includes First Responders (e.g. firefighters, paramedics, emergency medical technicians, or police officers) who would be responsible for administering the dose if no one had been able to do so at the time the first responders arrive at the scene. Therefore the product design and IFU must be demonstrated to be understood by generally non-medically trained responders.

In order to assure naïve user comprehension, the IFU should be evaluated in a simulated use validation study in accordance with the FDA Human Factors Draft Guidance to Industry[4].

6.2 HUMAN FACTORS STUDY DESIGN

The main objectives of the validation study should be to:

- Validate whether the device, labeling, and associated instructions, can be correctly, safely, and effectively used by the intended user populations (Lay Responders and First Responders).
- Determine if specific aspects of the device, labeling and/or Instructions for Use will lead to any patterns of high risk use errors when used by the intended user populations. Successful validation will be demonstrated by the absence of any preventable patterns of use failure or difficulties with the procedure.

The following items should be included as the major characteristics of the human factors study.

6.2.1 Study Population

The study should include the two main intended user populations for this device. The first population, Lay Responders and the second population, First Responders.

The study should include healthy adults and adolescents (i.e. 15 – 17 year old) as Lay Responders and actual First Responders to represent these populations. As such, this design will validate the device and instructions with the actual user population for whom the device has been designed.

The participants should consist of individuals who have no experience with the device. Thus all users are naïve to the device being studied.

Each group should contain 15 participants, the minimum number of participants based on the FDA human factors guidance that states, *"at least 15 participants from each group should participate in validation testing".*

6.2.2 Level of Training Categories

The study should include both trained and untrained groups in order to test the "learnability" of the device under different learning conditions.

For those who are trained, the unaided trial would occur at a designated time after training to allow for memory decay. When trained participants are in-between sessions, they should not have access to any of the training materials or the IFU. This will test how memorable the device procedure is.

Unaided trials (completely naïve users) should be performed without any instruction from the test moderator. All unaided participants should perform a single unaided trial using a manikin that will be lying on their side on the floor. The unaided trials will thereby represent the most realistic actual use conditions, and provide the most relevant data in support of the appropriate and safe use of the device.

6.2.3 "Stressful" Testing Environment

It is intended that the device will be used in environments such as the home or outdoor setting, where a patient may be found after an opioid overdose. Accordingly, the test

room for the unaided dose administration trials should be set up to simulate a home setting, that is, not a healthcare setting.

All unaided trials should incorporate background sounds to mimic the realistic environment and sounds that users would encounter during a rescue.

6.2.4 Speed of Delivery

The amount of time needed to read the IFU and administer the medication should be short. Users administering the medication should be able to complete the review of the instructions, opening the packaging, and administering the dose within one minute.

6.2.5 Evaluative Measures

Measures should be determined and used to evaluate successful understanding of the IFU. Sample categories of measures could include:

Performance measures, defined as a successful dose administration, with no critical use errors, further defined as a participant assembling the unit without any accidental excess drug expulsion, performing the correct administration procedure with the device, and administering the full dose into the nostril.

Behavioral measures included as indices of excessive effort or frustration, verbal comments made by the participant during the study (when applicable), and their reactions to the device or instructions for use.

Subjective measures should be evaluated. This should be done after performing the dosing procedure using the device, where participants will be asked to provide subjective feedback on various aspects of the procedure. Participants should also provide subjective feedback related to the instructions for use.

6.3 CLASS LABELING

There should be standardized class labeling for all intranasal naloxone products. This class labeling should describe standardized indications, warnings and precautions and any other important safety information, specifically for identifying the signs and symptoms of opioid overdose and handling the victim after administration. For example, consideration should be given to discussion of taking basic life support action (BLSA).

6.4 SINGLE ADMINISTRATION

In order to provide for standardized administration, all products should be provided as a single administration, that is the unit should be administered into one nostril, not

requiring partial administration into multiple nostrils. Should a second dose be required, the package or kit should also contain an identical unit for a second administration.

7. RISK BENEFIT DISCUSSION

7.1 OPIOID OVERDOSE AS A MAJOR PUBLIC HEALTH PROBLEM

Drug-induced deaths have reached a public health crisis level for unintentional mortality. Overdose deaths now exceed automobile accidents as a preventable cause of death in the United States. Opioids, as a class of medications, are responsible for the majority of drug-induced deaths.

7.2 MEDICAL NEED FOR IN NALOXONE

As naloxone injection is primarily delivered through IV, IM or SC administration, it can be difficult to use for most lay people. There has been concern about the potential for accidental needle stick injury and transmission of hepatitis or HIV infection. Therefore, based on the limited availability of alternatives to naloxone injection, an unmet medical need has been identified to have greater availability of user-friendly, needle-free naloxone delivery systems for medical professionals, first responders and at home family member use. The addition of an easy to use product that can meet the public health demand in the context of an opioid abuse epidemic, with little to no associated risk, and with product characteristics ensuring performance reliability would be of great public health benefit.

7.3 IN NALOXONE EFFECTIVENESS IN COMPARISON TO INJECTABLE FORM

The totality of data from studies should demonstrate the efficacy of proposed IN naloxone in "**the complete or partial reversal of opioid depression, including respiratory depression**". In addition, it should be concluded that IN naloxone is generally safe and well-tolerated at multiple dose levels. In the absence of significant safety concerns, the life-saving benefit of Naloxone far outweighs its risk to those facing a life-threatening opioid overdose.

The expected advantages of IN naloxone, compared to naloxone HCl injection are:

- Intranasal administration of naloxone should demonstrate a quicker onset of action and higher systemic exposure.
- Intranasal administration of naloxone is intrinsically easier to use and
- Intranasal administration allows individuals to safely administer the medication without the risk of needle sticks and potential transmission of HIV, hepatitis and other serious illnesses.

The major improvements of IN naloxone over currently off-label used Naloxone HCl Injection can include:

- Smaller volume of dose
- Higher concentration of active ingredient
- Single-nostril delivery
- No need to assemble intranasal tip and
- Convenient two-unit pack configuration for double dosing, if needed

7.4 CONCLUSION

The last few decades have witnessed a tremendous increase in opioid overdose and mortality. IN naloxone can provide a user-friendly, needle-free route of administration for medical professionals, first responders and at home family members and caregivers to address one of the country's most urgent medical needs. The addition of such an easy to use product, that can meet the public health demand in the context of an opioid overdose epidemic, with little to no associated risk, would be of potentially great public health importance.

8. REFERENCES

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