

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212045Orig1s000

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

CLINICAL PHARMACOLOGY REVIEW

NDA or BLA Number	212045
Link to EDR	\\cdsesub1\evsprod\NDA212045
Submission Date	4/30/19
Submission Type	Standard
Brand Name	TBD
Generic Name	Naloxone Hydrochloride Nasal Spray 8 mg
Dosage Form and Strength	Solution in pre-filled intranasal device; 8 mg per spray in 0.1 mL
Route of Administration	Intranasal
Proposed Indication	• Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression in adults and pediatric patients. • Immediate administration as emergency therapy in settings where opioids may be present. • It is not a substitute for emergency medical care.
Applicant	Hikma Pharmaceuticals USA Inc. (acquired ownership from Insys Development Company, Inc. on 8/29/19)
Associated IND	IND 134954
OCP Review Team	Wei Qiu, PhD., Yun Xu, MD, PhD.

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1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Neuropsychiatric Pharmacology (OCP/DNP) has reviewed the NDA 212045 submission dated 4/30/19 and finds it acceptable from clinical pharmacology perspective.

1.2 Summary of Clinical Pharmacology Findings

Key Clinical Pharmacology Findings:

1. In two comparative bioavailability studies, a single dose of Naloxone Nasal Spray 8 mg containing 20% alcohol (the final to-be-marketed formulation) exhibits comparable median T_{max} (15 min), greater unconjugated naloxone concentrations at all time points including earlier time points (i.e., 2, 4, 6, 8, 10 min post-dose), 14-fold greater C_{max} and 10-fold greater AUC_{last} or AUC_{0-inf} values than a single dose of 0.4 mg intramuscular (IM) injection, which is within the approved initial dose range (i.e., 0.4 to 2 mg) for the listed drug Narcan Injectable. The relative bioavailability of Naloxone Nasal Spray 8 mg containing 20% alcohol is 41.6 – 47.4% in comparison to an IM injection based on dose normalized exposure.
2. A single dose of Naloxone Nasal Spray 8 mg containing 20% alcohol exhibits an unconjugated naloxone C_{max} value of 12.8 ng/mL, which is lower than the unconjugated naloxone concentration at 2 min post-dose (26.2 ng/mL) for a

single dose of the listed drug Narcan Injectable at 2 mg IV injection. The corresponding AUC_{last} and AUC_{0-inf} values for Naloxone Nasal Spray 8 mg containing 20% alcohol are 42% and 48% greater than the 2 mg IV injection, respectively. The absolute bioavailability is 36.6% for the Naloxone Nasal Spray 8 mg containing 20% alcohol in comparison to an IV injection based on dose normalized exposure.

Summary

Naloxone HCl has been approved for IV, IM, SC, and IN administration. The sponsor developed a higher strength of naloxone hydrochloride in prefilled intranasal device (8 mg per spray in 0.1 mL containing 20% alcohol) for IN administration for the emergency treatment of known or suspected opioid over dosage, as manifested by respiratory and/or central nervous system depression. Another formulation for intranasal spray with a higher concentration of alcohol (8 mg per spray in 0.1 mL containing (b) (4)% alcohol) was also evaluated during the drug development process. However, the sponsor is not planning to market the formulation containing (b) (4)% alcohol.

The clinical/clinical pharmacology database supporting this NDA consists of two comparative bioavailability studies (Study INS012-17-108 and Study INS012-18-119). In Study INS012-17-108, a single dose of Naloxone Nasal Spray 8 mg containing 20% or (b) (4)% alcohol were compared with a single dose of 0.4 mg IM injection. In Study INS012-18-119, a single dose of Naloxone Nasal Spray 8 mg containing 20% or (b) (4)% alcohol were compared with a single dose of 0.4 mg IM injection and 2 mg IV injection. The final to-be-marketed product (formulation and device) of Naloxone Nasal Spray 8 mg containing 20% alcohol was used in both comparative bioavailability studies. Because the approved initial dose of Narcan injectable is from 0.4 mg to 2 mg in adults and rapid onset of action is critical for reversal of opioid overdose, the sponsor conducted these comparative bioavailability studies to demonstrate that Naloxone Nasal Spray 8 mg would provide comparable or higher naloxone exposure (e.g., C_{max}, AUC_{last}, and AUC_{0-inf}), and comparable or higher exposure during the early absorption phase (e.g., naloxone concentrations at 2 to 5 min post-dose) in comparison to the reference product at the tested dose of 0.4 mg via IM injection. In addition, the comparison with a 2 mg IV

injection was to, in part, support the systemic safety of the naloxone exposures achieved with their proposed naloxone nasal spray 8 mg.

Comparative Bioavailability of Naloxone Nasal Spray 8 mg containing 20% alcohol in Comparison to 0.4 mg IM Injection:

A single dose of Naloxone Nasal Spray 8 mg containing 20% alcohol exhibited greater unconjugated naloxone concentrations at all timepoints including earlier time points (e.g., 2, 4, 6, 8, 10 min) (**Figure 1** and **Table 1**). Median T_{max} values (15 min) were similar. The relative bioavailability of Naloxone Nasal Spray 8 mg containing 20% alcohol is 41.6 – 47.4% in comparison to the IM injection based on dose normalized exposure (**Table 2**). Naloxone Nasal Spray 8 mg containing 20% alcohol shows approximately 14-fold greater unconjugated naloxone C_{max} and 10-fold greater unconjugated naloxone AUC_{last} or AUC_{0-inf} values than a single dose of 0.4 mg IM injection. In Study INS012-17-108, the point estimates of the geometric mean ratio (Naloxone Nasal Spray 8 mg containing 20% alcohol/0.4 mg IM injection) for unconjugated naloxone C_{max} , AUC_{last} and AUC_{0-inf} were 1320%, 971%, and 847%, respectively. The corresponding 90% confidence intervals (CIs) were 1100 - 1580%, 864 - 1090%, and 742 - 967%, respectively. In Study INS012-18-119, the point estimates of the geometric mean ratio (Naloxone Nasal Spray 8 mg containing 20% alcohol/0.4 mg IM injection) for unconjugated naloxone C_{max} , AUC_{last} and AUC_{0-inf} were 1400%, 961%, and 958%, respectively. The corresponding 90% confidence intervals (CIs) were 1130 - 1750%, 861 - 1070%, and 865 - 1060%, respectively (**Table 3**).

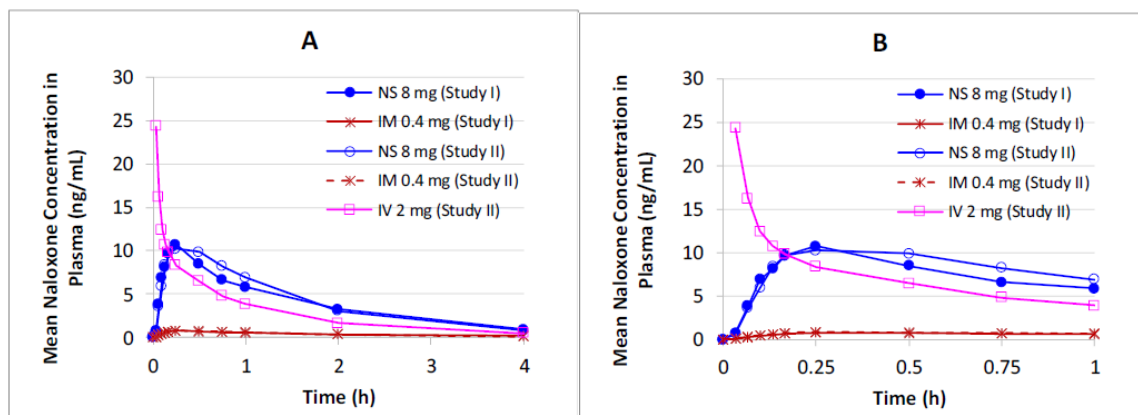


Figure 1 Mean Plasma Concentration Profiles of Unconjugated Naloxone Following a Single Dose of Naloxone Nasal Spray 8 mg Containing 20% Alcohol (NS 8 mg) versus 0.4 mg IM Injection (IM 0.4 mg) and 2 mg IV Injection (IV 2 mg) in Healthy Subjects (Panel A: 0 – 4 h and Panel B: 0 – 1 h) (Studies INS012-17-108 [Study I] and INS012-18-119 [Study II])

Table 1 Mean (SD) Unconjugated Naloxone Plasma Concentrations at Early Time Points for a Single Dose of Naloxone Nasal Spray 8 mg Containing 20% Alcohol and a Single Dose of 0.4 mg IM Injection

Timepoint (min)	Mean (SD) (min, max) Unconjugated Naloxone Plasma Concentration (ng/mL)			
	Study INS012-17-108 (n = 24)		Study INS012-18-119 (n = 23)	
	Naloxone Nasal Spray 8 mg Containing 20% Alcohol	0.4 mg IM Injection	Naloxone Nasal Spray 8 mg Containing 20% Alcohol	0.4 mg IM Injection
2	0.725 (0.666) (0.0112, 2.35)	0.0527 (0.06) (0.00, 0.0287)	0.635 (0.735) (0.0301, 2.74)	0.0734 (0.0859) (0.00, 0.0525)
4	3.84 (3.48) (0.191, 12.9)	0.241 (0.228) (0.0129, 1.07)	3.58 (3.49) (0.323, 13.7)	0.263 (0.194) (0.238, 0.838)
6	6.87 (5.63) (0.489, 21.1)	0.420 (0.270) (0.0444, 1.05)	5.87 (4.26) (1.04, 15.6)	0.455 (0.261) (0.0966, 1.19) ^a
8	8.07 (6.43) (0.75, 23.4)	0.547 (0.336) (0.113, 1.38)	8.32 (5.08) (1.97, 25.3)	0.573 (0.338) (0.201, 1.77) ^a
10	9.64 (6.40) (1.57, 25.2)	0.660 (0.344) (0.187, 1.56)	9.68 (4.67) (3.25, 20.6)	0.690 (0.304) (0.217, 1.77)
15	10.7 (6.87) (2.64, 33.4)	0.792 (0.321) (0.367, 1.58)	10.2 (4.52) (3.66, 18.9)	0.826 (0.348) (0.309, 2.04)

^a: n = 21

Source: Study INS012-17-108 Report Table 14.4.1.1 and Study INS012-18-119 Report Table 14.4.1.1

Table 2 Mean (%CV) [Geometric Mean] Plasma PK Parameters of Unconjugated Naloxone Following a Single Dose of Naloxone Nasal Spray 8 mg Containing 20% Alcohol, 0.4 mg IM Injection, and 2 mg IV Injection in Healthy Subjects (Study I: INS012-17-108 and Study II: INS012-18-119)

Parameter	Naloxone Nasal Spray 8 mg		0.4 mg IM Injection		2 mg IV Injection
Study	Study I	Study II	Study I	Study II	Study II
N	24	23 ^a	24	23 ^a	24
T _{max} (h) ^b	0.25 (0.10 – 1.00)	0.25 (0.10 – 1.00)	0.25 (0.13 – 1.00)	0.25 (0.10 – 1.00)	NA
C _{max} (ng/mL)	12.3 (55.4) [10.9]	12.8 (37.0) [12.0]	0.876 (36.7) [0.821]	0.910 (36.8) [0.857]	26.2 (82.4) [20.8] ^f
AUC _{last} (ng•h/mL)	18.0 (29.6) [17.2]	18.4 (33.4) [17.4]	1.82 (24.0) [1.77]	1.87 (24.7) [1.81]	12.7 (27.6) [12.3]
AUC _{0-inf} (ng•h/mL)	16.7 (31.9) [15.9] ^c	19.0 (32.7) [18.0] ^d	1.94 (20.9) [1.91] ^e	1.95 (21.9) [1.90]	12.8 (27.5) [12.3]
t _{1/2} (h)	2.69 (69.9) [2.24] ^c	1.76 (39.7) [1.66] ^d	1.41 (20.0) [1.38] ^e	1.40 (38.9) [1.34]	1.22 (16.4) [1.21]
Dose Normalized Relative BA vs IM Injection (%) ^g	41.6	47.4	100	100	NA
Dose Normalized Absolute BA vs IV Injection (%) ^h	NA	36.6	NA	77.2	100

NA= Not applicable

^a N=23 due to one subject withdrawal. ^b Tmax reported as median (minimum - maximum). ^c N=15, ^d N=19, ^e N=22 for AUC_{0-inf} and t_{1/2}. ^f Cmax of 2 mg IV injection was observed value from the first sampling time of 2 minutes post-dose.

^gDose normalized relative BA vs IM injection (%) = (Geometric mean AUC_{0-inf} of test formulation/dose) / (Geometric mean AUC_{0-inf} of reference formulation/dose) × 100%, representing relative bioavailability of the test Naloxone Nasal Spray formulations compared to the reference formulation 0.4 mg IM injection

^hDose normalized absolute BA vs IV injection (%) = (Geometric mean AUC_{0-inf} of extravascular formulation/dose) / (Geometric mean AUC_{0-inf} of IV formulation/dose) × 100%, representing absolute bioavailability of the test Naloxone Nasal Spray and the IM formulations compared to the IV formulation

Source: Study INS012-17-108 Report Table 14.4.2.1; Study INS012-18-119 Report Table 14.4.1.3

Table 3 Geometric Mean Ratios (90% CI) for Comparisons of Unconjugated Naloxone Cmax, AUClast, and AUC0-inf Following a Single Dose of Naloxone Nasal Spray 8 mg Containing 20% Alcohol vs 0.4 mg IM Injection or 2 mg IV Injection in Healthy Subjects

Study	PK Parameters	Naloxone Nasal Spray 8 mg Containing 20% Alcohol vs 0.4 mg IM injection	Naloxone Nasal Spray 8 mg Containing 20% Alcohol vs 2 mg IV injection
INS012-17-108	Cmax (%)	1320 (1100-1580)	NA
	AUClast (%)	971 (864-1090)	
	AUC0-inf (%)	847 (742-967)	
INS012-18-119	Cmax (%)	1400 (1130-1750)	57.6 (46.2-71.6)
	AUClast (%)	961 (861-1070)	142 (127-158)
	AUC0-inf (%)	958 (865-1060)	148 (133-163)

Source: summary-biopharm Table 7 and Table 12

Absolute Bioavailability of Naloxone Nasal Spray 8 mg Containing 20% Alcohol in Comparison to 2 mg IV Injection:

The absolute bioavailability of Naloxone Nasal Spray 8 mg containing 20% alcohol is 36.6% based on dose normalized exposure (**Table 2**). The Cmax of unconjugated naloxone for a single dose of Naloxone Nasal Spray 8 mg containing 20% alcohol is 12.8 ng/ml, which is lower than the unconjugated naloxone concentration at 2 min post-dose for the single dose IV injection of 2 mg naloxone (i.e., C2 min of 26.2 ng/mL). The corresponding AUClast and AUC0-inf values for Naloxone Nasal Spray 8 mg containing 20% alcohol is approximately 42 and 48% greater than a single 2 mg IV injection, respectively (**Table 3**). The point estimates of the geometric mean ratio (Naloxone Nasal Spray 8 mg Containing 20% Alcohol/2 mg IV injection) for unconjugated naloxone Cmax, AUClast and AUC0-inf were 57.6%, 142%, and 148%, respectively. The corresponding 90% confidence intervals (CIs) were 46.2 – 71.6%, 127 - 158%, and 133 - 163%, respectively (**Table 3**).

2 QBR

2.1 *What pertinent regulatory background or history contribute to the current assessment of the clinical pharmacology of this drug product?*

Narcan injectable (NDA 16636) was approved for emergency treatment of known or suspected opioid overdose to reverse central nervous system depression and restore respiration. In adults with opioid overdose, an initial dose of 0.4 mg to 2 mg of Narcan may be administered via IV route. IM or SC administration may be necessary if the IV route is not available. Narcan injectable (NDA 016636) has been discontinued but not for efficacy or safety reason. Generic naloxone injectable products are commercially available. Naloxone is also available as a prefilled autoinjector (Evzio, NDA 209862) at a dose of 2 mg for IM or SC administration. Narcan nasal spray (4 mg/spray) is approved under NDA 208411 for intranasal administration and has relative bioavailability of 44.2% in comparison to an IM injection based on dose normalized exposure. The sponsor developed a higher strength of naloxone hydrochloride as Naloxone Nasal Spray 8 mg in a pre-filled intranasal device designed to deliver a single spray of 8 mg of naloxone HCl in 0.1 mL solution intranasally.

On 4/30/19, the sponsor submitted a 505(b)(2) NDA 212045 to rely on the agency's previous finding of safety and effectiveness of the identified list drug product, approved drug product Narcan injectable, NDA 016636. Two comparative bioavailability study (INS012-17-108 and INS012-18-119) were submitted to support their 505(b)(2) NDA. Because Narcan injection (NDA 016636) is discontinued but not because of safety or efficacy reasons, the sponsor conducted the comparative bioavailability studies using Hospira Inc's ANDA 070256 Naloxone HCl injectable product (0.4 mg/mL) given as 1 mL IM injection and International Medication System's ANDA 072076 naloxone HCl injectable product (1 mg/mL) given as 2 mL IV injection as comparators to establish PK bridging. Both ANDA 070256 and ANDA products are listed as reference standard in the orange book. This approach of using generic products to the original NDA was deemed acceptable per Type C meeting minutes dated 2/22/18 under IND 134954. Because the approved initial dose of Narcan injectable is from 0.4 mg to 2 mg in adults and rapid onset of action is critical for reversal of opioid overdose, the sponsor conducted these comparative bioavailability studies to demonstrate that Naloxone Nasal Spray 8 mg would provide comparable or higher naloxone exposure (e.g., C_{max}, AUC_{last}, and

AUC_{0-inf}), and comparable or higher exposure during the early absorption phase (e.g., naloxone concentrations at 2 to 5 min post-dose) in comparison to the reference product at the tested dose of 0.4 mg via IM injection. In addition, the comparison with a 2 mg IV injection was to, in part, support the safety of the naloxone exposures achieved with their product.

The final to-be-marketed product was used in these comparative bioavailability studies INS012-17-108 and INS012-18-119. OSIS declined to conduct inspections on both the clinical and analytical sites for both studies because inspections are not warranted based on their previous inspection.

2.2 What is the comparative bioavailability of naloxone following the administration of a single dose of Naloxone Nasal Spray 8 mg Containing 20% alcohol intranasally in comparison to 0.4 mg IM injection?

Study INS012-17-108 was an open-label, randomized, single-dose, 3-treatment crossover bioavailability study comparing two test formulations of Naloxone Nasal Spray 8 mg containing 20% alcohol or (b) (4) % alcohol and reference product of Naloxone HCl IM 0.4 mg (0.4 mg/mL solution) in 24 healthy male and female subjects under fasted conditions. There was a 4 days washout period between treatments. Blood samples for PK determination for unconjugated and total naloxone were collected from each subject at pre-dose, and 2, 4, 6, 8, 10, 15, 30 and 45 minutes; 1, 2, 4, 8, 12, and 24 hours post-dose.

Study INS012-18-119 was an open-label, randomized, 4-treatment, crossover bioavailability study comparing a single-dose administration of Naloxone Nasal Spray 8 mg containing 20% or (b) (4) % alcohol versus a single dose of Naloxone IV 2 mg and IM 0.4 mg in 24 healthy male and female subjects under fasted conditions. There was a 4 days washout period between treatments. Blood samples for PK determination for unconjugated and total naloxone were collected from each subject at pre-dose, and 2, 4, 6, 8, 10, 15, 30 and 45 minutes; 1, 2, 4, 8, 12, and 24 hours post-dose.

In both studies, the dose of Naloxone Nasal Spray was given to seated subjects who were instructed to tilt their heads back. Subjects were instructed not to breathe through their nose during nasal administration and to keep their head tilted for approximately 60 seconds after the nasal spray administration. Subjects remained seated for at least 4 hours after dose administration. Subjects were instructed not to sneeze, blow their nose, or clear their nose immediately after dose administration. The dose of IM injection was given in the subject's dorsal gluteal area using a 23-gauge needle. In Study INS012-18-119, the dose of IV injection was given in the subject's right or left arm via established IV access as a bolus.

The mean unconjugated naloxone plasma concentration-time profiles for the proposed to-be-marketed formulation (Naloxone Nasal Spray 8 mg containing 20% alcohol) are shown in **Figure 1**. The unconjugated naloxone plasma concentrations at early time points, PK results and statistical analysis results of unconjugated naloxone PK parameters including C_{max}, AUC_{last}, and AUC_{inf} are presented in **Tables 1, 2, and 3** in the **Executive Summary**, respectively.

Naloxone Nasal Spray 8 mg containing 20% alcohol showed greater unconjugated naloxone plasma concentrations at all time points including earlier time points (e.g., 2, 4, 6, 8, 10 min) (**Figure 1 and Table 1**) with a similar median T_{max} (15 min) in comparison to the 0.4 mg IM injection. The relative bioavailability of Naloxone Nasal Spray 8 mg containing 20% alcohol is 41.6 – 47.4% in comparison to the IM injection based on dose normalized exposure (**Table 2**). Naloxone Nasal Spray 8 mg containing 20% alcohol showed approximately 14-fold greater C_{max} and 10-fold greater AUC values than a single 0.4 mg IM injection. In Study INS012-17-108, the point estimates of the geometric mean ratio (Naloxone Nasal Spray 8 mg containing 20% alcohol/0.4 mg IM injection) for unconjugated naloxone C_{max}, AUC_{last} and AUC_{0-inf} were 1320%, 971%, and 847%, respectively. The corresponding 90% confidence intervals (CIs) were 1100 - 1580%, 864 - 1090%, and 742 - 967%, respectively. In Study INS012-18-119, the point estimates of the geometric mean ratio (Naloxone Nasal Spray 8 mg containing 20% alcohol/0.4 mg IM injection) for unconjugated naloxone C_{max}, AUC_{last} and AUC_{0-inf} were 1400%, 961%, and 958%, respectively. The corresponding 90% confidence intervals (CIs) were 1130 - 1750%, 861 - 1070%, and 865 - 1060%, respectively (**Table 3**).

2.3 What is the bioavailability of naloxone following the administration of a single dose of Naloxone Nasal Spray 8 mg Containing 20% alcohol in comparison to 2 mg IV injection?

The bioavailability of Naloxone Nasal Spray 8 mg containing 20% alcohol in comparison to 2 mg IV injection was assessed in Study INS012-18-119. The absolute bioavailability of Naloxone Nasal Spray 8 mg containing 20% alcohol was 36.6% compared to Naloxone 2 mg IV injection based on dose normalized exposure. The C_{max} of unconjugated naloxone for a single dose of Naloxone Nasal Spray 8 mg containing 20% alcohol is 12.8 ng/ml, which is lower than the unconjugated naloxone concentration at 2 min post-dose for the single dose IV injection of 2 mg naloxone (i.e., C_{2 min} of 26.2 ng/mL) (**Table 2**). The corresponding AUC_{last} and AUC_{0-inf} values were 42% and 48% greater than a single 2 mg IV injection, respectively. The point estimates of the geometric mean ratio (Naloxone Nasal Spray 8 mg containing 20% alcohol/2 mg IV injection) for unconjugated naloxone C_{max}, AUC_{last} and AUC_{0-inf} were 57.6%, 142%, and 148%, respectively. The corresponding 90% confidence intervals (CIs) were 46.2 – 71.6%, 127 - 158%, and 133 - 163%, respectively (**Table 3**).

2.4 What is the difference in bioavailability between Naloxone Nasal Spray 8 mg Containing either 20% or (b) (4) % alcohol?

Naloxone Nasal Spray 8 mg containing (b) (4) % alcohol showed greater unconjugated naloxone concentrations than the formulation containing 20% alcohol (**Figure 2**). Both Naloxone Nasal Spray 8 mg formulations showed comparable median T_{max} (~15 min) and t_{1/2} values (2 to 3 hours). Unconjugated naloxone C_{max}, and AUC_{last} or AUC_{0-inf} values were 92-154% and 49-86% greater, respectively, for the formulation containing (b) (4) % alcohol than the formulation containing 20% alcohol (**Table 4**).

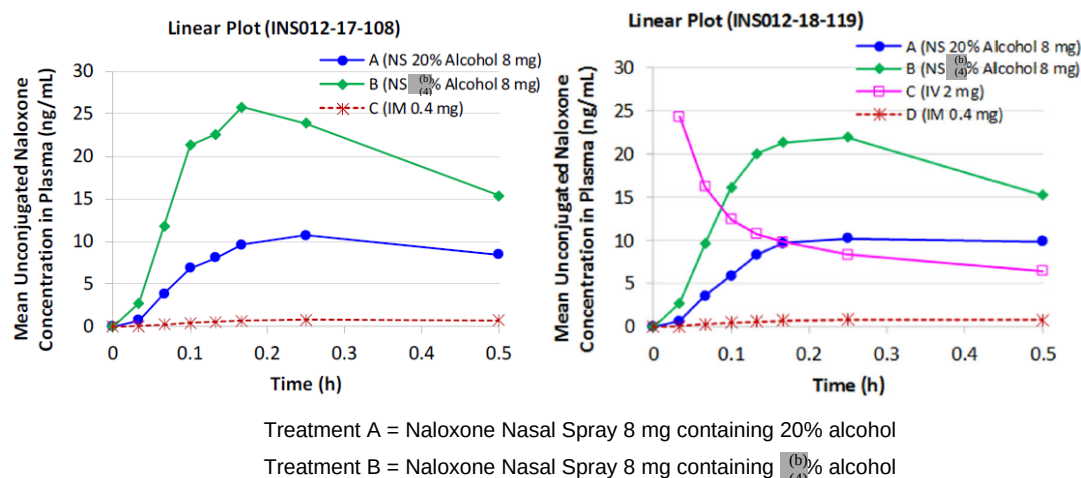


Figure 2 Mean Plasma Concentration-Time Profiles of Unconjugated Naloxone in Study INS012-17-108 (n = 24, Left Panel) and Study INS 012-18-119 (n = 24, Right Panel)

Table 4 Mean (%CV) [Geometric Mean] Plasma PK Parameters of Unconjugated Naloxone for Naloxone Nasal Spray Containing 20% or (b)(4)% Alcohol (Study INS012-17-108 and Study INS012-18-119)

PK Parameter	Study INS012-17-108		Study INS012-18-119	
	Naloxone Nasal Spray 8 mg Containing 20% alcohol (n = 24)	Naloxone Nasal Spray 8 mg Containing (b)(4)% alcohol (n = 24)	Naloxone Nasal Spray 8 mg Containing 20% alcohol (n = 23) ^b	Naloxone Nasal Spray 8 mg Containing (b)(4)% alcohol (n = 24)
C _{max} (ng/mL)	12.3 (55.4) [10.9]	30.4 (44.7) [27.7]	12.8 (37.0) [12.0]	25.6 (44.5) [23.1]
T _{max} ^a (h)	0.250 (0.100 – 1.00)	0.167 (0.100 – 0.750)	0.250 (0.100- 1.00)	0.250 (0.100 – 0.500)
AUC _{last} (ng.h/mL)	18.0 (29.6) [17.2]	29.4 (32.3) [27.9]	18.4 (33.4) [17.4]	27.3 (31.6) [25.9]
AUC _{0inf} (ng.h/mL)	16.7 (31.9) [15.9] ^c	30.7 (29.2) [29.6] ^d	19.0 (32.7) [18.0] ^e	28.3 (28.3) [27.1] ^f
T _{1/2} (h)	2.69 (69.9) [2.24] ^c	2.84 (59.5) [2.39] ^d	1.76 (39.7) [1.66] ^e	2.03 (77.8) [1.73] ^f

^a Reported as median (min – max) ^b n = 23 due to one subject withdrawal ^c n = 15 ^d n = 19 ^e n = 19 ^f n = 20 representing the number of subjects for which log-linear terminal phase could be determined.

Source: summary-biopharm Tables 6 and 11

2.5 Is the bioanalytical assay adequately validated?

The bioanalytical LC/MS/MS method for the determination of unconjugated naloxone in human plasma was adequately validated. The assay precision and accuracy of the analytical method are summarized in **Table 5**.

Table 5 Unconjugated Naloxone Assay Precision and Accuracy

	Study INS012-17-108 and INS012-18-119
Nominal range for the calibration curve	0.01 – 10.0 ng/mL
LLOQ	0.01 ng/mL
QC	0.03, 0.49, 8 and 50.0 ng/mL
Precision (%CV)	3.1% – 5.6%
Accuracy (% difference from theoretical)	-7.9% – - 4.8%

2.6 OSIS Inspection assessment

OSIS declined to conduct inspections on both the clinical and analytical sites for the comparative bioavailability studies INS012-17-108 and INS012-18-119 because inspections are not warranted based on their previous inspection.

3 Labeling Recommendations

Pending labeling negotiation as today (1/10/2020).



Note: recommend removal to keep it consistent with other approved naloxone products in PLR format

Section 8.5 Geriatric Use

Clinical studies of naloxone hydrochloride did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. ~~In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.~~

Note: to keep it consistent with other approved naloxone products in PLR format.

Section 12.3 Pharmacodynamics

When naloxone hydrochloride is administered intravenously, the onset of action is generally apparent within two minutes. The time to onset of action is shorter for intravenous compared to subcutaneous or intramuscular routes of administration. The duration of action is dependent upon the dose and route of administration of naloxone hydrochloride.

Note: the sponsor's proposed wording is consistent with approved naloxone products in PLR format and is acceptable.

Section 12.3 Pharmacokinetics

In two pharmacokinetic studies in up to 24 healthy adult volunteers for each study, the bioavailability (BA) of (b) (4) a single 8 mg dose (one spray) of TRADENAME (b) (4) was compared to a single 0.4 mg intramuscular dose and a single 2 mg intravenous dose. Naloxone plasma concentration versus time profiles are shown in Figure 1. The pharmacokinetic parameters of naloxone are summarized in [Table 1](#).

Figure 1: Mean $\pm$ SD Plasma Concentration-Time Profiles of Naloxone Following A Single Dose of Intranasal versus Intramuscular/Intravenous Administration in Healthy Subjects. (A: 0-4 h and B: 0-1 h)

(b) (4)

Note: ask the sponsor to change the (b) (4) graph to 0-30 min so early time points will be clearly shown. In addition, ask sponsor to create the figure in black/white showing mean $\pm$ SD plasma concentration-time profiles. The label of NS 8 mg should be changed to Nasal Spray 8 mg and IM 0.4 mg should be changed to Intramuscular Injection 0.4 mg, IV 2 mg should be changed to Intravenous Injection 2 mg.

Table 1: Mean (CV%) ^{(b) (4)} Plasma Pharmacokinetic Parameters of Naloxone Following a Single Dose of Intranasal and Intramuscular/Intravenous Administration in Healthy Subjects

(b) (4)

Absorption

(b) (4)

Distribution

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

Note: sponsor's proposed wording for Distribution is consistent with listed drug product and is acceptable.

(b) (4)

Elimination

(b) (4)

(b) (4)

In a neonatal study of naloxone hydrochloride the mean ($\pm$ SD) plasma half-life was observed to be 3.1 ± 0.5 hours.

Metabolism

Naloxone hydrochloride is (b) (4) metabolized in the liver, primarily by glucuronide conjugation, with naloxone-3-glucuronide as the major metabolite.

Excretion

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

*Note: Neonate PK is from the listed drug product, Narcan Injectable label, and is added.
Sponsor's proposed Excretion is consistent with listed drug product and other naloxone products
in PLR format.*

4 Appendix

(b) (4)



4.2 Study INS012-17-108 Synopsis

Clinical Study Report

Naloxone Nasal Spray (INS012-17-108)

2. SYNOPSIS

Name of Sponsor/Company: Insys Development Company, Inc.	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Naloxone Nasal Spray		
Name of Active Ingredient: Naloxone Hydrochloride		
Title of Study: A Phase 1, Open-Label, Randomized, Crossover, Comparative Bioavailability Study of Naloxone Nasal Spray and Naloxone Hydrochloride Intramuscular Injection in Healthy Volunteers		
Principal Investigator: George J. Atiee, MD Investigators: Cynthia A. Zamora, MD; Robert G. Bass, Jr., MD; Nancy K. Himitt, MD; Elizabeth Camacho, MSN, FNP-BC; Lydia Trejo, MSN, FNP-BC, BSN RN		
Study center: Worldwide Clinical Trials Early Phase Services, LLC, 2455 NE Loop 410, Suite 150 San Antonio, Texas 78217		
Publications (reference): None		
Study period: Date first subject dosed: 07 August 2017 Date last subject completed: 16 August 2017		Phase of development: 1
Objectives: Primary: The primary objective of this study was: - To compare early exposures (plasma concentrations at each time point and partial AUCs) up to 1 hour following a single dose of two test formulations of Naloxone Nasal Spray (8 mg/spray containing 20% alcohol and 8 mg/spray containing (b)(4)% alcohol) with the reference formulation of Naloxone Hydrochloride (HCl) Intramuscular (IM) Injection (0.4 mg/mL) under fasted conditions. Secondary: The secondary objectives of this study were: - To compare the bioavailability of a test formulation of a single dose of 8 mg containing 20% alcohol Naloxone Nasal Spray and 8 mg containing (b)(4)% alcohol of Naloxone Nasal Spray to a single dose of Naloxone HCl IM (0.4 mg/mL) under fasted conditions; - To evaluate the safety and tolerability of Naloxone Nasal Spray.		

Methodology:

This was a single-dose, open-label, randomized, three-treatment, six-sequence, three-way crossover study. Each dose of study treatment was separated by a washout period of 4 days. Healthy volunteer subjects received one dose of 8 mg containing 20% alcohol Naloxone Nasal Spray, one dose of 8 mg containing (b) (4)% alcohol Naloxone Nasal Spray, and a single dose of Naloxone HCl IM 0.4 mg/mL.

This study consisted of four periods, a Screening Period and three Treatment Periods. During Screening (Day -28 to Day -1), subjects signed the informed consent and eligibility was determined. Twenty-four (24) subjects received a single dose of study drug administered on Day 1 (Period 1), Day 5 (Period 2), and Day 9 (Period 3) following an overnight fast of at least 10 hours. Subjects were confined before dosing to ensure adherence to the 10-hour fast and remained confined until all study procedures were completed on Day 10. No food was allowed until 4 hours after each dose administration. Meals were provided at scheduled times.

A total of 420 mL in blood samples was collected from each subject over the entire study. In each treatment period, blood samples (1 x 10 mL) pharmacokinetic (PK) analyses were collected in a Vacutainer tube containing K₂-EDTA as a preservative at 0 hour (predose), 2, 4, 6, 8, 10, 15, 30, and 45 minutes, and at 1, 2, 4, 8, 12, and 24 hours post dose (15 time points). Blood (plasma) samples were analyzed for unconjugated naloxone and total naloxone using validated LC/MS/MS assays. Safety and tolerability were assessed throughout the study.

Number of subjects: Planned: 24 Analyzed: 24

Diagnosis and main criteria for inclusion:

Subjects were non-smoking, healthy male and non-pregnant female volunteers (with approximately equal numbers of each gender), between 18 and 45 years of age (inclusive), able to understand and provide written consent, and who met all the inclusion and none of the exclusion criteria.

Test products, dose and mode of administration, lot numbers:Treatment A

Naloxone Nasal Spray, 8 mg/spray (20% ethyl alcohol)

Dose = 8 mg (1 spray), nasal administration

Lot: 162343

Retest Date: (b) (4)

Manufacture Date: 21 December 2016

Treatment B

Naloxone Nasal Spray, 8 mg/spray (b) (4)% ethyl alcohol

Dose = 8 mg (1 spray), nasal administration

Lot: 162342

Retest Date: (b) (4)

Manufacture Date: 19 December 2016

Duration of treatment: Three single doses were administered with a 4-day washout period between each dose.

Reference therapy, dose and mode of administration, lot numbers:Treatment C

Naloxone HCl IM Injection, 0.4 mg/mL

Dose = 0.4 mg (1 mL), administered via IM injection

Lot: 72-141-EV

Expiration Date: 01 December 2018

Criteria for evaluation:**Pharmacokinetics:**

The comparisons of the plasma concentrations at each time point up to 1 hour postdose were performed for assessment of early unconjugated and total naloxone exposure.

The pharmacokinetic parameters for unconjugated naloxone and total naloxone in plasma were: area under the curve from time 0 to each of the collection time-points up to 1 hour postdose (AUC_{0-x}), area under the curve from time 0 to the last measured concentration (AUC_{0-t}), area under the curve extrapolated to infinity (AUC_{0-inf}), percentage of AUC_{0-inf} obtained by extrapolation (AUC_{extrap}), maximum plasma concentration (C_{max}), time to reach maximum plasma concentration (T_{max}), last quantifiable concentration (C_{last}), time of the last quantifiable concentration (T_{last}), the time prior to the first measurable (non-zero) concentration (T_{lag}), elimination rate constant (λ_z), and elimination half-life ($t_{1/2}$).

Safety:

Safety assessments included physical and nasal cavity examinations, nasal irritation examination, olfactory function testing (BSIT), injection site assessments, vital signs (seated blood pressure, pulse rate, respiration rate, and temperature), clinical laboratory tests, pregnancy screens, ECGs, concomitant medications, and AE assessments.

Efficacy:

Efficacy was not evaluated in this study.

Statistical methods:**Pharmacokinetic Analysis**

All PK analyses were performed on the PK population. The PK population was defined as all subjects who had completed at least one treatment period. Arithmetic means, standard deviations, median, minimum, maximum, and coefficients of variation were calculated for all pharmacokinetic parameters. Additionally, geometric means were calculated for plasma concentrations and geometric means and geometric CV% were reported for $C_{\max}$ and AUCs.

No values for $AUC_{0-\text{inf}}$, λ_z , and $t_{1/2}$ were reported for cases that did not exhibit a terminal log-linear phase in the concentration-time data.

The elimination rate constant, λ_z , was calculated as the negative of the slope of the terminal log-linear segment of the plasma concentration-time curve; the range of data used was determined by visual inspection of a semi-logarithmic plot of concentration vs. time. Elimination half-life ($t_{1/2}$) was calculated according to the following equation: $t_{1/2} = \ln(2)/\lambda_z$.

Area under the curve to the final sample with a concentration greater than the limit of quantification (LOQ [AUC_{0-t}]) was calculated using the Linear-Log trapezoidal method and extrapolated to infinity using:

$AUC_{0-\text{inf}} = AUC_{0-t} + C_{\text{last}}/\lambda_z$, where C_{last} is the final concentration $\geq$ LOQ.

Analyses of variance (ANOVA) with effects for sequence, subject nested within sequence, period, and treatment were performed on the ln-transformed plasma concentrations at each time point up to 1 hour postdose and the ln-transformed PK parameters such as AUC_{0-t} , $AUC_{0-\text{inf}}$, partial AUCs, and $C_{\max}$. Each ANOVA included calculation of least-squares means (LSMs), the differences between adjusted means, and the standard error associated with these differences. Ratios of means were calculated using the LSM for ln-transformed plasma concentrations at each time point up to 1 hour post dose and ln-transformed AUC_{0-t} , $AUC_{0-\text{inf}}$, partial AUCs, and $C_{\max}$.

The comparative bioavailability of unconjugated naloxone and total naloxone between each of the two test (Naloxone Nasal Spray [8 mg/spray containing 20% alcohol] and Naloxone Nasal Spray [8mg/spray containing (b)(4)% alcohol]) and reference (Naloxone Hydrochloride IM Injection [0.4 mg/mL]) formulations were investigated using the point estimates (test/reference ratios of means) and the corresponding 90% confidence intervals (CIs) for plasma concentrations at each time point up to 1 hour post dose and AUC_{0-t} , $AUC_{0-\text{inf}}$, partial AUCs, and $C_{\max}$. The CIs were expressed as a percentage relative to the LSM.

Safety Analyses

All safety analyses were performed on the safety population. The safety population was defined as all subjects who had received one dose of study drug. Treatment-emergent AEs; clinical laboratory tests; vital signs (seated blood pressure, pulse rate, respiration rate and temperature); 12-lead ECGs; physical and nasal cavity examinations; nasal irritation examination, olfactory function testing (BSIT), injection site assessments, pregnancy screens; drug, alcohol, and cotinine screens; and concomitant medications were summarized.

AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) terms and are summarized by system organ class (SOC) and preferred term within SOC.

Pharmacokinetic and statistical analyses were performed using appropriate software, e.g. PhoenixTM WinNonlin[®] (Version 6.3, Pharsight Corporation) and SAS[®] (Version 9.4, SAS Institute Inc.).

SUMMARY – RESULTS**PHARMACOKINETICS RESULTS:**

Twenty-four (24) subjects who completed at least one study period were included in the pharmacokinetic analysis. Mean concentration-time data for unconjugated naloxone through 1 h postdose are shown in Synopsis Table 1 and [Synopsis Figure 1](#). Area under the concentration-time curve from time-zero to each scheduled sample time through 1 h postdose (partial AUCs) for unconjugated naloxone are shown in [Synopsis Table 2](#).

Ratios of the geometric mean concentrations and partial AUCs for each Naloxone Nasal Spray treatment relative to Naloxone HCl 0.4 mg IM are shown in [Synopsis Table 3](#) and [Synopsis Table 4](#), respectively.

Synopsis Table 1 Mean Plasma Concentrations of Unconjugated Naloxone through 1 Hour after Administration of Naloxone Nasal Spray 8 mg (20% alcohol) (Treatment A), Naloxone Nasal Spray 8 mg (b)(4)% alcohol) (Treatment B), and Naloxone HCL IM Injection 0.4 mg (Treatment C)

Treatment Description	n	2 min Mean	4 min Mean	6 min Mean	8 min Mean	10 min Mean	15 min Mean	30 min Mean	45 min Mean	60 min Mean
Naloxone Nasal Spray 8 mg (20% alcohol)	24	0.725	3.84	6.87	8.07	9.64	10.7	8.44	6.59	5.83
Naloxone Nasal Spray 8 mg (b)(4)% alcohol)	24	2.77	11.8	21.3	22.6	25.8	23.9	15.4	11.1	9.06
Naloxone HCL IM Injection 0.4 mg	24	0.0527	0.241	0.420	0.547	0.660	0.792	0.699	0.628	0.570

Note: Mean concentrations reported in ng/mL to 3 significant figures

IM= intramuscular administration

Source data: [Tables 14.4.1.1](#)

The mean unconjugated naloxone concentrations after the administration of Naloxone Nasal Spray 8 mg containing 20% alcohol and containing (b)(4)% alcohol were appreciably higher than those observed after the administration of Naloxone HCl 0.4 mg IM at all timepoints from 2 minutes (0.725 and 2.77 ng/mL versus 0.0527 ng/mL) through 1 h postdose.

A similar trend was observed for partial areas calculated through 1 hour postdose. The mean partial unconjugated naloxone AUCs after the administration of Naloxone Nasal Spray 8 mg containing 20% alcohol or containing (b)(4)% alcohol were appreciably higher than those observed after the administration of Naloxone HCl 0.4 mg IM at all timepoints from 2 minutes through 1 h postdose.

Additionally, mean unconjugated naloxone concentrations and mean partial unconjugated naloxone AUCs after the administration of Naloxone Nasal Spray 8 mg containing (b)(4)% alcohol were higher than those observed after the administration of Naloxone Nasal Spray 8 mg containing 20% alcohol at all timepoints from 2 minutes through 1 h postdose, suggesting the higher alcohol percentage of alcohol enhanced the relative bioavailability of the Naloxone Nasal Spray product.

Synopsis Table 2 Mean Partial AUCs of Unconjugated Naloxone through 1 Hour after Administration of Naloxone Nasal Spray 8 mg (20% alcohol) (Treatment A), Naloxone Nasal Spray 8 mg (b)(4)% alcohol (Treatment B), and Naloxone HCL IM Injection 0.4 mg (Treatment C)

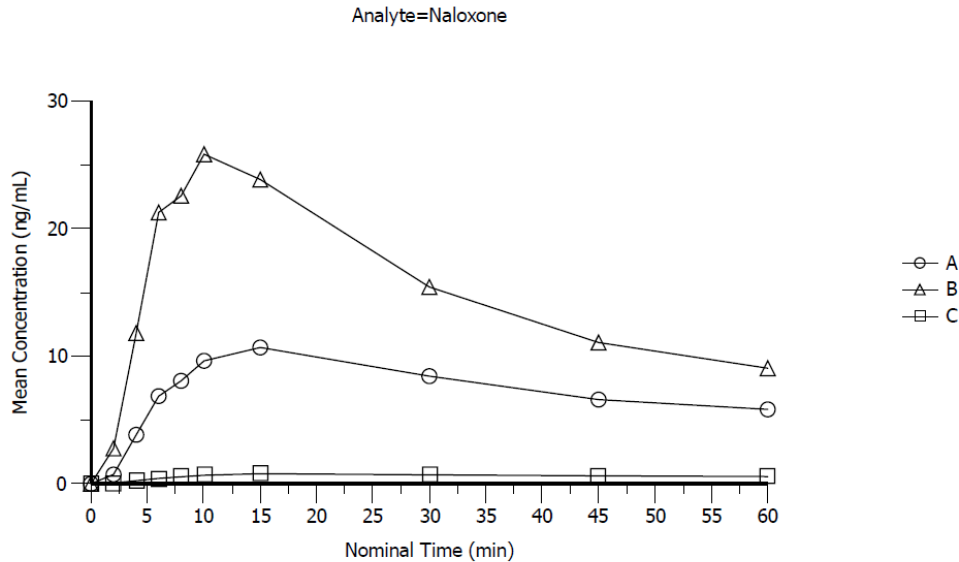
Treatment Description	n	AUC 2min Mean	AUC 4min Mean	AUC 6min Mean	AUC 8min Mean	AUC 10min Mean	AUC 15min Mean	AUC 30min Mean	AUC 45min Mean	AUC 60min Mean
Naloxone Nasal Spray 8 mg (20% alcohol)	24	0.0116	0.0860	0.257	0.502	0.809	1.64	4.03	5.90	7.45
Naloxone Nasal Spray 8 mg (b)(4)% alcohol	24	0.0458	0.286	0.826	1.53	2.34	4.36	9.06	12.3	14.8
Naloxone HCL IM Injection 0.4 mg	24	0.000877	0.00553	0.0164	0.0322	0.0526	0.113	0.298	0.463	0.612

Note: Partial AUCs reported in h*ng/mL to 3 significant figures

IM= intramuscular administration

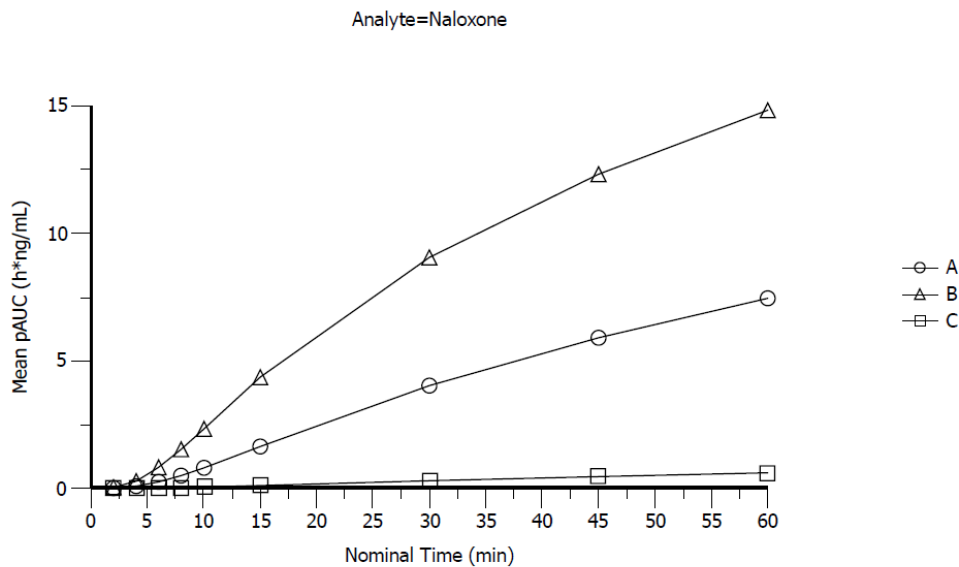
Source data: [Tables 14.4.2.1](#)

Synopsis Figure 1: Mean Unconjugated Naloxone Concentration-Time Profiles through 1 Hour after Administration of Naloxone Nasal Spray 8 mg (20% alcohol) (Treatment A), Naloxone Nasal Spray 8 mg (b)(4)% alcohol (Treatment B), and Naloxone HCL IM Injection 0.4 mg (Treatment C) on Linear Scale



Source data: [Table 14.4.1.1](#)

Synopsis Figure 2: Mean Unconjugated Naloxone Partial AUC Profiles through 1 Hour after Administration of Naloxone Nasal Spray 8 mg (20% alcohol) (Treatment A), Naloxone Nasal Spray 8 mg (b)(4)% alcohol (Treatment B), and Naloxone HCL IM Injection 0.4 mg (Treatment C) on Linear Scale



Source data: [Table 14.4.2.1](#)

Synopsis Table 3: Ratios of the Geometric Mean Plasma Concentrations of Unconjugated Naloxone through 1 Hour Postdose for Naloxone Nasal Spray Treatment Relative to Naloxone HCl 0.4 mg IM

	Time (min)								
	2	4	6	8	10	15	30	45	60
Treatment	Ratio to Naloxone HCl 0.4 mg IM								
Naloxone Nasal Spray 8 mg (20% alcohol)	10.8	14.6	15.2	12.3	13.6	12.3	11.6	10.6	10.0
Naloxone Nasal Spray 8 mg (b)(4)% alcohol)	40.5	50.4	49.8	41.4	39.7	29.5	21.3	17.1	15.2

Note: Ratios of geometric mean reported to 1 decimal place

Source data: Listings 16.2.6.5.2 through 16.2.6.5.4

As shown in the table above, geometric mean plasma concentrations are substantially higher after administrations of Naloxone Nasal Spray 8 mg containing 20% or (b)(4)% alcohol relative to that after IM administration of 0.4 mg Naloxone HCl from 2 minutes (10.8- and 40.5-fold) through 1 hour postdose. Unconjugated naloxone concentrations were approximately 10-fold to 15-fold higher after Naloxone Nasal Spray 8 mg administered containing 20% alcohol compared to that after Naloxone HCl 0.4 mg IM. Unconjugated naloxone concentrations were approximately 15-fold to 50-fold higher after Naloxone Nasal Spray 8 mg administered containing (b)(4)% alcohol compared to that after Naloxone HCl 0.4 mg IM.

Synopsis Table 4: Ratios of the Geometric Mean Partial AUCs of Unconjugated Naloxone through 1 Hour for Naloxone Nasal Spray Treatment Relative to Naloxone HCl 0.4 mg IM

	Partial AUC								
	AUC 2min	AUC 4min	AUC 6min	AUC 8min	AUC 10min	AUC 15min	AUC 30min	AUC 30min	AUC 60min
Treatment	Ratio to Naloxone HCl 0.4 mg IM								
Naloxone Nasal Spray 8 mg (20% alcohol)	10.6	14.9	14.1	13.9	13.9	13.3	12.6	12.2	11.8
Naloxone Nasal Spray 8 mg (b)(4)% alcohol)	42.2	52.7	49.7	47.7	45.4	38.9	30.3	26.4	24.0

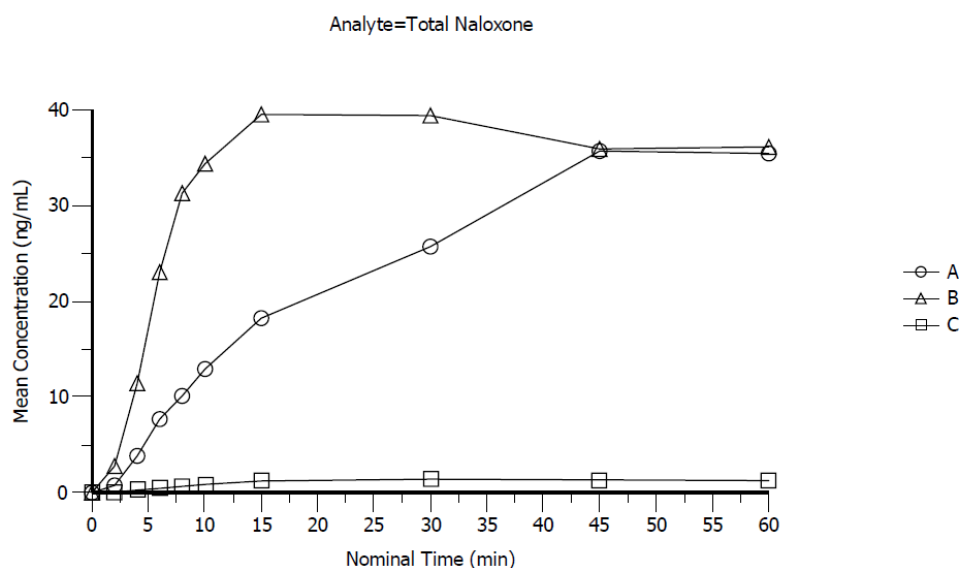
Note: Ratios of geometric mean reported to 1 decimal place

Source data: Listings 16.2.6.5.10 through 16.2.6.5.12

A similar trend was observed for geometric mean partial areas calculated through 1 hour postdose. Early unconjugated naloxone exposure was approximately 11-fold to 15-fold higher after Naloxone Nasal Spray 8 mg administered containing 20% alcohol compared to that after Naloxone HCl 0.4 mg IM. Early unconjugated naloxone exposure was approximately 24-fold to 53-fold higher after Naloxone Nasal Spray 8 mg administered containing (b)(4)% alcohol compared to that after Naloxone HCl 0.4 mg IM.

Mean concentration-time data for total naloxone through 1 h postdose are shown in Synopsis Figure 3. Similarly, early exposure to total naloxone (plasma concentrations and partial AUCs) through 1 hour postdose was higher after administration of Naloxone Nasal Spray formulation with 20% alcohol (test) than those observed after the administration of Naloxone HCl 0.4 mg IM.

Synopsis Figure 3 Mean Total Naloxone Concentration-Time Profiles through 1 Hour after Administration of Naloxone Nasal Spray 8 mg (20% alcohol) (Treatment A), Naloxone Nasal Spray 8 mg (b)(4)% alcohol (Treatment B), and Naloxone HCl IM Injection 0.4 mg (Treatment C) on Linear Scale



Source data: [Table 14.4.1.2](#)

SAFETY RESULTS:

No AEs were serious or led to a subject discontinuation. A total of eight AEs were reported by five subjects (20.8%), all following dose administration. All AEs were mild in severity and resolved without intervention in less than 12 hours.

Two subjects reported an AE following Treatment A (Naloxone Nasal Spray, 8 mg (containing 20% alcohol). Of these, one AE (abdominal pain) was judged by the Investigator as unlikely related to treatment and the other AE (musculoskeletal chest pain) was judged not related to treatment.

Two subjects reported five AEs following Treatment B (Naloxone Nasal Spray, 8 mg (containing (b)(4)% alcohol). Of these, three AEs (vomiting, nausea, and headache) were judged probably related to treatment and two AEs (dizziness and hypoacusis) were judged possibly related to treatment.

One subject reported an AE (headache) following Treatment C (Naloxone HCl IM Injection, 0.4 mg/mL), which was judged unlikely related to treatment.

The most common AE was headache, which was reported twice during the study (once following Treatments B and C). All other AEs were reported once.

No AEs were related to physical examinations, ECGs, vital signs, or clinical laboratory data. Additionally, no AEs were related to nasal cavity examinations, nasal irritation, or BSIT.

CONCLUSIONS:

In summary, this study evaluated unconjugated and total naloxone exposure after intranasal administrations of the Insys Naloxone Nasal Spray containing 20% or (b)(4)% alcohol and IM administration of Naloxone HCl. The results indicate that:

- Naloxone Nasal Spray 8 mg administered containing 20% alcohol provides higher plasma concentrations and exposure of unconjugated naloxone (based on partial AUCs) than those

achieved by administration of 0.4 mg IM starting from 2 minutes following administration.

- Naloxone Nasal Spray 8 mg containing (b) (4)% alcohol provides higher plasma concentrations and exposure of unconjugated naloxone (based on partial AUCs) than those achieved by administration of 0.4 mg IM starting from 2 minutes following administration.
- Naloxone Nasal Spray 8 mg containing (b) (4)% alcohol provides higher plasma concentrations and exposure of unconjugated naloxone (based on partial AUCs) than those achieved by administration of Naloxone Nasal Spray 8 mg containing 20% alcohol starting from 2 minutes following administration.
- Naloxone Nasal Sprays 8 mg containing 20% alcohol or (b) (4)% alcohol were generally safe and well-tolerated by the healthy and fasting subjects in this study.

Insys Naloxone Nasal Spray 8 mg containing 20% or (b) (4)% alcohol administered by intranasal route may offer a beneficial, needle-free option for the treatment of opioid overdose because it provides exposures of unconjugated naloxone that exceed those achieved by Naloxone 0.4 mg IM, which might be critically important when addressing overdoses from fentanyl.

Date of report: 07 December 2017

4.3 Study INS012-18-119 Synopsis

Clinical Study Report

Naloxone Nasal Spray (INS012-18-119)

2. SYNOPSIS

Name of Sponsor/Company: Insys Development Company, Inc.	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: Naloxone Nasal Spray		
Name of Active Ingredient: Naloxone hydrochloride		
Title of Study: A Phase 1, Open-Label, Randomized, Crossover, Comparative Bioavailability Study of Naloxone Nasal Spray and Naloxone Hydrochloride Intravenous and Intramuscular Injection in Healthy Volunteers.		
Principal Investigator: George J. Atiee, MD Sub-Investigators: Cynthia A. Zamora, MD; John A. Gibbons, DO., MPH; Robert G. Bass, Jr., MD; Nancy K. Hinit, MD; Elizabeth Crockett, MSN, FNP-BC; Lydia Trejo, MSN, FNP-BC, BSN, RN; Melissa L. Hearrell, MSN, APRN, FNP-C		
Study center: Worldwide Clinical Trials Early Phase Services, LLC, 2455 NE Loop 410, Suite 150, San Antonio, Texas 78217		
Publications (reference): None		
Studied period (years): Date first subject enrolled: 23 Apr 2018 Date last subject completed: 06 May 2018		Phase of development: 1
Objectives: Primary: - To assess naloxone pharmacokinetics (PK) following a single dose of two test formulations of Naloxone Nasal Spray, 8 mg (containing 20% alcohol and (b)(4)% alcohol) and reference formulations of Naloxone Hydrochloride (HCl) Intravenous (IV) Injection 2 mg (1 mg/mL) and Naloxone HCl Intramuscular (IM) Injection (0.4 mg/mL; 1 mL) under fasted conditions. - To compare the bioavailability of the tested formulations of Naloxone Nasal Spray with the reference formulations of Naloxone IV and IM injection. Secondary: - To compare early exposures (plasma concentrations at each time point and partial areas under the curve [AUCs]) up to 2 hours following a single dose of two formulations of Naloxone Nasal Spray, 8 mg (containing 20% alcohol and (b)(4)% alcohol) to a single dose of 2 mg Naloxone HCl IV Injection (1 mg/mL) and a single dose of Naloxone HCl IM Injection (0.4 mg/mL; 1 mL) under fasted conditions. - To evaluate the safety and tolerability of Naloxone Nasal Spray.		

Methodology:

This was a single-dose, open-label, randomized, four-treatment, four-way crossover study. Healthy volunteer subjects received one dose of 8 mg Naloxone Nasal Spray (containing 20% alcohol), one dose of 8 mg Naloxone Nasal Spray (containing 24% alcohol), one dose of 2 mg Naloxone HCl IV Injection (1 mg/mL), and one dose of Naloxone HCl IM Injection (0.4 mg/mL; 1 mL) separated by a washout period of 4 days between each dose of study treatment.

This study consisted of five periods, a Screening Period and four Treatment Periods. During Screening (Day -28 to Day -1), subjects signed the informed consent and eligibility was determined. Twenty-four (24) subjects were planned to receive a single dose of study drug administered on Day 1 Period 1, Day 5 Period 2, Day 9 Period 3, and Day 13 Period 4, following an overnight fast of at least 10 hours. Subjects were confined before dosing to ensure adherence to the 10-hour fast and remained confined until all study procedures were completed on Day 14. No food was allowed until 4 hours after each dose administration. Meals were provided at scheduled times. Safety and tolerability were assessed throughout the study.

In each treatment period, blood samples (1 x 10 mL) for unconjugated naloxone and total naloxone analysis were collected in a Vacutainer tube containing K₂-EDTA as a preservative at 0 hour (predose), 2, 4, 6, 8, 10, 15, 30, and 45 minutes, and 1, 2, 4, 8, 12, and 24 hours postdose (15 timepoints). Plasma samples were analyzed for unconjugated naloxone and total naloxone using validated liquid chromatography with tandem mass spectrometry (LC/MS/MS) assays with the lower limit of quantification (LLOQ) of 0.0100 ng/mL for unconjugated naloxone and 0.0500 ng/mL for total naloxone.

Number of subjects:

Planned: 24

Treated: 24 (N = 6 per cohort)

Evaluated: 24 for safety
24 for PK

Diagnosis and main criteria for inclusion:

Subjects were non-smoking, healthy male and non-pregnant female volunteers (with approximately equal numbers of each gender), between 18 and 45 years of age (inclusive), who were able to understand and provide written informed consent, and who meet all the inclusion and none of the exclusion criteria.

Investigational products:**Test Formulations:**

Naloxone Nasal Spray, 8 mg (containing naloxone 80 mg/mL in 20% alcohol)

Treatment A

Lot: 10261017

Retest Date: (b) (4)

Manufacture Date: 17 Oct 2017

Dose regimen: single dose 8 mg (1 spray), intranasal administration

Naloxone Nasal Spray, 8 mg (containing naloxone 80 mg/mL in (b) (4)% alcohol)

Treatment B

Lot: 10301017

Retest Date: (b) (4)

Manufacture Date: 13 Nov 2017

Dose regimen: single dose 8 mg (1 spray), intranasal administration

Reference Formulations:

Naloxone HCl Intravenous (IV) Injection, 2 mg (1 mg/mL)

Treatment C

Lot: RL076B8

Expiration Date: 31 Jan 2020

Dose regimen: single dose 2 mg (2 mL), IV injection

Naloxone HCl Intramuscular (IM) Injection (0.4 mg/mL)

Treatment D

Lot: 72-141-EV

Expiration Date: 01 Dec 2018

Dose regimen: single dose 0.4 mg (1 mL), IM injection

Duration of treatment: Single-dose in each of the four treatment periods with a washout period of 4 days between two periods.

Criteria for evaluation:**Pharmacokinetics**

Plasma concentrations of unconjugated naloxone and total naloxone (which includes conjugated naloxone) were used to determine the following PK parameters using noncompartmental PK analysis (NCA):

Maximum plasma concentration observed (C_{max}), initial plasma concentration at time 0 for IV bolus administration (C_0), time to reach maximum plasma concentration (T_{max}), last quantifiable concentration (C_{last}), time of the last quantifiable concentration (T_{last}), the time prior to the first measurable (non-zero) concentration (T_{lag}), area under the curve from time 0 to each of the collection time-points up to 2 h postdose (AUC_{0-x}), area under the curve from time 0 to the last measured concentration (AUC_{last}), area under the curve extrapolated to infinity (AUC_{0-inf}), percentage of AUC_{0-inf} obtained by extrapolation (AUC_{extrap}), elimination rate constant (λ_z), terminal elimination half-life ($t_{1/2}$), apparent total body clearance of naloxone (CL after IV, CL/F after extravascular), and apparent volume of distribution in the terminal phase of naloxone (V_z after IV, V_z/F after extravascular).

Note: CL, CL/F, V_z , and V_z/F were only determined for unconjugated naloxone and are not applicable for total naloxone.

Safety

The Investigator evaluated safety using the following assessments: physical and nasal cavity and nasal irritation examinations, olfactory function testing (The Brief Smell Identification Test [BSIT]), injection site assessment, vital sign (seated blood pressure, pulse rate, respiration rate, and temperature), clinical laboratory tests, pregnancy screens, drug, alcohol and cotinine screens, electrocardiograms (ECGs), concomitant medications, and adverse events (AE) assessments. Subjects were monitored for any AEs from the beginning of confinement through the end of the study.

Efficacy

Not applicable.

Statistical Methods:**Analysis Populations**

Statistical analyses were done on the following populations:

- Randomized Population, defined as all subjects who receive a subject number and a randomization number.
- Safety Population, defined as all subjects who received one dose of study drug.
- PK Population, defined as all subjects who completed at least one treatment period.

Analysis of Pharmacokinetic Data

Analyses of variance (ANOVA) with effects for sequence, subject nested within sequence, period, and treatment were performed for unconjugated naloxone and total naloxone on the ln-transformed plasma concentrations at each time point up to 2 h postdose and the ln-transformed PK parameters such as AUC_{last} , AUC_{0-inf} , partial AUCs, and C_{max} . Each ANOVA included calculation of least-squares means (LSMs), the differences between adjusted means, and the standard error associated with these differences. Ratios of means were calculated using the LSMs. The comparisons of interest were:

- Naloxone Nasal Spray, 8 mg (20% alcohol, Treatment A) vs. Naloxone HCl IV Injection 2 mg (Treatment C)
- Naloxone Nasal Spray, 8 mg ((b)₍₄₎% alcohol, Treatment B) vs. Naloxone HCl IV Injection 2 mg (Treatment C)
- Naloxone Nasal Spray, 8 mg (20% alcohol, Treatment A) vs. Naloxone HCl IM Injection 0.4 mg (Treatment D)
- Naloxone Nasal Spray, 8 mg ((b)₍₄₎% alcohol, Treatment B) vs. Naloxone HCl IM Injection 0.4 mg (Treatment D)
- Naloxone Nasal Spray, 8 mg (20% alcohol, Treatment A) vs. Naloxone Nasal Spray, 8 mg ((b)₍₄₎% alcohol, Treatment B)

Safety Analysis

All safety analyses were performed on the safety population. Treatment-emergent AEs; clinical laboratory tests; vital signs (blood pressure, pulse rate, respiration rate, and temperature); ECGs; physical and nasal examinations; nasal irritation examinations; olfactory function test (BSIT); pregnancy screens; drug, alcohol, and cotinine screens; and concomitant medications were summarized. Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA 21.0) terms and summarized by system organ class (SOC) and preferred term within SOC.

SUMMARY – RESULTS**PHARMACOKINETICS RESULTS:****Plasma Concentrations**

Up to 24 subjects who completed at least one study period were included in the pharmacokinetic analysis. Mean plasma concentrations of unconjugated naloxone at early times through 2 h post-dose for each treatment are listed in Synopsis Table 1 for comparison.

Mean unconjugated naloxone plasma concentration-time profiles are shown in [Synopsis Figure 1](#).

Synopsis Table 1. Arithmetic Mean Plasma Concentrations of Unconjugated Naloxone Through 2 h Postdose

Formulation	Time (min)									
	2	4	6	8	10	15	30	45	60	120
Naloxone Nasal Spray 8 mg (20% alcohol) (N=23)	0.635	3.58	5.87	8.32	9.68	10.2	9.84	8.20	6.89	3.09
Naloxone Nasal Spray 8 mg ((b) (4) % alcohol) (N=24)	2.71	9.58	16.1	20.0	21.3	21.9	15.2	11.6	9.15	3.97
Naloxone HCl IV Injection 2 mg (N=24)	24.3	16.2	12.4	10.7	9.82	8.32	6.47	4.79	3.88	1.68
Naloxone HCl IM Injection 0.4 mg (N=23)	0.0734	0.263	0.455	0.573	0.69	0.826	0.771	0.686	0.642	0.379

Note: Arithmetic mean concentrations reported in ng/mL to 3 significant figures

Treatment A=Naloxone Nasal Spray 8 mg (20% alcohol), Treatment B=Naloxone Nasal Spray 8 mg ((b) (4) % alcohol), Treatment C=Naloxone HCl IV Injection 2 mg, Treatment D=Naloxone HCl IM Injection 0.4 mg.

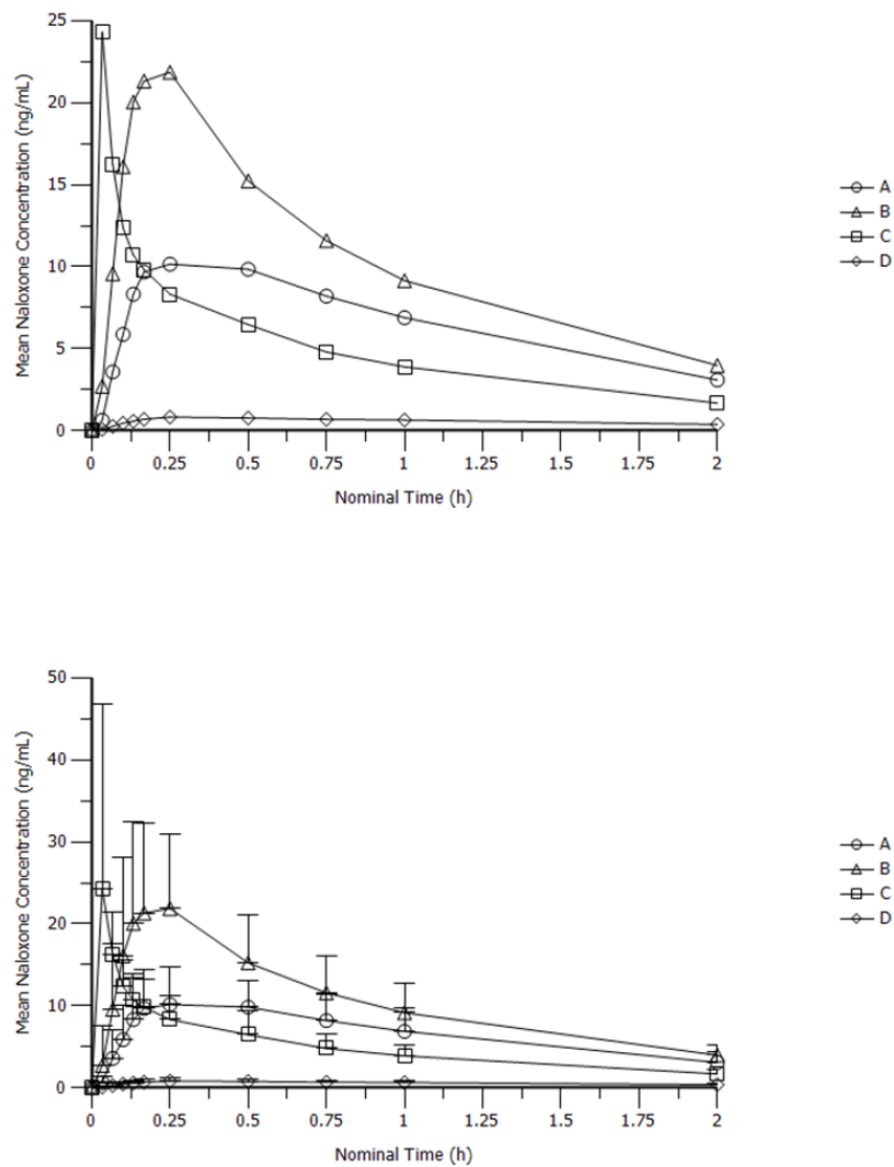
Source Data: [Table 14.4.1.1](#)

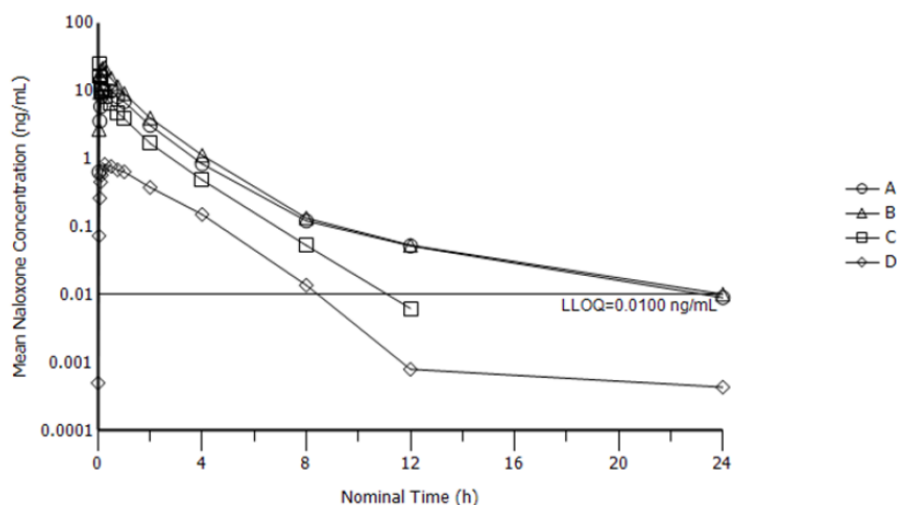
The mean unconjugated naloxone concentrations after the administration of Naloxone Nasal Spray 8 mg containing 20% alcohol or (b) (4) % alcohol were appreciably higher than those observed after the administration of Naloxone HCl 0.4 mg IM at all timepoints from 2 minutes (0.635 and 2.71 ng/mL versus 0.0734 ng/mL) through 24 h postdose.

Based on the mean plasma concentration-time profiles, the highest unconjugated naloxone plasma levels were achieved after administration of Naloxone HCl IV Injection 2 mg, followed by Naloxone Nasal Spray 8 mg ((b) (4) % alcohol), Naloxone Nasal Spray 8 mg (20% alcohol), and Naloxone HCl IM Injection 0.4 mg.

Additionally, mean unconjugated naloxone concentrations after the administration of Naloxone Nasal Spray 8 mg containing (b) (4) % alcohol were higher than those observed after the administration of Naloxone Nasal Spray 8 mg containing 20% alcohol at all timepoints from 2 minutes through 8 h postdose; mean unconjugated naloxone concentrations for the two Naloxone Nasal Spray formulations were similar after 8 h and through the last timepoint at 24 h postdose.

Synopsis Figure 1. Mean Unconjugated Naloxone Plasma Concentration-Time Profiles on Linear Scale (over 2 h), +SD on Linear Scale (over 2 h), and Semi-Logarithmic Scale (over 24 h)





Treatment A=Naloxone Nasal Spray 8 mg (20% alcohol) (N=23), Treatment B=Naloxone Nasal Spray 8 mg ((b)(4)% alcohol) (N=24), Treatment C=Naloxone HCl IV Injection 2 mg (N=24), Treatment D=Naloxone HCl IM Injection 0.4 mg (N=23).

Note: One subject (Subject (b)(6)) was withdrawn by the Investigator on Day 9 of the study due to concomitant medication. This subject received only Treatments B and C (N=24) and was not dosed with Treatments A and D (N=23).

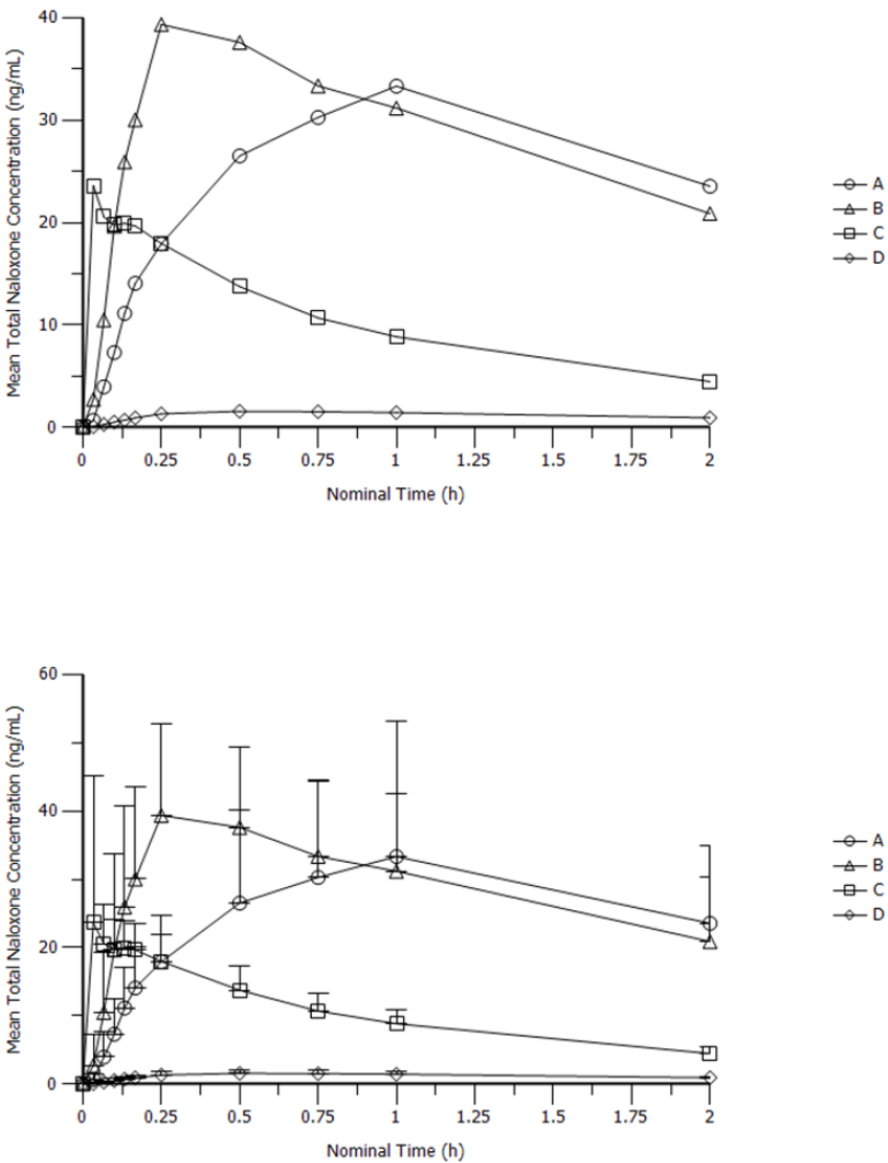
Source data: [Table 14.4.1.1](#)

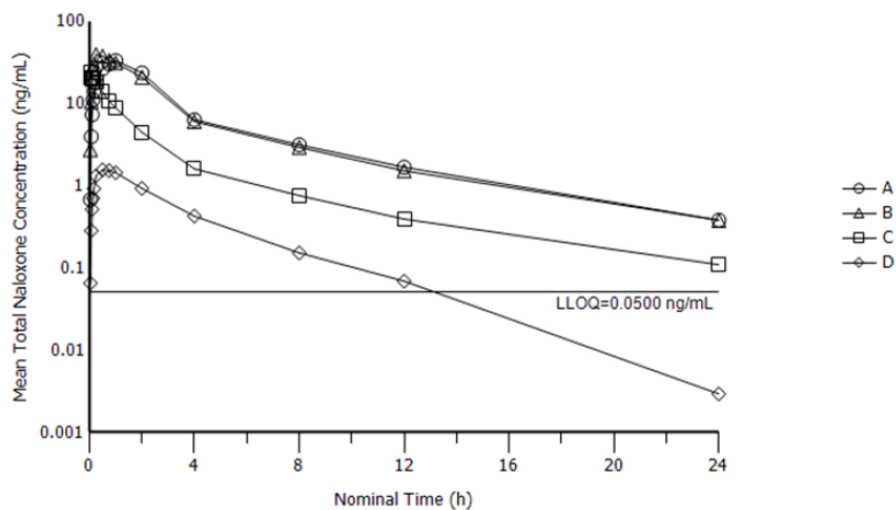
Mean total naloxone plasma concentration-time profiles are shown in [Synopsis Figure 2](#).

Based on the mean plasma concentration-time profiles, the highest total naloxone plasma levels were achieved after administration of Nasal Spray 8 mg ((b)(4)% alcohol), followed by Naloxone Nasal Spray 8 mg (20% alcohol), Naloxone HCl IV Injection 2 mg, and Naloxone HCl IM Injection 0.4 mg.

Additionally, mean total naloxone concentrations after the administration of Naloxone Nasal Spray 8 mg containing ((b)(4)% alcohol) were higher than those observed after the administration of Naloxone Nasal Spray 8 mg containing 20% alcohol at all timepoints from 2 through 45 minutes postdose, and similar after 1 h until the last timepoint at 24 h postdose.

Synopsis Figure 2. Mean Total Naloxone Plasma Concentration-Time Profiles on Linear Scale (over 2 h), +SD on Linear Scale (over 2 h), and Semi-Logarithmic Scale (over 24 h)





Treatment A=Naloxone Nasal Spray 8 mg (20% alcohol) (N=23), Treatment B=Naloxone Nasal Spray 8 mg (0.4% alcohol) (N=24), Treatment C=Naloxone HCl IV Injection 2 mg (N=24), Treatment D=Naloxone HCl IM Injection 0.4 mg (N=23).
 Note: One subject (Subject (b) (6)) was withdrawn by the Investigator on Day 9 of the study due to concomitant medication. This subject received only Treatments B and C (N=24) and was not dosed with Treatments A and D (N=23).

Source data: Table 14.4.1.2

Pharmacokinetic Parameters

Geometric mean partial AUCs of unconjugated naloxone at early times through 2 h postdose are listed in Synopsis Table 2 for comparison across formulations.

Geometric mean partial AUCs of unconjugated naloxone after the administration of Naloxone HCl IV Injection 2 mg were the highest through 10 min postdose.

Partial AUCs of unconjugated naloxone after the administration of Naloxone Nasal Spray 8 mg (90% alcohol) were the highest at 15 min postdose and later times.

Compared to Naloxone HCl 0.4 mg IM, partial AUCs of unconjugated naloxone for both formulations of Naloxone Nasal Spray were appreciably higher at all time points.

Synopsis Table 2. Geometric Mean Partial AUCs of Unconjugated Naloxone Through 2 h Postdose

Formulation	Time (min)									
	2	4	6	8	10	15	30	45	60	120
Naloxone Nasal Spray 8 mg (20% alcohol) (N=23)	0.00567	0.0541	0.174	0.371	0.647	1.42	3.82	6.01	7.81	12.3
Naloxone Nasal Spray 8 mg (90% alcohol) (N=24)	0.0220	0.172	0.507	1.00	1.62	3.28	7.63	10.8	13.2	19.1
Naloxone HCl IV Injection 2 mg (N=24)	0.302	0.879	1.36	1.75	2.11	2.87	4.67	6.01	7.05	9.60
Naloxone HCl IM Injection 0.4 mg (N=23)	NC	0.00513	0.0153	0.0304	0.0500	0.108	0.297	0.472	0.633	1.13

Note: Geometric mean partial AUCs reported in h*ng/mL to 3 significant figures.

Treatment A=Naloxone Nasal Spray 8 mg (20% alcohol), Treatment B=Naloxone Nasal Spray 8 mg (90% alcohol), Treatment C=Naloxone HCl IV Injection 2 mg, Treatment D=Naloxone HCl IM Injection 0.4 mg.

NC=not calculated due to zero value AUC for one subject in Treatment D

Source data: [Table 14.4.1.3](#)

The pharmacokinetic parameters of unconjugated naloxone are summarized below by treatment and formulation in [Synopsis Table 3](#) (primary PK parameters). Exposure parameter ratios between formulations with 90% confidence intervals are shown in [Synopsis Table 4](#).

Synopsis Table 3. Mean±SD (CV%) [Geometric Mean] Plasma Pharmacokinetic Parameters of Unconjugated Naloxone

Treatment	A	B	C	D
Formulation / Route	Naloxone Nasal Spray (20% alcohol)	Naloxone Nasal Spray ((b) (4) % alcohol)	Naloxone IV (1 mg/mL)	Naloxone IM (0.4 mg/mL)
Dose (mg)	8	8	2	0.4
N ^a	23 (19)	24 (20)	24 (24)	23 (23)
C _{max} ^b (ng/mL)	12.8 ± 4.73 (37.0) [12.0]	25.6 ± 11.4 (44.5) [23.1]	26.2 ± 21.6 (82.4) [20.8]	0.910 ± 0.335 (36.8) [0.857]
C ₀ ^c (ng/mL)	0.00	0.00	53.9 ± 85.0 (158) [24.4]	0.000500
T _{max} ^d (h)	0.250 (0.100 – 1.00)	0.250 (0.100 – 0.500)	0.0500 (0.0333 – 0.100)	0.250 (0.100 – 1.00)
AUC _{0-0.25} (ng•h/mL)	1.60 ± 0.808 (50.5) [1.42]	3.75 ± 1.97 (52.6) [3.28]	3.01 ± 1.09 (36.2) [2.87]	0.119 ± 0.0528 (44.3) [0.108]
AUC ₀₋₂ (ng•h/mL)	12.9 ± 4.17 (32.2) [12.3]	20.4 ± 7.11 (34.9) [19.1]	9.95 ± 2.96 (29.7) [9.60]	1.16 ± 0.320 (27.4) [1.13]
AUC _{last} (ng•h/mL)	18.4 ± 6.13 (33.4) [17.4]	27.3 ± 8.63 (31.6) [25.9]	12.7 ± 3.51 (27.6) [12.3]	1.87 ± 0.460 (24.7) [1.81]
AUC _{0-inf} (ng•h/mL)	19.0 ± 6.21 (32.7) [18.0]	28.3 ± 8.00 (28.3) [27.1]	12.8 ± 3.52 (27.5) [12.3]	1.95 ± 0.427 (21.9) [1.90]
t _{1/2} (h)	1.76 ± 0.697 (39.7) [1.66]	2.03 ± 1.58 (77.8) [1.73]	1.22 ± 0.201 (16.4) [1.21]	1.40 ± 0.543 (38.9) [1.34]
CL ^e or CL/F (L/h)	468 ± 164 (35.0) [443]	310 ± 111 (35.9) [295]	167 ± 40.3 (24.1) [162]	215 ± 48.3 (22.4) [210]
Vz ^e or Vz/F (L)	1130 ± 432 (38.3) [1060]	954 ± 986 (103) [737]	297 ± 94.7 (31.9) [282]	432 ± 165 (38.2) [406]

^a Reported as total number of subjects (number of subjects with reportable AUC_{0-inf}, t_{1/2}, CL/F, CL, Vz/F, and Vz, for which a log-linear terminal phase could be determined).

^b C_{max} of Naloxone IV was observed value from the first sampling time of 2 min postdose.

^c C₀ was measured value at 0 h (predose) for Naloxone Nasal Spray and IM formulations (Treatments A, B, and D, Table 14.4.1.1); C₀ was estimated by back-extrapolation to time 0 for Naloxone IV (Treatment C, Table 14.4.1.3).

^d Reported as median (min - max)

^e Reported only for IV dose

Note: One subject (Subject (b) (6)) was withdrawn by the Investigator on Day 9 of the study due to concomitant medication. This subject received only Treatments B and C (N=24) and was not dosed with Treatments A and D (N=23).

Source data: Table 14.4.1.3

Synopsis Table 4. Geometric Mean Ratios (90% CI) for Comparisons of Unconjugated Naloxone C_{max}, AUC_{last}, and AUC_{0-inf} across Treatments

Treatment	A vs. C	B vs. C	A vs. D	B vs. D	A vs. B
C _{max} (%)	57.6 (46.2-71.6)	111 (89.4-138)	1400 (1130-1750)	2700 (2170-3370)	51.9 (41.7-64.6)
AUC _{last} (%)	142 (127-158)	211 (189-235)	961 (861-1070)	1430 (1280-1590)	67.3 (60.3-75.1)
AUC _{0-inf} (%)	148 (133-163)	222 (201-245)	958 (865-1060)	1440 (1300-1590)	66.6 (59.9-74.1)

Note: Ratios (90% CI) represented as percentages

Treatment A=Naloxone Nasal Spray 8 mg (20% alcohol), Treatment B=Naloxone Nasal Spray 8 mg ((b) (4) % alcohol), Treatment C=Naloxone HCl IV Injection 2 mg, Treatment D=Naloxone HCl IM Injection 0.4 mg

Source data: Listings 16.2.6.5.15 through 16.2.6.5.21

Following a single 8 mg dose of Naloxone Nasal Spray containing 20% alcohol or (b)(4)% alcohol versus a single 2 mg IV and 0.4 mg IM injection:

- Unconjugated naloxone mean plasma concentrations were highest after Naloxone HCl IV Injection 2 mg, followed by Naloxone Nasal Spray 8 mg ((b)(4)% alcohol), Naloxone Nasal Spray 8 mg (20% alcohol), and Naloxone HCl IM Injection 0.4 mg.
- Unconjugated naloxone was absorbed rapidly into the systemic circulation with a median T_{max} of 15 min, which was comparable to the T_{max} after a single dose of 0.4 mg IM Naloxone.
- Unconjugated naloxone geometric mean C_{max} after administration of Naloxone Nasal Spray was 14- to 27-fold higher than that for Naloxone 0.4 mg IM and, similar (1.1-fold for the Naloxone Nasal Spray in (b)(4)% alcohol) or lower (0.58-fold for Naloxone Nasal Spray in 20% alcohol) compared to the observed C_{max} at 2 min postdose (the first postdose sampling time) after administration of Naloxone 2 mg IV. The estimated C_0 (geometric mean of 24.4 ng/mL) for the 2 mg IV was higher than the observed C_{max} for both test Naloxone Nasal Spray formulations.
- Unconjugated naloxone geometric mean AUC_{last} and AUC_{0-inf} after administration of Naloxone Nasal Spray formulations were 9.6- to 14-fold higher than the reference Naloxone 0.4 mg IM and 1.4- to 2.2-fold higher than the reference Naloxone 2 mg IV.
- Geometric mean partial AUCs of unconjugated naloxone after the administration of Naloxone Nasal Spray 8 mg containing 20% alcohol or (b)(4)% alcohol were appreciably lower than those after the administration of Naloxone HCl 2 mg IV from 2 minutes (0.00567 and 0.0220 h*ng/mL versus 0.302 h*ng/mL) through 10 minutes postdose.
- Unconjugated naloxone exposure (based on C_{max} , AUC_{last} , and AUC_{0-inf}) of the 8 mg test nasal spray formulation in (b)(4)% alcohol was 1.5- to 1.9-fold higher than that for the test formulation in 20% alcohol.

The pharmacokinetic parameters of total naloxone are summarized below by treatment and formulation in [Synopsis Table 5](#). Exposure parameter ratios between formulations with 90% confidence intervals are shown in [Synopsis Table 6](#).

Synopsis Table 5. Mean±SD (CV%) [Geometric Mean] Plasma Pharmacokinetic Parameters of Total Naloxone

Treatment	A	B	C	D
Formulation / Route	Naloxone Nasal Spray (20% alcohol)	Naloxone Nasal Spray ((b)(4))% alcohol)	Naloxone IV (1 mg/mL)	Naloxone IM (0.4 mg/mL)
Dose (mg)	8	8	2	0.4
N ^a	23 (21)	24 (20)	24 (21)	23 (23)
C _{max} (ng/mL)	39.9 ± 19.8 (49.5) [35.6]	44.5 ± 12.0 (27.0) [43.0]	29.3 ± 18.8 (64.2) [25.9]	1.66 ± 0.480 (28.9) [1.60]
T _{max} ^b (h)	1.00 (0.25-2.00)	0.500 (0.100-2.00)	0.100 (0.0333-0.500)	0.500 (0.167-1.00)
AUC _{0-0.25} (ng•h/mL)	2.33 ± 1.05 (45.2) [2.11]	5.32 ± 2.50 (46.9) [4.80]	4.67 ± 1.29 (27.5) [4.53]	0.159 ± 0.0645 (40.5) [0.147]
AUC ₀₋₂ (ng•h/mL)	50.4 ± 18.4 (36.6) [46.8]	57.1 ± 15.7 (27.4) [55.0]	20.5 ± 4.21 (20.5) [20.1]	2.44 ± 0.574 (23.5) [2.38]
AUC _{last} (ng•h/mL)	114 ± 38.3 (33.6) [107]	116 ± 30.6 (26.4) [112]	35.2 ± 7.37 (21.0) [34.4]	5.25 ± 1.12 (21.4) [5.12]
AUC _{0-inf} (ng•h/mL)	120 ± 40.2 (33.6) [112]	117 ± 32.5 (27.7) [113]	37.0 ± 7.69 (20.8) [36.1]	5.57 ± 1.18 (21.2) [5.44]
t _{1/2} (h)	5.14 ± 1.38 (26.8) [4.98]	5.31 ± 1.26 (23.7) [5.17]	4.98 ± 1.59 (32.0) [4.70]	3.00 ± 1.18 (39.4) [2.86]

^a Reported as number of total subject (number of subjects with reportable AUC_{0-inf} and t_{1/2}, for which a log-linear terminal phase could be determined)

^b Reported as median (min - max)

Note: One subject (Subject (b)(6)) was withdrawn by the Investigator on Day 9 of the study due to concomitant medication. This subject received only Treatments B and C (N=24) and was not dosed with Treatments A and D (N=23).

Source data: Table 14.4.1.4

Synopsis Table 6. Geometric Mean Ratios (90% CI) for Comparisons of Total Naloxone C_{max}, AUC_{last}, AUC_{0-inf} across Treatments

Treatment	A vs C	B vs C	A vs D	B vs D	A vs B
C _{max} (%)	138 (115-165)	166 (138-198)	2230 (1850-2680)	2680 (2240-3220)	83.0 (69.2-99.6)
AUC _{last} (%)	310 (275-348)	326 (290-365)	2090 (1860-2350)	2200 (1950-2470)	95.1 (84.6-107)
AUC _{0-inf} (%)	306 (271-346)	306 (271-347)	2070 (1840-2330)	2070 (1830-2340)	99.9 (88.2-113)

Note: Ratios (90% CI) represented as percentages

Treatment A=Naloxone Nasal Spray 8 mg (20% alcohol), Treatment B=Naloxone Nasal Spray 8 mg ((b)(4))% alcohol), Treatment C=Naloxone HCl IV Injection 2 mg, Treatment D=Naloxone HCl IM Injection 0.4 mg

Source data: Listings 16.2.6.5.22 through 16.2.6.5.28

Following a single 8 mg dose of Naloxone Nasal Spray containing 20% alcohol or (b) (4)% alcohol versus a single 2 mg IV and 0.4 mg IM injection:

- Total naloxone after a single 8 mg dose of Naloxone Nasal Spray ((b) (4)% alcohol) was present in the systemic circulation with a median T_{max} of 30 min, which is comparable to the T_{max} after a single dose of 0.4 mg IM Naloxone. Median T_{max} of 60 min was observed for Naloxone Nasal Spray 8 mg (20% alcohol).
- Total naloxone geometric mean C_{max} after a single 8 mg dose of Naloxone Nasal Spray formulations were 22- to 27-fold higher than the reference Naloxone 0.4 mg IM, and 1.4- to 1.7-fold higher than the observed total naloxone C_{max} at 2 min postdose (the first postdose sampling time) after a single 2 mg of Naloxone IV.
- Total naloxone geometric mean AUC_{last} and AUC_{0-inf} after the administration of Naloxone Nasal Spray formulations were 21- to 22-fold higher than the reference Naloxone 0.4 mg IM, and 3.1- to 3.3-fold higher than the reference Naloxone 2 mg IV.
- Total naloxone geometric mean values of C_{max} , AUC_{last} and AUC_{0-inf} were similar between the two nasal spray formulations with 1.0- to 1.2-fold difference.

SAFETY RESULTS:

No AEs were serious or led to a subject discontinuation. A total of 57 AEs were reported by 16 (66.7%) subjects following dose administration. All other AEs were mild or moderate in severity.

A total of 19 AEs were reported by 10 (43.5%) subjects following Naloxone Nasal Spray, 8 mg (containing 20% alcohol). Of these, 2 AEs (nasal discomfort reported by 2 subjects) were judged by the Investigator as definitely related to treatment, 1 AE (asthenia) was judged probably related, and 8 AEs (dizziness reported by 2 subjects, asthenia reported by 1 subject, palpitations reported by 1 subject, dry mouth reported by 1 subject, headache reported by 1 subject, somnolence reported by 1 subject, and tremor reported by 1 subject) reported by were judged possibly related. The remaining AEs were judged as unlikely or not related to treatment.

A total of 10 AEs were reported by 8 (33.3%) subjects following Naloxone Nasal Spray, 8 mg (containing (b) (4)% alcohol). Of these, one AE (dizziness) was judged as definitely related to treatment and 2 AEs (somnolence and diarrhoea) were judged possibly related. The remaining AEs were judged as unlikely or not related to treatment.

A total of 15 AEs were reported by 9 (37.5%) subjects following Naloxone HCl IV Injection, 2 mg (1 mg/mL). Of these, 2 AEs (dizziness reported by 1 subject and vision blurred reported by 1 subject) were judged as probably related to treatment, 6 AEs (dizziness reported by 3 subjects, fatigue reported by 1 subject, dyspepsia reported by 1 subject, and presyncope reported by 1 subject) were judged possibly related. The remaining AEs were judged as unlikely or not related to treatment.

A total of 13 AEs were reported by 5 (21.7%) subjects following Naloxone HCl IM Injection, (0.4 mg/mL). Of these, 2 AEs (nasal congestion reported by 1 subject and distractibility reported by 1 subject) were judged by the Investigator as probably related to treatment and 3 AEs (dizziness reported by 2 subjects and headache reported by 1 subject) were judged possibly related. The remaining AEs were judged as unlikely or not related to treatment.

An overview of the AEs reported during this study is provided in the [table](#) below.

Adverse Events, Overall Summary of Treatment-Emergent Adverse Events (TEAEs) - Safety Population

	Naloxone Nasal Spray, 8 mg (20% alcohol) (N=23)	Naloxone Nasal Spray, 8 mg (b)(4)% alcohol (N=24)	Naloxone HCL IV Injection, 2 mg (1 mg/mL) (N=24)	Naloxone HCL IM Injection, 0.4 mg/mL (N=23)	Overall (N=24)
Treatment	A	B	C	D	
At Least 1 Treatment-Emergent Adverse Event	10 (43.5)	8 (33.3)	9 (37.5)	5 (21.7)	16 (66.7)
At Least 1 Study Drug-Related Adverse Event	7 (30.4)	3 (12.5)	6 (25.0)	3 (13.0)	9 (37.5)
At Least 1 Serious Treatment-Emergent Adverse Event	0	0	0	0	0
At Least 1 Serious Study Drug-Related Adverse Event	0	0	0	0	0
At Least 1 Treatment-Emergent Adverse Event Leading to Treatment Discontinuation	0	0	0	0	0
At Least 1 Treatment-Emergent Adverse Event Leading to Death	0	0	0	0	0

Source: Table 14.3.1.1

Adverse Events were coded by system organ class and preferred term based on the Medical Dictionary for Regulatory Affairs (MedDRA) coding dictionary version 21.0.

The most frequently reported AE was dizziness (reported by 2 subjects following Naloxone Nasal Spray, 8 mg [20% alcohol], reported by 1 subject following Naloxone Nasal Spray, 8 mg (b)(4)% alcohol], reported by 5 subjects following Naloxone HCL IV Injection, 2 mg [1mg/mL], and reported by 2 subjects following Naloxone HCL IM Injection, 0.4 mg/mL). The Investigator judged all AEs as mild in severity except for two judged as moderate; toothache following Naloxone HCL IV Injection, 2 mg (1mg/mL) judged not related to treatment and presyncope following Naloxone Nasal Spray, 8 mg (20% alcohol) judged unlikely related to treatment. Of the total 57 AEs, 3 (5.3%) were judged definitely related to study treatment, 5 (8.8%) were judged probably related to treatment, 19 (33.4%) were judged possibly related to treatment, 21 (36.8%) was judged unlikely related to treatment, and 9 (15.8%) were judged as not related to treatment.

The number of subjects with TEAEs by system organ class and preferred term is presented in the table below.

Adverse Event, Number (%) of Subjects with Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Safety Population

MedDRA Primary System Organ Class MedDRA Preferred Term	Number of Subjects Reporting				Overall (N=24)
	Naloxone Nasal Spray, 8 mg (20% alcohol) (N=23)	Naloxone Nasal Spray, 8 mg (b)(4)% alcohol (N=24)	Naloxone HCL IV Injection, 2 mg (1 mg/mL) (N=24)	Naloxone HCL IM Injection, 0.4 mg/mL (N=23)	
Treatment	A	B	C	D	

Blood and lymphatic system disorders					
Neutropenia	0	1 (4.2)	0	0	1 (4.2)
Cardiac disorders					
Palpitations	1 (4.3)	0	0	0	1 (4.2)
Eye disorders					
Conjunctival hyperaemia	1 (4.3)	0	0	0	1 (4.2)
Vision blurred	0	0	1 (4.2)	0	1 (4.2)
Gastrointestinal disorders					
Abdominal discomfort	0	1 (4.2)	0	0	1 (4.2)
Abdominal pain	1 (4.3)	0	0	0	1 (4.2)
Aphthous ulcer	0	0	1 (4.2)	0	1 (4.2)
Dental discomfort	0	0	1 (4.2)	0	1 (4.2)
Diarrhoea	0	1 (4.2)	0	1 (4.3)	2 (8.3)
Dry mouth	1 (4.3)	0	0	1 (4.3)	2 (8.3)
Dyspepsia	0	0	1 (4.2)	1 (4.3)	2 (8.3)
Nausea	1 (4.3)	0	0	1 (4.3)	2 (8.3)
Salivary hypersecretion	1 (4.3)	0	0	0	1 (4.2)
Toothache	0	0	1 (4.2)	0	1 (4.2)
General disorders and administration site conditions					
Asthenia	2 (8.7)	0	0	0	2 (8.3)
Fatigue	0	0	1 (4.2)	1 (4.3)	2 (8.3)
Vessel puncture site pain	0	0	0	1 (4.3)	1 (4.2)
Injury, poisoning and procedural complications					
Tooth fracture	0	0	1 (4.2)	0	1 (4.2)
Musculoskeletal and connective tissue disorders					
Back pain	0	1 (4.2)	0	0	1 (4.2)
Nervous system disorders					
Dizziness	2 (8.7)	1 (4.2)	5 (20.8)	2 (8.7)	6 (25.0)
Headache	2 (8.7)	1 (4.2)	1 (4.2)	1 (4.3)	2 (8.3)
Presyncope	2 (8.7)	0	1 (4.2)	0	2 (8.3)
Somnolence	1 (4.3)	1 (4.2)	0	0	1 (4.2)
Tremor	1 (4.3)	0	0	0	1 (4.2)
Psychiatric disorders					
Distractibility	0	0	0	1 (4.3)	1 (4.2)
Renal and urinary disorders					
Urine odor abnormal	0	1 (4.2)	0	0	1 (4.2)
Respiratory, thoracic and mediastinal disorders					
Nasal congestion	0	0	1 (4.2)	2 (8.7)	2 (8.3)
Nasal discomfort	2 (8.7)	0	0	0	2 (8.3)
Skin and subcutaneous tissue disorders					
Dermatitis	0	1 (4.2)	0	0	1 (4.2)
Vascular disorders					
Flushing	0	1 (4.2)	0	0	1 (4.2)
Orthostatic hypotension	1 (4.3)	0	0	0	1 (4.2)
Subjects are counted once, per treatment group or once overall within a system organ class and preferred term.					

Adverse events were coded using MedDRA Version 21.0

Source: [Table 14.3.1.2](#)

No deaths, or other serious AEs occurred during the conduct of this study. Two significant AEs (neutropenia and orthostatic hypotension) were reported. Narratives are provided in [Section 12.3.2](#).

EFFICACY RESULTS:

Not applicable.

CONCLUSIONS:

Following a single 8 mg dose of two test formulations of Naloxone Nasal Spray containing 20% alcohol or (b)(4)% alcohol versus a single 2 mg IV or 0.4 mg IM, unconjugated naloxone was rapidly absorbed into systemic circulation with a median T_{max} of 15 min for both of the test formulations, which is comparable to the T_{max} after a single dose of 0.4 mg IM Naloxone. The mean unconjugated naloxone concentrations after the administration of the two test formulations were appreciably higher than those observed after the administration of the IM dose at all timepoints from 2 minutes (0.635 and 2.71 ng/mL versus 0.0734 ng/mL) through 24 h postdose.

The geometric mean values of unconjugated naloxone exposure (C_{max} , AUC_{last} , AUC_{0-inf}) generated from the Naloxone Nasal Spray formulations were 9.6- to 27-fold higher compared to Naloxone 0.4 mg IM.

Unconjugated naloxone geometric mean C_{max} after administration of Naloxone Nasal Spray formulations was similar (1.1-fold for the Nasal Spray in (b)(4)% alcohol) or lower (0.58-fold for the Nasal Spray in 20% alcohol) compared to the observed C_{max} at 2 min postdose (the first postdose sampling time) after administration of Naloxone 2 mg IV. In addition, the observed C_{max} for both test formulations was lower than the estimated C_0 (geometric mean of 24.4 ng/mL) for the 2 mg IV. The geometric mean AUC_{last} and AUC_{0-inf} of unconjugated naloxone generated from the two test formulations were 1.4- to 2.2-fold higher compared to Naloxone 2 mg IV.

The Naloxone Nasal Spray in (b)(4)% alcohol achieved 1.5- to 1.9-fold higher unconjugated naloxone exposure levels than the Naloxone Nasal Spray in 20% alcohol.

Unconjugated naloxone was eliminated rapidly with a geometric mean terminal $t_{1/2}$ less than 2 h for all study formulations.

Total naloxone exposure (C_{max} , AUC_{last} , AUC_{0-inf}) was from 21- to 27-fold higher for the two test formulations compared to the 0.4 mg IM, and 1.4- to 3.3-fold higher compared to the 2 mg IV injection. In general, comparable total naloxone exposure was observed between the two test formulations with exposure ratios (Naloxone Nasal Spray in 20% versus (b)(4)% alcohol) from 0.83 to 1.0.

Overall, the investigational products were generally well-tolerated in healthy subjects. Although efficacy was not measured in the current study, the pharmacokinetic results demonstrated similar unconjugated naloxone concentration levels for the Naloxone Nasal Spray 8 mg formulations and intravenous naloxone 2 mg, and systemic exposure to unconjugated naloxone was on the same order for both routes of administration.

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