Office of Clinical Pharmacology Review

NDA or BLA Number	215487
Link to EDR	\\CDSESUB1\evsprod\NDA215487\0001
Submission Date	3/24/2023
Submission Type	Original 505 (b)(2) submission Standard review: PDUFA date: 1/24/2024 (proposed early action on 11/17/2023)
Brand Name	TBD
Generic Name	Naloxone hydrochloride (HCl) nasal spray 10 mg
Dosage Form and Strength	Solution for pre-filled intranasal spray device (b) (4) one spray (0.11 mL) delivers 10 mg naloxone HCl
Route of Administration	Intranasal
Indication	TRADENAME Nasal Spray is an opioid antagonist for the emergency treatment of known or suspected opioid ((b) (4) overdose, as manifested by respiratory and/or central nervous system depression. TRADENAME Nasal Spray is intended for immediate administration as emergency therapy in settings where opioids may be present. TRADENAME Nasal Spray is not a substitute for emergency medical care.
Dosage and Administration	• TRADENAME Nasal Spray is for intranasal use only. Seek emergency medical care immediately after use. • Administration of a single spray of TRADENAME Nasal Spray intranasally into one nostril. • If the patient does not respond within 2 minutes or responds and then relapses into respiratory depression, a second dose of TRADNAME Nasal Spray may be given into the other nostril with a new device. • Do not administer more than 2 sprays of TRADENAME Nasal Spray per day. • Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance.
Applicant	Summit Biosciences Inc
Associated IND	IND 142850, and PIND 141634
OCP Reviewer	Wei Qiu, Ph.D.
OCP Team leader	Yun Xu, Ph.D.

Table of Contents

1. EXECUTIVE SUMMARY

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Neuropsychiatric Pharmacology (OCP/DNP) has reviewed the information submitted in the current application, NDA 215487, for Naloxone HCl nasal spray 10 mg, submitted on 3/24/2023. From a clinical pharmacology perspective, the information submitted in the NDA submission is acceptable.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	In the comparative bioavailability study 11875901, the mean partial AUC values, AUC0-2.5min, AUC0-5min, and AUC0-10min, during the early absorption phase for an intranasal (IN) administration of a single spray of the proposed Naloxone HCl nasal spray 10 mg (i.e., 10 mg IN dose) in one nostril were 4.4-fold, 4.1-fold, and 5.2-fold greater than that for a single 0.4 mg intramuscular (IM) injection. A single 10 mg IN dose showed 12-fold greater Cmax, 9.8- to 9.9-fold greater AUC0-t and AUC0-inf values than a single dose of 0.4 mg IM injection. Because the approved initial dose of Narcan injection (NDA 016636) is from 0.4 mg to 2 mg in adults via IV, IM or SC administration, the Applicant's proposed reliance on

	effectiveness findings of Narcan injection (NDA 016636) is warranted.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Same dosing recommendation as the listed drug Narcan Injection (NDA 016636)
Labeling	See labeling comments in Section 2.4
Bridge between the to-be-marketed and clinical trial formulations	The clinical formulation used in the comparative bioavailability study is identical to the proposed commercial formulation
Other (specify)	Not applicable.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

(1) A single spray of the proposed Naloxone HCl nasal spray 10 mg in one nostril (i.e., 10 mg IN dose) exhibited a median (min, max) Tmax of 0.75 hour (0.25, 1.03 hour). The median (min, max) Tmax for 0.4 mg IM injection was 0.50 hour (0.17, 2.00 hour).

(2) A 10 mg IN dose of the proposed Naloxone HCl nasal spray 10 mg showed higher naloxone plasma concentrations than 0.4 mg IM injection at all post-dose timepoints including early absorption phase. The mean partial AUC values, AUC0-2.5min, AUC0-5min, and AUC0-10min, during the early absorption phase for a 10 mg IN dose were 4.4-fold, 4.1-fold, and 5.2-fold greater than those for a 0.4 mg IM injection. A 10 mg IN dose showed 12-fold greater Cmax, 9.9-fold greater AUC0-t and 9.8-fold greater AUC0-inf values than a 0.4 mg IM injection. Because the approved initial dose of Narcan injection (NDA 016636) is from 0.4 mg to 2 mg in adults via IV, IM or SC administration, the Applicant's proposed reliance on effectiveness findings of Narcan injection (NDA 016636) is warranted.

(3) A 10 mg IN dose of the proposed Naloxone HCl nasal spray 10 mg showed 49% lower Cmax, but 58% and 60% greater AUC0-t and AUC0-inf values, respectively, than a 2 mg intravenous (IV) injection. The mean absolute bioavailability of naloxone based on AUC0-inf for IN dosing was 34% relative to IV dosing. The applicant is relying on data from the published literature that document the use of higher doses of naloxone in order to support the systemic safety of the higher systemic naloxone exposures that are achieved with the proposed product as compared to the relied-upon Narcan product (Naloxone 2 mg IV injection). The data described in the submitted literature are scientifically relevant to the proposed product because the studies used the same active pharmaceutical ingredient as contained in the applicant's drug product and the doses used in the reported studies are relevant to the proposed dose (see more details in Clinical Review).

- **Regulatory History**

The Applicant submitted a 505(b)(2) NDA 215487 on 3/24/2023 for Naloxone HCl nasal spray 10 mg in 0.11 mL solution in a pre-filled intranasal device as a prescription product for emergency treatment of opioid overdose. The Applicant proposed to rely on the FDA's previous finding of safety and effectiveness for Narcan (naloxone HCl) injection (NDA 016636) and published literature to support the safety and effectiveness of Naloxone HCl nasal spray 10 mg. Narcan injection (NDA 016636) was approved for emergency treatment of known or suspected opioid overdose. In adults with opioid overdose, an initial dose of 0.4 mg to 2 mg of Narcan may be administered via IV route. If the desired degree of counteraction and improvement in respiratory functions are not obtained, it may be repeated at two- to three-minute intervals. If no response is observed after 10 mg of Narcan have been administered, the diagnosis of opioid-induced or partial opioid-induced toxicity should be questioned. IM or SC administration may be necessary if the IV route is not available. Currently, the original NDA 016636 for Narcan injection was withdrawn not for reasons of safety or effectiveness.

Because the original NDA 016636 for Narcan injection was withdrawn not for reasons of safety or effectiveness, the Applicant conducted the comparative bioavailability Study 11875901 in healthy adult volunteers using Hospira Inc's Naloxone HCl injection (0.4 mg/mL) (ANDA 070256) to the original NDA 016636 given as 1 mL IM injection (0.4 mg IM dose) as the comparator to establish PK bridge. This approach of using generic product to the original NDA was deemed acceptable per Pre-IND 141634 meeting held on 2/7/2019. Because the approved initial dose of Narcan injection is from 0.4 mg to 2 mg in adults, using 0.4 mg IM injection as the comparator to establish a scientific bridge to Narcan injection was deemed acceptable per Pre-IND 141634 meeting minutes dated 3/7/2019. The Applicant was further recommended that "*Since rapid onset of action is critical for reversal of opioid overdose, your proposed product must demonstrate comparable or higher exposure to the comparator in the comparative bioavailability study during the early absorption phase. Based on the listed drug's label, if the desired response is not obtained after 2 or 3 minutes, an additional dose will be administered. Therefore, the early time period, especially the first 2 to 5 minutes, is critical to effectiveness of the product and patient survival. It is expected that your product will demonstrate comparable or higher exposure to the reference from the first blood sampling time point (i.e., AUC0-2.5 min, or drug concentration at 2.5 min in your study). Your proposed product may be suitable to reverse opioid overdose in the community only if it demonstrates comparable or higher systemic exposure, and comparable or quicker onset of action (i.e., by examining Tmax, Cmax, partial AUC, AUCt, and AUCinf values) to the reference drug given at an approved dose and by an approved route of administration in your comparative bioavailability study. If your product demonstrates a substantially higher systemic exposure than the reference product, additional data or justification may be required to assure that the higher exposure does not represent a safety concern*". In the Advice letter for IND 142850 date 12/11/2019, the Applicant was recommended "*you may consider adding an additional treatment arm with the reference product administered by the IV route at the highest approved initial dose (i.e., 2 mg) to support systemic safety of your proposed higher-strength nasal spray product*". The sponsor added a third treatment arm (2 mg IV bolus) to Study 11875901. In the IND 142850 Type C WRO meeting minutes dated 10/27/2020, the Applicant was recommended "*As you stated in the meeting package, naloxone AUC0-t and AUC0-inf values from a single 10 mg IN administration are approximately 1.6-fold higher than those from a single 2 mg IV injection. It would be expected that following the approved dosing regimen for Narcan injectable (i.e., repeated doses at two- to three-minute intervals), the AUC values for your proposed product are*

greater than the 2 mg IV dose. You should provide additional safety information for your proposed 10 mg IN product in your NDA submission".

The final to-be-marketed formulation was used in the comparative bioavailability study 11875901.

- **Summary of Pharmacokinetic Results**

Comparative Bioavailability of Proposed Naloxone HCl Nasal Spray 10 mg in Comparison with 0.4 mg IM Injection and 2 mg IV Injection (Results from Study 11875901)

The 10 mg IN administration of the proposed Naloxone HCl nasal spray 10 mg showed a median (min, max) Tmax of 0.75 hour (0.25, 1.03 hour). The median (min, max) Tmax was 0.50 hour (0.17, 2.00 hour) for 0.4 mg IM injection. The mean absolute bioavailability of naloxone for IN dosing based on AUC0-inf was 34% relative to IV dosing. The mean terminal half-life values were 1.33 hour, 1.22 hour, and 1.18 hour for IN dosing, IM dosing, and IV bolus dosing, respectively.

The systemic plasma exposure of naloxone from a single 10 mg IN administration of the proposed Naloxone HCl Nasal Spray 10 mg (Treatment A) was higher than that from a single 0.4 mg IM injection (Treatment B) at all post-dose timepoints. The mean early partial AUC values, AUC0-2.5min, AUC0-5min, and AUC0-10min during the early absorption phase for a single 10 mg IN dose were 4.4-fold, 4.1-fold, and 5.2-fold greater than those for a single 0.4 mg IM injection. The mean AUC0-t, AUC0-inf, and Cmax values for a single 10 mg IN dose were 9.9-fold, 9.8-fold, and 12-fold greater than 0.4 mg IM injection because the geometric mean ratios (90% CI) for AUC0-t, AUC0-inf, and Cmax for 10 mg IN dose/0.4 mg IM injection were 991.93% (895.14% - 1099.18%), 976.69% (883.69% - 1079.48%), and 1248.65% (1072.00% - 1454.41%), respectively.

The systemic plasma exposure of naloxone from a single 10 mg IN administration of Naloxone HCl Nasal Spray 10 mg (Treatment A) were lower than that from a single 2 mg IV injection (Treatment C) at early time points. The mean partial AUC values, AUC0-2.5min, AUC0-5min, and AUC0-10min during the early absorption phase for a single 10 mg IN dose were 0.98%, 2.45%, and 8% of those for a single 2 mg IV injection. Naloxone Cmax for a single 10 mg IN dose was 49% lower than that for a single 2 mg IV injection because the geometric mean ratio (95% upper 1-sided confidence interval) for Cmax for a single 10 mg IN dose/2 mg IV injection were 51.42% (62%). Naloxone AUC0-t and AUC0-inf values for a single 10 mg IN dose were 58% and 60% greater than that for a single 2 mg IV injection because the geometric mean ratios (90% upper 1-sided confidence interval) for AUC0-t and AUC0-inf for 10 mg IN dose/2 mg IV injection were 158.44% (176.41%) and 160.11% (178.23%), respectively.

The comparative bioavailability study 11875901 was an open-label, single-dose, randomized, three-treatment, three-period, two-sequence cross-over (Periods I and II: Treatment A and Treatment B), fixed-sequence (Period III: Treatment C) study under fasted conditions in 30 healthy adult male and female subjects (24 subjects continuing to Period III). The primary objectives were to compare the PK of a single 10 mg IN dose of the proposed Naloxone HC nasal spray 10 mg to a single 0.4 mg IM naloxone HCl injection and to confirm that the IN dose achieves comparable or higher systemic exposure at all early time points relative to that of 0.4 mg IM injection. The

secondary objective was to assess the safety and tolerability of the 10 mg IN dose. The tertiary objective was to confirm that the systemic exposure of the 10 mg IN dose does not substantially exceed that of a single 2 mg IV dose.

Treatment A (Test): a single 10 mg IN dose of Naloxone HCl nasal spray 10 mg (10 mg/spray x 1 spray)
Treatment B (Reference): a single 0.4 mg IM dose of Naloxone HCl Injection 0.4 mg/mL (ANDA 070256 product from Hospira) (0.4 mg/mL x 1 mL)
Treatment C (Reference): single 2 mg IV bolus dose of Naloxone HCl Injection 0.4 mg/mL (ANDA 070256 product from Hospira) (0.4 mg/mL x 5 mL)

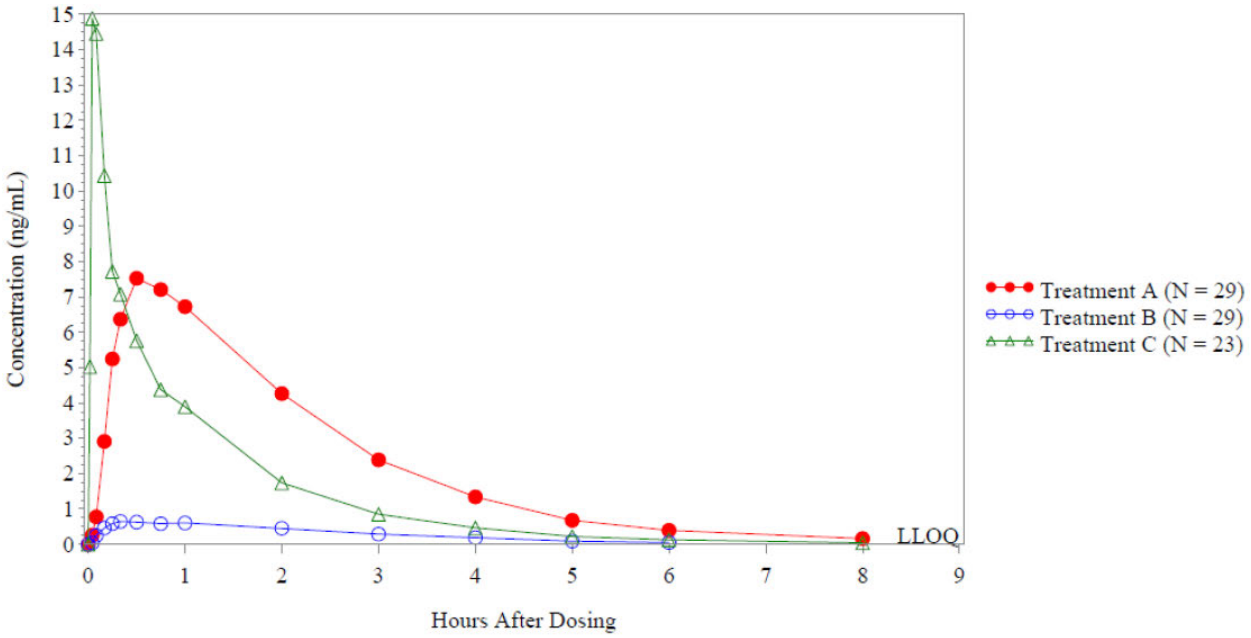
Treatment A [10 mg IN dose] was given via IN administration of one spray into one nostril with subjects in a fully supine position. The subjects were instructed not to breathe through the nose during administration of the nasal spray and remained fully supine for approximately one- hour post-dose. Treatment B [0.4 mg IM dose] was administered as a 1 mL IM injection to the gluteus maximus muscle. Treatment C [2 mg IV dose] was given as a 5 mL IV bolus injection. To avoid any carry-over effect, the washout period between treatments was at least 4 days.

In Periods I and II (Treatment A [10 mg IN dose] and Treatment B [0.4 mg IM dose]), blood samples for determination of unconjugated (or free) naloxone concentrations in plasma were collected at pre-dose (0) and at 2.5, 5, 10, 15, 20, 30, and 45 minutes, and at 1, 2, 3, 4, 5, 6, and 8 hours post-dose. In Period III (Treatment C [2 mg IV dose]), blood samples were collected at Pre-dose (0) and at 1, 2.5, 5, 10, 15, 20, 30, and 45 minutes, and at 1, 2, 3, 4, 5, 6, and 8 hours post-dose. The PK parameters including AUC0-t, AUCinf, AUC0-1min (for Treatment C only), AUC0-2.5min, AUC0-5min, AUC0-10min, AUC0-15min, AUC0-30min, Cmax and Tmax were determined for unconjugated naloxone. Statistical analyses were performed to compare Cmax and AUCs of the IN test formulation (Treatment A) relative to the IM and IV dosing of the reference product (Treatment B and Treatment C, respectively).

A total of 30 subjects were enrolled and all 30 subjects completed Periods I and II (Treatments A and B) of the study. Of the 30 subjects, 24 continued to Period III. Twenty-three (23) of the 24 subjects who continued to Period III (Treatment C) completed Period III (Treatment C). Subject (b) (6)'s Treatment A (Period II) concentration data were excluded from the statistical analysis of bioequivalence for the comparison of Treatments A and B owing to an incomplete dose administration based on review of the pre-dose and post-dose nasal spray device weights.

The mean naloxone plasma concentration-time profiles following a single dose of one IN spray Naloxone HCl nasal spray 10 mg (Treatment A, Test) versus 0.4 mg IM Injection (Treatment B, Reference) and 2 mg IV injection (Treatment C, Reference) are shown in **Figure 1**. Naloxone PK parameters are summarized in **Table 1**. The statistical comparisons of naloxone Cmax, AUC0-t, AUC0-inf, AUC0-5min, AUC0-2.5min, and AUC0-10min between 10 mg IN dose versus 0.4 mg IM Injection or 2 mg IV injection are shown in **Table 2** and **Table 3**, respectively.

Figure 1 Mean Plasma Concentration Time Profiles of Naloxone Following a Single Dose of One IN Spray of Naloxone HCl Nasal Spray 10 mg (Treatment A, Test) versus 0.4 mg IM Injection (Treatment B, Reference) and 2 mg IV Injection (Treatment C, Reference) from 0-8 hours (Study 11875901)



Mean concentration values below LLOQ (<0.020) in the terminal phase are not plotted

Treatment A – 1 × 110 µL actuation of Naloxone Hydrochloride Nasal Spray, 10 mg/spray (Summit Biosciences Inc.) – 10 mg total dose
Treatment B – 1 × 1.0 mL IM injection of Naloxone Hydrochloride Injection, 0.4 mg/mL (Hospira, Inc.) – 0.4 mg total dose
Treatment C – 1 × 5.0 mL IV bolus of Naloxone Hydrochloride Injection, 0.4 mg/mL (Hospira, Inc.) – 2.0 mg total dose

Source: Study report 11875901 Figure 11-1

Table 1 Mean ± SD (%CV) Naloxone Pharmacokinetic Parameters for 10 mg IN dose of Naloxone HCl Nasal Spray 10 mg versus 0.4 mg IM Injection and 2 mg IV Injection (Study 11875901)

Pharmacokinetic Parameter	Treatment (naloxone hydrochloride)	N	Arithmetic mean ± SD (%CV)
$AUC_{0\text{-}1min}$ (h·ng/mL)	2 mg IV Bolus	23	0.0419 ± 0.0473 (112.8084)
$AUC_{0\text{-}2.5min}$ (h·ng/mL)	10 mg IN	24	0.0044 ± 0.0083 (187.4431)
	0.4 mg IM	27	0.0006 ± 0.0008 (140.6044)
	2 mg IV Bolus	23	0.2919 ± 0.1996 (68.3868)
$AUC_{0\text{-}5min}$ (h·ng/mL)	10 mg IN	28	0.0265 ± 0.0274 (103.5125)
	0.4 mg IM	30	0.0065 ± 0.0059 (90.8921)
	2 mg IV Bolus	23	0.9121 ± 0.4324 (47.4029)
$AUC_{0\text{-}10min}$ (h·ng/mL)	10 mg IN	29	0.1821 ± 0.1333 (73.2232)
	0.4 mg IM	30	0.0358 ± 0.0272 (75.9963)
	2 mg IV Bolus	23	1.9537 ± 0.5520 (28.2538)
$AUC_{0\text{-}15min}$ (h·ng/mL)	10 mg IN	29	0.5298 ± 0.3427 (64.6832)
	0.4 mg IM	30	0.0788 ± 0.0486 (61.7050)
	2 mg IV Bolus	23	2.7168 ± 0.6583 (24.2320)
$AUC_{0\text{-}30min}$ (h·ng/mL)	10 mg IN	29	2.2153 ± 1.1024 (49.7645)
	0.4 mg IM	30	0.2361 ± 0.0968 (40.9869)
	2 mg IV Bolus	23	4.4132 ± 1.0982 (24.8844)
$AUC_{0\text{-}t}$ (h·ng/mL)	10 mg IN	29	19.1861 ± 4.7598 (24.8084)
	0.4 mg IM	30	1.9208 ± 0.3794 (19.7531)
	2 mg IV Bolus	23	12.1759 ± 2.9588 (24.3002)
$AUC_{0\text{-}\infty}$ (h·ng/mL)	10 mg IN	29	19.5161 ± 4.8365 (24.7818)
	0.4 mg IM	30	1.9813 ± 0.3801 (19.1828)
	2 mg IV Bolus	23	12.2521 ± 2.9672 (24.2182)
C_{max} (ng/mL)	10 mg IN	29	9.1087 ± 3.2287 (35.4464)
	0.4 mg IM	30	0.7370 ± 0.2699 (36.6261)
	2 mg IV Bolus	23	18.4134 ± 8.4853 (46.0824)
T_{max} (h)*	10 mg IN	29	0.7500 (0.2500, 1.0333)
	0.4 mg IM	30	0.5000 (0.1667, 2.0000)
	2 mg IV Bolus	23	0.0833 (0.0167, 0.1833)
$T_{1/2}$ (h)	10 mg IN	29	1.3311 ± 0.2141 (16.0863)
	0.4 mg IM	30	1.2213 ± 0.2257 (18.4841)
	2 mg IV Bolus	23	1.1772 ± 0.1364 (11.5862)
λ_z (h^{-1})	10 mg IN	29	0.5330 ± 0.0801 (15.0281)
	0.4 mg IM	30	0.5894 ± 0.1268 (21.5177)
	2 mg IV Bolus	23	0.5965 ± 0.0700 (11.7333)
CL / F_{IN} (L/h)	10 mg IN	29	488.0803 ± 115.5084 (23.6659)
CL / F_{IM} (L/h)	0.4 mg IM	30	188.3538 ± 37.6464 (19.9871)
CL (L/h)	2 mg IV Bolus	23	156.3897 ± 44.3038 (28.3291)
F_{IM}	0.4 mg IM	23	0.8405 ± 0.2442 (29.0598)
F_{IN}	10 mg IN	22	0.3360 ± 0.1026 (30.5343)

*T_{max} presented as median (minimum, maximum)

AUC=area under the curve; min=minutes; $AUC_{0\text{-}t}$=area under the curve from 0 to 8 hours; $AUC_{0\text{-}\infty}$=area under the curve from 0 to infinity; C_{max}=maximum concentration; F_{IM}=absolute bioavailability of IM; F_{IN}=absolute bioavailability of IN; $T_{1/2}$=half-life; T_{max}=time to maximum concentration

Treatment A (N = 29): PK parameters for Treatment A could not be estimated for one subject (b) (6) because concentrations were below the lower limit of quantitation (0.02 ng/mL) owing to a dosing error (per study report, it was stated that Novum pharmacy staff reviewed the total observed weight of study drug administration was only 0.0006 gm, which was significantly less than the expected dose weight of the nasal spray product (approximately 0.1100 gm). The sponsor noted that the device was virtually full and that the snap rings on the plunger inside the device were broken). AUC0-2.5 min (N = 24, missing data for subject (b) (6) large blood collection time deviations (> 1 minute) in 4 subjects (b) (6) and AUC0-5min (N = 28, large blood collection time deviations (> 1 minute) in subject (b) (6)

Treatment B (N = 30): AUC0-2.5min (N = 27, missing data for subject (b) (6), large blood collection time deviations (> 1 min) in 2 subjects (b) (6)

Treatment C (N = 23): subject (b) (6) did not complete this period of the study.
Source: Clinical overview Table 3, study report 11875901 Tables 11-3, 11-9, 11-10, and 11-11.

The median (min, max) Tmax values were 0.75 hour (0.25 to 1.03 hour) and 0.50 hour (0.17 to 2.00 hour) for the 10 mg IN dose of Naloxone HCl nasal spray 10 mg and 0.4 mg IM injection, respectively. The median (min, max) Tmax value was 0.08 hour (0.017, 0.18 hour) for the 2 mg IV injection. Mean half-life values of naloxone were 1.33 hour, 1.22 hour, and 1.18 hour for 10 mg IN dose, 0.4 mg IM injection and 2 mg IV injection, respectively (**Table 1**). The absolute bioavailability of 10 mg IN dose was 34% in comparison to 2 mg IV injection. The absolute bioavailability of 0.4 mg IM dose was 84% in comparison to 2 mg IV injection.

Table 2 Statistical Analysis of Naloxone AUC0-2.5min, AUC0-5min, AUC0-10min, Cmax, AUC0-t, and AUC0-inf for A 10 mg IN dose of Naloxone HCl Nasal Spray 10 mg (T) and 0.4 mg IM Injection (R) (From Study 11875901)

Parameter	**Geometric Least Squares Means**		**Ratio (T/R) (%)**	**90% CI**
	10 mg IN Dose of Naloxone HCl Nasal Spray 10 mg (T)	**0.4 mg IM Injection (R)**		
AUC0-2.5min (ng.h/mL)	0.004267	0.0009796	435.63	225.42 – 841.87
AUC0-5min (ng.h/mL)	0.01765	0.004316	409.00	279.78 – 597.91
AUC0-10min (ng.h/mL)	0.1446	0.02788	518.79	396.15 – 679.39
AUC0-t (ng.h/mL)	18.65	1.88	991.93	895.14 – 1099.18
AUC0-inf (ng.h/mL)	18.97	1.943	976.69	883.69 – 1079.48
Cmax (ng/mL)	8.658	0.6934	1248.65	1072.00 – 1454.41

For the comparison of Treatment A and Treatment B, there are 58 sets of data (29 Treatment A [10 mg IN dose (Test)] and 29 Treatment B [0.4 mg IM injection (Reference)]) from 29 subjects (n = 9 for AUC0-2.5 min, n = 28 for AUC0-5min) eligible for the comparison of naloxone PK in this study.
Source: Clinical overview Table 4, Study report 11875901 Table 11-5

Table 3 Statistical Analysis of Naloxone AUC0-2.5min, AUC0-5min, AUC0-10min, Cmax, AUC0-t, and AUC0-inf for A 10 mg IN dose of Naloxone HCl Nasal Spray 10 mg (T) and 2 mg IV Injection (R) (From Study 11875901)

Parameter	**Geometric Least Squares Means**		**Ratio (T/R) (%)**	**95% Upper 1-Sided CI (%)**
	10 mg IN Dose of Naloxone HCl Nasal Spray 10 mg (T)	**2 mg IV Injection (R)**		
AUC0-2.5min (ng.h/mL)	0.002630	0.2681	0.98	1.76
AUC0-5min (ng.h/mL)	0.02008	0.8194	2.45	3.54
AUC0-10min (ng.h/mL)	0.1505	1.882	8.00	10.78
AUC0-t (ng.h/mL)	18.72	11.82	158.44	176.41
AUC0-inf (ng.h/mL)	19.04	11.89	160.11	178.23
Cmax (ng/mL)	8.735	16.99	51.42	62.00

For the comparison of Treatment A and Treatment C, there are 46 sets of data (23 Treatment A [10 mg IN dose (Test)] and 23 Treatment C [2 mg IV injection (Reference)]) from 23 subjects (n = 16 for AUC0-2.5 min, n = 22 for AUC0-5min) eligible for the comparison of naloxone PK in this study.
Source: Clinical overview Table 5, Study report 11875901 Table 11-6

A single 10 mg IN dose of Naloxone HCl nasal spray 10 mg exhibited higher naloxone concentrations at all post-dose timepoints including the early absorption phase (e.g., 2.5, 5 min post-dose) than 0.4 mg IM injection (**Figure 1** and **Table 1**). The mean early partial AUC values, AUC0-2.5min, AUC0-5min, and AUC0-10min during the early absorption phase for a single 10 mg IN dose were 4.4-fold, 4.1-fold, and 5.2-fold greater than those for a single 0.4 mg IM injection. The mean AUC0-t, AUC0-inf, and Cmax values for a single 10 mg IN dose were 9.9-fold, 9.8-fold, and 12-fold greater than 0.4 mg IM injection because the geometric mean ratios (90% CI) for AUC0-t, AUC0-inf, and Cmax for 10 mg IN dose/0.4 mg IM injection were 991.93% (895.14% - 1099.18%), 976.69% (883.69% - 1079.48%), and 1248.65% (1072.00% - 1454.41%), respectively (**Table 2**).

A single 10 mg IN dose of Naloxone HCl nasal spray 10 mg exhibited lower naloxone concentrations during the early absorption phase (e.g., 2.5, 5 min post-dose) than 2 mg IV injection (**Figure 1** and **Table 1**). The mean partial AUC values, AUC0-2.5min, AUC0-5min, and AUC0-10min during the early absorption phase for a single 10 mg IN dose were 0.98%, 2.45%, and 8% of those for a single 2 mg IV injection. The mean Cmax value for 10 mg IN dose was 49% lower than 2 mg IV injection because the geometric mean ratio (95% upper 1-sided confidence interval) for Cmax for 10 mg IN dose/2 mg IV injection was 51.42% (62%). The mean AUC0-t, and AUC0-inf values for 10 mg IN dose were 58% and 60% greater than 2 mg IV injection because the geometric mean ratios (90% upper 1-sided confidence interval) for AUC0-t and AUC0-inf for 10 mg IN dose/2 mg IV injection were 158.44% (176.41%) and 160.11% (178.23%), respectively (**Table 3**).

Reviewer's comment: *Study results showed that a single 10 mg IN dose of the proposed Naloxone HCl nasal spray 10 mg showed higher naloxone plasma concentrations at all post-dose timepoints including early absorption phase, greater Cmax, AUC0-t and AUC0-inf values than a single dose of 0.4 mg IM injection. Because the approved initial dose of Narcan injection (NDA 016636) is from 0.4 mg to 2 mg in adults via IV, IM or SC injection, the Applicant's proposed reliance on effectiveness findings of Narcan injectable (NDA 016636) is warranted.*

A single 10 mg IN dose of the proposed Naloxone HCl nasal spray 10 mg showed 49% lower Cmax than a single 2 mg IV injection. The AUC0-t and AUC0-inf values for a single 10 mg IN dose were 58% and 60% greater, respectively, than that for a single 2 mg IV injection. The mean absolute bioavailability of naloxone for IN dosing based on AUC0-inf was 34% relative to IV dosing. The applicant is relying on data from the published literature that document the use of higher doses of naloxone in order to support the systemic safety of the higher systemic naloxone exposures (i.e., AUC) that are achieved with the proposed product as compared to the relied-upon Narcan product (Naloxone 2 mg IV injection). The data described in the submitted literature are scientifically relevant to the proposed product because the studies used the same active pharmaceutical ingredient as contained in the applicant's drug product and the doses used in the reported studies are relevant to the proposed dose. Refer to the clinical review for detailed information.

As a background, two other naloxone products for the same indication, Kloxxado™ nasal spray 8 mg, and Zimhi™ IM/SC injection 5 mg, were approved recently. The systemic exposure after single dose administration, especially AUC values, were compared among them since AUC of the proposed product is higher than Naloxone 2 mg IV injection.

*A single dose of the proposed product (10 mg IN) appears to have lower Cmax and similar AUC0-inf to Kloxxado™ nasal spray 8 mg, and lower Cmax and AUC0-inf than Zimhi™ IM/SC injection 5 mg, based on cross-study comparison (**Table 4**). Numerically, the systemic naloxone exposures of these three products are within the same proximity. Based on team discussion, from naloxone systemic exposure perspective, it is considered reasonable to use similar dosing recommendations for these products.*

Table 4 Cross-study Comparison of Mean (CV%) Naloxone PK Parameters

PK Parameter	NDA 215487 Naloxone HCl Nasal Spray 10 mg (from Study 11875901)	NDA 212045 Kloxxado Nasal Spray 8 mg		NDA 212854 Zimhi 5 mg IM/SC (from Study APC6000-03)**
		Study I*	Study II*	
Cmax (ng/mL)	9.11 (35.45)	12.3 (55.4)	12.8 (37)	17.2 (44)
AUC0-inf (ng.h/mL)	19.52 (24.78)	16.7 (31.9)	19.0 (32.7)	26.6 (21.2)

*Kloxxado package insert; **Zimhi package insert

2.1 Formulations of the Proposed Naloxone HCl Nasal Spray 10 mg

The compositions of proposed Naloxone HCl nasal spray 10 mg are shown in **Table** 5. The proposed product Naloxone HCl nasal spray 10 mg (10 mg/110 µL) is available in a pre-filled, unit-dose delivery system (b) (4).

Table 5 Compositions of Proposed Naloxone HCl nasal spray 10 mg

Component	Grade	Function	Composition		
			mg/mL	% w/w	mg/dose[1]
Naloxone HCl Dihydrate *(Corresponding to Naloxone HCl)*	USP	API	(b) (4)		
Glycerin	USP	(b) (4)			
Sodium Citrate Dihydrate	USP				
Hydrochloric Acid	NF	pH Adjustment	AR	AR	AR
Sodium Hydroxide	NF	pH Adjustment	AR	AR	AR
Purified Water	USP	(b) (4)	QS	QS	QS
		Total:	(b) (4)		

[1] mg/dose is equivalent to mg/0.11 mL AR = As Required to Target pH (b) (4) QS = *quantum satis*

Source: Clinical overview Table 2, Description and composition Table 1

2.2 Dosing and Therapeutic Individualization

2.2.1 Dosage and Administration

The proposed dosage and administration for the proposed Naloxone HCl nasal spray 10 mg is:

• For intranasal use only. Seek emergency medical care immediately after use.

• Administration of a single spray of Naloxone HCl Nasal Spray 10 mg intranasally into one nostril.

• If the patient does not respond within 2 minutes or responds and then relapses into respiratory depression, a second dose of Naloxone HCl Nasal Spray 10 mg may be given into the other nostril with a new device.

• Do not administer more than 2 sprays of Naloxone HCl Nasal Spray 10 mg per day.

• Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance.

2.3 Outstanding Issues

There are no outstanding issues.

2.4 Summary of Labeling Recommendations

Pending negotiation of labeling as of 10/24/2023.

(b) (4)

3 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/ TS) immediately following this page

3. APPENDICES

3.1 Summary of Bioanalytical Method Validation and Performance

The bioanalytical HPLC/MS/MS method for the determination of unconjugated naloxone concentrations in human plasma in Study 11875901 was adequately validated. The lower limit of quantitation is 0.020 ng/mL. The standard calibration range was from 0.020 ng/mL to 19.978 ng/mL. The assay precision (%CV) and accuracy (% of nominal concentrations) for quality control samples were from 2.7% to 7.2% and from 100.8% to 104.7%, respectively.

3.2 Office of Study Integrity and Surveillance (OSIS) Inspection Assessment

OSIS inspection on the clinical site (Novum Pharmaceutical Research Services Inc. at 3760 Pecos McLeod, Las Vegas, NV) and analytical site (b) (4) for the comparative bioavailability study 11875901 was requested on

May 16, 2023, because this is the pivotal study for PK bridging to the listed drug product Narcan injection (016636). Because opioid overdose is a public health issue, DAAP planned to take early action on November 17, 2023. Thus, the requested review goal date was September 29, 2023. Per OSIS memo in DARRTS dated August 30, 2023, OSIS declined to conduct an on-site inspection. OSIS determined that new inspections for this applicant are not needed.

OSIS noted their inspection histories for the clinical and analytical sites. For the Clinical Site at Novum, Las Vegas, "*the Office of Regulatory Affairs (ORA) conducted an inspection in September 2022. The inspection was conducted under the following submission:* (b) (4) *OSIS concluded that data from the reviewed studies were reliable*". For the analytical site at (b) (4) *. OSIS concluded that data from the reviewed studies were reliable*".

In conclusion, OSIS concluded that the new inspections are not needed for this application because the data from the reviewed studies were reliable in the inspections at the Clinical Site in September 2022 or RRA at the analytical site in October 2022.

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