CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217470Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

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Supporting document/s:	1, 4, 20, 21, and 31
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Product:	Nalmefene Nasal Spray
Indication:	For the complete or partial reversal of opioid drug effects, including respiratory depression, induced by either natural or synthetic opioids
Applicant:	Opiant Pharmaceuticals
Review Division:	Division of Pharm/Tox for Neuroscience (DPT-N)
Reviewer:	Min Zhang, PhD
Supervisor:	Newton Woo, PhD
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Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

Opiant submitted a New Drug Application, via a 505(b)(2) regulatory pathway, for Nalmefene Nasal Spray and proposes the following indication: for the complete or partial reversal of opioid drug effects including respiratory depression induced by either natural or synthetic opioids. The NDA relies upon FDA's previous findings of safety and efficacy for Revex, which is the listed drug (LD). The Applicant has conducted bioequivalent studies as a scientific bridge to the LD. Nalmefene is an antagonist at the mu receptor. The drug product comprises a single-use nasal spray device intended for intranasal delivery of 100 mcL of nalmefene hydrochloride solution as a 2.7 mg dose of nalmefene base. The adequacy of nonclinical data to support the safety of the drug product is assessed against a maximum recommended human daily dose (MRHD) of 5.4 mg of nalmefene base delivered by two nasal sprays. At this MRHD, the associated systemic exposures are C_{max} of 22.2 ng/mL and $AUC_{0\text{-}inf}$ of 89.5 ng*h/mL, which was reported in the human PK Study OPNT003-PK-002.

1.2 Brief Discussion of Nonclinical Findings

In support of the nalmefene nasal spray, the Applicant submitted nonclinical toxicology studies to qualify the change in route of administration, safety of the higher nalmefene systemic exposures when compared to the LD, as well as to qualify the safety of the new excipient. The Applicant also conducted PK bridging studies to allow comparisons with the listed drug, Revex, and to inform labeling.

The Applicant's specifications for the drug substance and drug product impurities are deemed acceptable. Although one drug substance impurity, (b) (4) was noted to exceed ICH Q3A(R2), this impurity is also a drug product impurity that is controlled within ICH Q3B(R2) limits. Therefore, the specification for the drug substance impurity, (b) (4) is not a safety concern given that this impurity is controlled at an acceptable limit in the drug product. Residual solvent specifications are within the levels outlined in ICH Q3C(R8). Elemental impurities are below the control threshold of 30% as recommended in ICH Q3D. To support the safety of the container closure system, the Applicant provided extractables and leachables studies. No leachable compounds were present over the 5 mcg/day qualification threshold and therefore there are no concerns with the safety of the container closure system.

The intranasal spray formulation is an aqueous solution consisting of a (b) (4) that are all within levels stated in the FDA Inactive Ingredients Database (IID). The drug product also contains Intravail® A3 (dodecylmaltoside, DDM), which is an excipient to improve the bioavailability of the drug administered by the intranasal (IN) route. DDM is not listed in the IID and thus it is considered as a new excipient. The Applicant submitted toxicology studies for DDM and submitted a letter of authorization (LoA) to reference the DDM data in DMF (b) (4) The systemic and local safety of DDM have been adequately characterized in 28-day

repeat-dose general toxicology studies in rats and dogs. There are no genotoxicity concerns with DDM. However, from the perspective of reproductive and developmental toxicity characterization, neither data submitted by the Applicant nor data in DMF (b) (4) adequately addresses all the reproductive and developmental toxicology (DART) endpoints. A study report for a preliminary embryo-fetal toxicology study (GLP) with DDM in rats was submitted, however, was not deemed acceptable. It is noted that the Applicant submitted human pharmacokinetic data that indicate administration of two nalmefene nasal sprays resulted in measurable systemic exposure to DDM. However, the Applicant has not demonstrated that the detected levels do not pose a risk to cause reproductive and developmental effects. Because the product is for a life-threatening indication and DDM did not show adverse effects in the preliminary GLP embryo-fetal toxicology study, the lack of data to characterize DDM in all of the DART endpoints was not considered an approval issue after discussions with the clinical team based on a benefit: risk analysis and given that the full battery of reproductive and developmental studies with the new excipient can be requested as a PMR for a product developed for a life-threatening indication.

Systemic and local toxicity of the drug product were evaluated in two GLP 28-day repeat-dose general toxicology studies in rats and dogs that received daily nasal administration of nalmefene for 28 days. From a local nasal tissue perspective, minimal to slight erosion/ulcer, focal hemorrhage or exudate; minimal metaplasia was observed in the rat study and minimal epithelium degeneration was observed in the dog study. Some of the local effects were also observed in the groups treated with vehicle that consisted of the drug excipients. These local effects are considered drug product related, and reversibility was demonstrated in the dog study. Comparing to the clinical nalmefene hydrochloride concentration at 30 mg/mL, the nonclinical studies have tested concentrations up to 3.3 times higher. Therefore, the local safety of the drug product has been adequately characterized. For systemic effects, moderate hemorrhage was observed in one high dose-treated rat; minimal to mild mixed cell infiltrate, inflammation, alveolar hemorrhage or alveolar granuloma was observed in the dog study without clear dose dependency. The lung findings tended to be focal and limited in distribution and are likely associated with the nasal route of administration. Moderate to marked seminiferous tubule degeneration accompanied by cellular debris and decreased sperm in the epididymides was observed in two high dose-treated rats. The systemic safety margin calculated against human $AUC_{0\text{-}inf}$ was at least 2.8x in the rat study and 13x in the dog study, while the safety margin calculated against human C_{max} at the MRHD was at least 12.3x in the rat study and 131x in the dog study. Taken together, the pivotal GLP 28-day repeat-dose general toxicology studies in rats and dogs have adequately characterized the local and systemic effects of nalmefene.

1.3 Recommendations

1.3.1 Approvability

From a nonclinical pharmacology and toxicology perspective, NDA 217430 for nalmefene nasal spray may be approved with the following recommended labeling

changes and postmarketing requirements pending the final clinical benefit:risk assessment.

1.3.2 Additional Nonclinical Recommendations

If the drug product is approved in this review cycle, the following additional studies are recommended, as postmarketing requirements, which include safety qualification studies for DDM (i.e., reproductive and developmental studies) and juvenile animal studies to qualify safety of the API and the DDM excipient as outlined in the agreed Pediatric Study Plan (PSP):

- Conduct a fertility and early embryonic development study in rats with dodecylmaltoside (DDM).
- Conduct an embryo-fetal development study in rats with dodecylmaltoside (DDM).
- Conduct an embryo-fetal development study in rabbits with dodecylmaltoside (DDM).
- Conduct a pre- and postnatal development study in rats dodecylmaltoside (DDM).
- Conduct a juvenile animal study in rats to support the initiation of clinical studies in pediatric patients from 3 to less than 12 years of age. This study will evaluate the effect of the drug on growth and development, specifically reproductive performance/sexual maturation, local tissues including the nasal and respiratory tract, immune capacity, and central nervous system histopathology and long-term behavioral effects.
- Conduct a juvenile animal study in rats to support the initiation of clinical studies in pediatric patients from birth to less than 3 years of age. This study will evaluate the effect of the drug on growth and development, specifically reproductive performance/sexual maturation, local tissues including the nasal and respiratory tract, immune capacity, and central nervous system histopathology and long-term behavioral effects.

1.3.3 Labeling

The table below contains the draft labeling proposed by the Applicant, changes suggested by this Reviewer, and the rationale for this Reviewer's changes. For final labeling, the reader is referred to the approval action letter.

4 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

2 Drug Information

2.1 Drug

CAS Registry Number
58895-64-0

Generic Name
Nalmefene hydrochloride

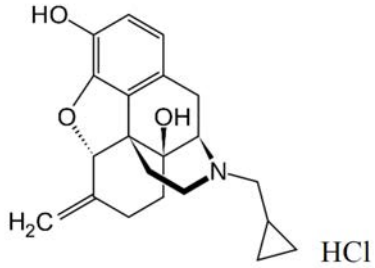
Code Name
5690

Chemical Name
17-(cyclopropylmethyl)-4,5α-epoxy-6-methylenemorphinan-3,14-diol, hydrochloride salt

Molecular Formula/Molecular Weight

Compound Name	Molecular Formula	Molecular Weight
Nalmefene hydrochloride	$C_{21}H_{25}NO_3 \cdot HCl$	375.89
Nalmefene (free base)	$C_{21}H_{25}NO_3$	339.43

Structure or Biochemical Description



Established Pharmacologic Class
Opioid antagonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

Application	Drug Product	Indication	Division	Status	Company
IND 136851	Nalmefene nasal spray	Opioid overdose	DAAP	Active	Opiant Pharmaceuticals
DMF (b) (4)	Intravail (Excipient)			Active	(b) (4)
NDA 20459	Revex	Reversal of opioid drug effects	DAAP	Discontinued	Baxter

2.3 Drug Formulation

Nalmefene nasal spray is an aqueous solution in a single use container. Each spray actuation delivers a dose that contains 2.7 mg nalmefene dispensed in a volume of 100 mcL. The components of nalmefene nasal spray solution and the function of each component are presented in Applicant's tables below.

Component	Function
Nalmefene	Active Ingredient
Sodium Chloride	(b) (4)
Dodecyl maltoside (DDM)	Permeation Enhancer
Disodium Edetate	(b) (4)
Benzalkonium Chloride	
Purified water	

Ingredients	Quality Standard	Quantity/mL	Quantity % w/v	Quantity/100 µL Spray Volume [a]
Nalmefene hydrochloride [b]	In-house	30.0 mg	3.0	3.0 mg [c]
Sodium chloride	USP	(b) (4)		
Dodecylmaltoside (DDM)	In-house			
Disodium edetate dihydrate	USP			
Benzalkonium chloride [d]	USP/NF			
Purified Water	USP			
Total		1.0 mL	100%	100 µL

(b) (4)

c 3.0 mg nalmefene hydrochloride is equivalent to 2.7 mg nalmefene free base.

(b) (4)

2.4 Comments on Novel Excipients

The excipients in the product, their concentration and total daily exposure based on the proposed MRHD of 2 nasal doses (0.2 mL nasal spray in total) in comparison to the maximum potency data from the FDA Inactive Ingredients database (IID), and the acceptability are presented in the table below.

Table 1: Acceptability of Excipients in the Drug Product

Excipient	Concentration (mg/mL)	Concentration Listed in IID for Nasal Products (mg/mL)	Max. Daily Exposure (mg)* (based upon 2 doses in 0.2 mL)	MDE* Listed in IID for Nasal Products (mg)	Acceptability and Rationale
Sodium chloride	(b) (4)	9	(b) (4)	36	Yes; via IID

Dodecylmaltoside (DDM)	(b) (4)	Not listed in IID	(b) (4)	Not listed in IID	See discussion below.
Disodium edetate dihydrate		2		4	Yes, via IID
Benzalkonium chloride		0.7		1	Yes, via IID
Purified Water					Yes

*Maximum daily exposure

The excipient dodecylmaltoside (DDM), a permeation enhancer, is not listed in FDA's IID and thus is considered as a new excipient. The Applicant has conducted 28-day repeat-dose toxicology studies to support the local and systemic safety of DDM and relies on the data in DMF (b) (4) to provide additional support on other aspects of safety qualification for the new excipient.

Safety qualification for Dodecyl maltoside (DDM)

Dodecylmaltoside has been included into the nalmefene nasal formulation to improve the bioavailability of the drug administered by the intranasal (IN) route. DDM has been used as an excipient in many intranasal drug products being developed but it is not listed in FDA's IID, and as such DDM is considered a new excipient. DDM is a malt sugar derivative and is expected to be hydrolyzed to maltose and dodecanol (a 12-carbon fatty alcohol) after oral administration. DDM was present in the vehicle of the test article in the 28-day repeat-dose rat and dog studies. DDM concentration in the vehicle was identical to that in the clinical formulation. The human equivalent dose (HED) of DDM in the vehicle group in the rat and dog study was (b) (4) the DDM daily intake at the MRHD, respectively (see the table below). Therefore, the local and general toxicity of this excipients has been adequately characterized for the proposed indication in the 28-day repeat-dose studies in rats and dogs.

Figure 1: Structure of Dodecylmaltoside

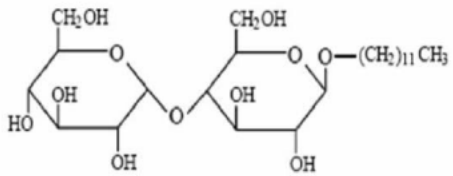


Table 2: DDM Dose Levels in Nonclinical Studies Compared to the Maximum Dose in Humans

Animal Studies	Dose of DDM	DDM HED Based upon BSA (mg/day)	Maximum Human Exposure to DDM (mg/day)	Safety Margin (HED/Max. Human Exposure)
28-day Rat Study	0.25 mg Vehicle group	(b) (4)		

28-day Dog Study	0.5 mg Vehicle group	(b) (4)	(b) (4)
EFD Study in Rats	30 mg/kg		

a: Calculated based upon average body weight of vehicle-treated rats (217.6 g) at the initiation of dosing and human body weight of 60 kg.
b: Calculated based upon average body weight of vehicle-treated dogs (7.13 kg) at the initiation of dosing and human body weight of 60 kg
c: Calculated based upon MRHD of nalmefene at 5.4 mg

In addition to the general toxicology studies conducted with DDM-containing nonclinical formulation, the Applicant submitted a LoA to reference Aegis Therapeutics's DMF (b) (4) a Type V submission, which contains nonclinical toxicology studies with DDM, to provide further safety qualifications for this excipient. After review of DMF (b) (4) and NDA submission, all endpoints from a complete battery of reproductive and developmental toxicology (DART) studies have not been addressed. The lack of DART data for DDM was identified in the 74-day letter and communicated to the Applicant.

The Applicant replied to the IR on April 24, 2023, and provided human PK levels of DDM from blood samples that were collected from Study OPNT003-PK-002. This human PK study was an open label 3 treatment, 3 period, cross over design evaluating healthy subjects that received one spray of 3 mg nalmefene in one nostril (Treatment 1; 3 mg nalmefene in total), or one spray of 3 mg nalmefene in each nostril (Treatment 2; 6 mg nalmefene in total), or two sprays of 3 mg nalmefene in one nostril (Treatment 3; 6 mg nalmefene in total). Data collected from twenty-four subjects in groups T1 and T2 were analyzed and are shown below.

Treatment	C_{max} (pg/mL)	AUC_{0-inf} (pg*h/mL)	T_{max} (h)	$t_{1/2}$ (h)
1	(b) (4)			
2				

As seen in the table above, DDM systemic exposures were observed after two nalmefene sprays with AUC_{0-inf} of (b) (4) ng*h/mL. The Applicant did not address whether this systemic level poses a risk to cause reproductive and developmental toxicity.

It is noted that a study report for a pilot GLP embryo-fetal development study was submitted to the NDA by the Applicant that evaluated IV administration of DDM to pregnant Wistar rats from Day 6 to 17 of gestation, at one dose level of 30 mg/kg (N=8), corresponding to a HED that is (b) (4) times the human DDM daily dose (see Table 2). No maternal or embryo-fetal adverse effects were reported in the study. However, this is a preliminary embryofetal study that did not evaluate an adequate number of pregnant females (i.e., at least 16 pregnant females). Given that DDM did not show adverse effects in the preliminary EFD study and this product is for a lifesaving indication, the lack of a complete battery of DART studies with DDM is not deemed an approval issue by this Reviewer and can be resolved as a PMR pending the clinical benefit:risk assessment.

2.5 Comments on Impurities/Degradants of Concern

Drug Substance Impurities and Drug Product Degradants
A list of drug substance (DS) and drug product (DP) impurity specifications, including comparisons to ICH Q3A(R2) and ICH Q3B(R2) qualification or identification thresholds and safety determination, are summarized in the tables below.

Table 3: Impurities in Drug Substance

Impurity	Proposed Specification	Maximum TDL* (mcg/ day)	Comparison to ICH Thresholds		Acceptable?
			Qualification Threshold Q3A(R2) 0.15% or 1.0 mg/per day whichever is lower	Identification Threshold Q3A(R2) 0.1% or 1.0 mg/per day whichever is lower	
(b) (4)	NMT (b) (4) % w/w	(b) (4)	Exceeds		Yes (see discussion below)
	NMT (b) (4) % w/w		Complies		Yes
Unspecified impurity (each)	NMT (b) (4) % w/w			Complies	

*: TDL: Total daily level calculated based upon proposed MRHD of 5.4 mg of nalmefene (two nasal sprays)

Table 4: Impurities in Drug Product

Impurity	Proposed Specification	Maximum TDI* (mcg/ day)	Comparison to ICH Thresholds		Acceptable?
			Qualification Threshold Q3B(R2) 1% or 50 mcg/day whichever is lower	Identification Thresholds Q3B(R2) 0.5% or 20 mcg/day whichever is lower	
(b) (4)	NMT (b) (4)%	(b) (4)	Complies		Yes
	NMT (b) (4)%				Yes
	NMT (b) (4)% w/w			Complies	
	NMT (b) (4)%			Complies	

*: TDI: Total daily intake calculated based upon proposed MRHD of 5.4 mg of nalmefene (two nasal sprays)

As shown in the tables above, the drug substance specification for (b) (4), NMT (b) (4)% (w/w), is greater than 0.15%, while the total daily level (TDL) of (b) (4) at the MRHD is expected to be less than the qualification threshold of 1 mg/day based upon MRHD of 5.4 mg nalmefene. (b) (4) is an active pharmaceutical ingredient in FDA-approved drug products. It is noted that (b) (4) is also deemed a drug product impurity and is within ICH Q3B(R2). Given that (b) (4) impurity is adequately controlled at the level of the drug product, the proposed DS (b) (4) specification does not pose a safety concern and is deemed acceptable.

Residual Solvents

The Applicant has evaluated several DS batches for Class 2 solvents ((b) (4) and Class 3 solvents (b) (4) used in the manufacture of nalmefene hydrochloride (b) (4). All the solvents screened were below 1/10th of the ICH Q3C limits; therefore, a routine test for these solvents is not needed. Refer to the CMC review for acceptability of the analysis.

The Applicant performed a screening for Class 1 solvent [redacted], a potential trace impurity, in several lots of [redacted] and several batches of DS. [redacted] were not detected (see CMC review for more details).

Elemental Impurities

[redacted] has evaluated elemental impurities that may be present in nalmefene hydrochloride as recommended by ICH Q3D. Refer to the CMC review for the acceptability of the analysis. No elemental impurities exceed the permitted daily exposures for an inhalation drug product; therefore, no specifications are required to be set. See the table below for the elements analyzed. Refer to the CMC review for adequacy of the submitted report.

Table 5: Evaluation of Elemental Impurities in Nalmefene Hydrochloride

Element	Class	Target (mcg/g)	Limit LOQ (mcg/g)	Inhalation PDE (mcg/day)	Acceptable Limit (ppm)*	Level in 1902000367 1902000369 1902000371 (registration batches) (ppm)
[redacted]						<LOQ
						<LOQ
						<LOQ
						<LOQ
						<LOQ
						<LOQ
						<LOQ
						<LOQ
						<LOQ

*Calculated against the MRHD of 5.4 mg of nalmefene

2.6 Container Closure System

The drug product solution is filled into unit dose 400 mcL [redacted] glass vials closed with a black [redacted] rubber stopper and then assembled into the Aptar Unidose Nasal Spray (UDS™) device, which is a single use product and is used in several FDA-approved products. As seen in the Figure on the right, the vial and stopper provide a fully enclosed container-closure system. The focus of the extractable and leachable studies has been on the glass vial and elastomeric stopper based upon a leachable risk assessment that concluded these parts have a high risk for leachables due to long term contact with drug formulation and the other parts of device have low risk for leachables due to very limited contact or no contact with the drug formulation and inert nature of the material.

Figure 1: Unidose Device Description

2.6.1 Extractable Studies

Extractable studies were conducted on the glass vial and stopper that have long term contact with the drug formulation.

The CMC review team noted that the extractable studies are acceptable, suggesting that the methods were acceptable and that potential leachables would be detected in drug product samples on stability testing. Refer to the CMC review for additional details.

For elemental impurities, the detection limits were set much less than the respective permitted daily exposures (PDEs) outlined in ICH Q3D where applicable.

For organic extractables, it appears that the Applicant has set an analytical evaluation threshold (AET) based upon a safety concern threshold (SCT) at (b) (4) mcg/day which is much lower than a SCT of 5 mcg/day (corresponding to AET of 2.5 mcg/unit), a threshold typically recommended by the Division as a qualification threshold to address the general toxicity of a compound.

Applicant's AET (mcg/spray device) = (b) (4) mcg/day/2-unit doses per day= (b) (4) mcg/unit

"As these were screening methods, an additional uncertainty factor of 2 was applied to all GC/MS methods and 5 for LC/MS based on a statistical evaluation of variation in (relative) response factors collected from authentic reference standards used to detect and identify substances present in the extracts." "Therefore, detection limits applied to GC based methods were (b) (4) mcg/unit, and for LC-MS based methods it was (b) (4) mcg/unit."

Vial Extractable Studies

The studies were conducted with ultrapure water at a pH of 4 as an extraction solvent for elemental impurities given that primary risk from the glass would be due to leaching of inorganic substances from the glass vial during storage of the drug product. The extraction conditions were 90°C for 24 hours within a closed extraction vessel. Results for extractable analyses with detection methods of ICP-OES and ICP-MS are provided in the Applicant's tables below.

Six inorganic elemental substances have been detected at levels greater than the method LOD. None of these six compounds exceed the ICH Q3D PDEs for inhalation products where applicable. Most of the substances detected have no controlled limit listed in ICH Q3D because of their limited toxicity. This Reviewer agrees with the Applicant that these elemental impurities do not have to be targeted in the leachable studies.

Substance (Element) Name	Results (µg / unit dose vial)	Limit of Detection (LOD) (µg/unit dose vial)	Calculated Daily Exposure[2] (µg/day)	ICH Q3D PDE (µg/day)
(b) (4)				N/A[1]
				N/A[1]
				N/A[1]
				3
				N/A[1]
				N/A[1]
				-
				-
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N/A = Not Applicable; ND = Not Detected; PDE = Permitted Daily Exposure

[1] Not considered to require controls in ICH Q3D

[2] Calculated Daily exposure based on a maximum of 2 units per day

Substance (Element) Name	Results (µg / unit dose vial)	Detection Limit (LOQ) - µg/unit dose vial
(b) (4)		

ND = Not Detected

Elastomeric Stopper Extractable Studies

The Applicant states that “As with the glass vial, the elastomeric stopper complies with all pharmacopeia standards.” Four different extraction conditions were used in the extractable studies (excerpt from Applicant’s submission):

- Closed Vessel extraction with Ultrapure water (pH 4) at 90°C for 24hrs
- Closed Vessel extraction with Ultrapure water (pH 4) at 90°C for 24hrs in a Plastic Vessel (Inorganic analysis)
- Closed Vessel extraction with 10% IPA (Isopropyl Alcohol) in water at 76°C for 24hrs
- Closed Vessel extraction with 50% IPA in water at 72°C for 24hrs

Five inorganic elemental substances were detected at levels greater than method LOD. None of the detection limits exceed the ICH Q3D PDEs for inhalation products. The substances detected have no controlled limit listed in ICH Q3D because of their limited toxicity. This Reviewer agrees with the Applicant that these elemental impurities do not have to be targeted in the leachable studies.

Substance (Element) Name	Results (µg/unit dose vial)	Detection Limit (LOD) (µg/unit dose vial)	Calculated Daily Exposure[2] (µg/day)	ICH Q3D PDE (µg/day)
			(b) (4)	N/A[1]
				N/A[1]
				N/A[1]
				N/A[1]
				N/A[1]
				-
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N/A = Not Applicable; ND = Not Detected
[1] Not considered to require controls in ICH Q3D
[2] Calculated Daily exposure based on a maximum of 2 units per day
[3] Detected above detection limit but below quantitation limit

Substance (Element) Name	Results (µg / unit dose vial)	Detection Limit (LOQ) - µg/unit dose vial
	(b) (4)	

ND Not Detected

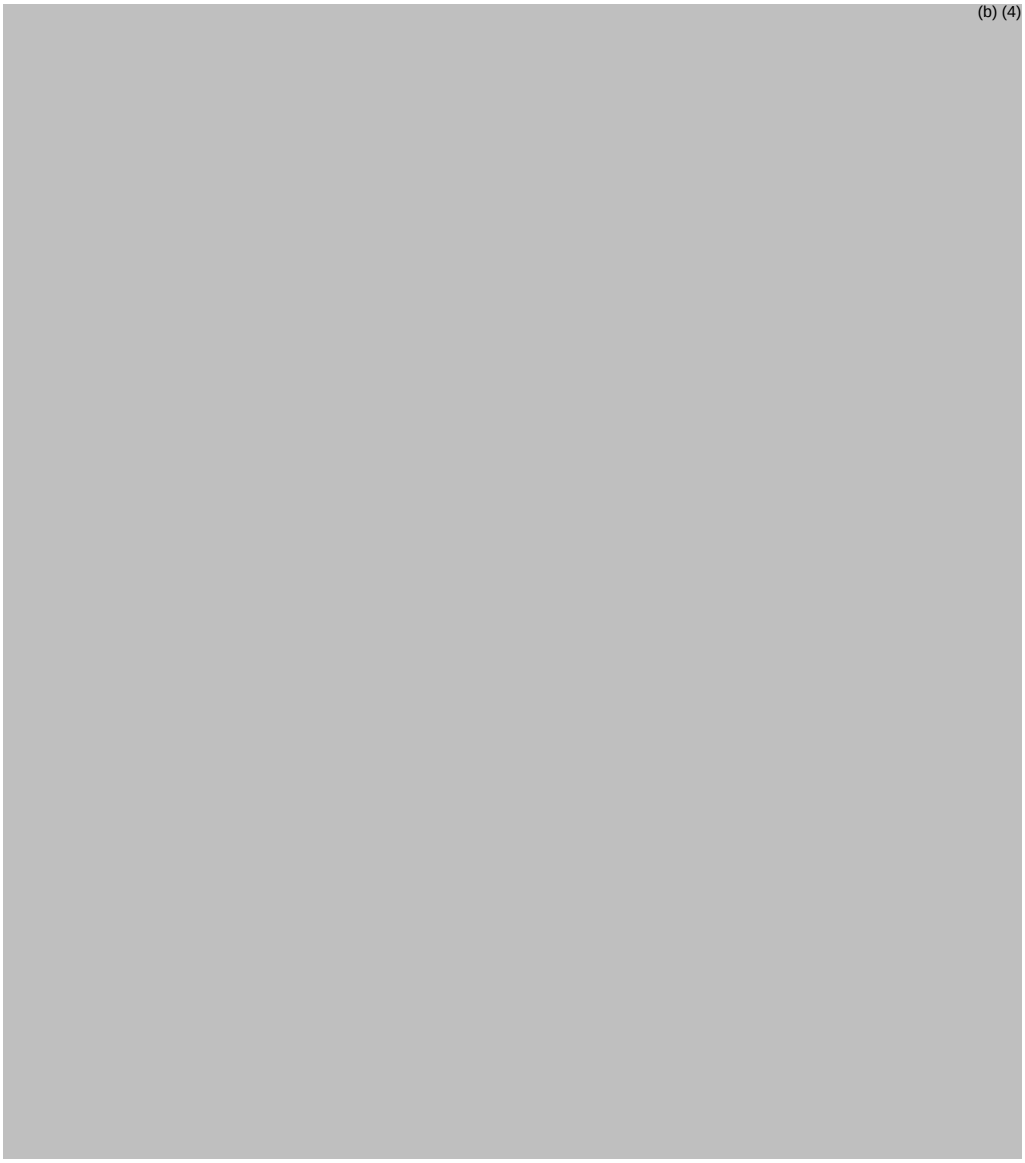
From the extractable studies, the Applicant identified organic extractables as target leachables (see the table below).

Table 6: Identified Extractable Compounds Targeted in the Leachables Studies

Target Substance	Worst Case Estimate* Exposure (mcg/unit)	Targeted in Leachable Study?	Comment
(b) (4)		Yes	Below SCT of 5 mcg/day
			Equal to 5 mcg/day; should be targeted.
			Below SCT of 5 mcg/day
			Above SCT of 5 mcg/day; should be targeted
		No	Inadequate; above SCT of 5 mcg/day and should be targeted in the leachable study.

*: Highest level under any extraction conditions

This Reviewer noted that (b) (4) and (b) (4) were not being targeted for leachable assessment despite their estimated concentrations to be (b) (4) mcg/unit, respectively, in the extractable studies with 50% IPA, exceeding the SCT of 5 mcg/day. An information request (IR), dated Feb 23, 2023, was sent to the Applicant regarding why these two compounds were not being targeted in the leachable studies. The Applicant provided the following justifications in their response to the IR (SDN 21), which are considered reasonable by this Reviewer. The CMC review team concurs that the Applicant's justification is acceptable.



2.6.2 Leachable Studies

Leachable testing was conducted on inverted filled vials from three registration batches stored at 25°C/60%RH for 3, 6, and 12 months and 40°C/75%RH for 6 months. Leachable data will also be generated at the 24-month and 36-month timepoints.

The compounds in the table above except (b) (4) and (b) (4) were targeted. The majority of the leachables detected in the three registration batches after 12 months at 25°C/60%RH and 6 months at 40°C/75%RH, are either less than the Applicant's SCT of (b) (4) mcg/day or close to that value. All organic leachables do not contain structure alerts and do not exceed an exposure of (b) (4) mcg/day, well within limits of < 5 mcg/day, therefore, no further risk assessment is needed for these compounds.

Taken together, the submitted extractables/leachables data adequately supports the safety of the container closure system.

2.7 Proposed Clinical Population and Dosing Regimen

Clinical Population: Adults and pediatric patients aged 12 years and older who require the emergency treatment or known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.

Dosing regimen: A single spray of (b) (4) Nasal Spray (2.7 mg nalmefene base) is administered intranasally into a nostril. If the patient does not respond or responds and then relapses into respiratory depression, additional doses of (b) (4) Nasal Spray may be given every 2 to 5 minutes to alternating nostrils until emergency medical assistance arrives.

2.8 Regulatory Background

- PIND 136861: 2/2018
    - Recommended IN repeat-dose toxicology studies with a treatment duration of 1 month in two species to support the NDA.
- (b) (4)
- Fast track designation granted on 11/2021
- PreNDA meeting: 3/2021
    - Full toxicology endpoints should be evaluated in two animal species to support higher exposures exceeding those associated with the referenced drug product. Safety margins should be calculated based upon MRHD.
    - Provide adequate safety justification for the novel excipient DDM.
- In the Agreed iPSP, the Division concurred with a deferral for clinically assessing the pharmacokinetics and pharmacodynamics of nalmefene in patients < 12 years of age (all age groups down to birth) because the drug may be approvable in patients > 12 years of age prior to the completion of pediatric studies.
    - Two juvenile animal studies will be conducted to support the clinical studies in patients < 12 years of age
        - Nonclinical repeat-dose toxicity study (Rat; PND 22 days to 77 days)
        - Nonclinical repeat-dose toxicity study (Rat; PND 7 days to 21 days)

3 Studies Submitted

3.1 Studies Reviewed

A complete list of nonclinical studies with nalmefene nasal spray is provided in the Applicant's table below:

Type of Study	Species / Strain	Method of Admin.	Dose	Duration of Dosing	GLP Compliance	Study Number
Safety Pharmacology:						
Cardiovascular and respiratory systems	Dog / Beagle	Intranasal	0, 2, 6, 17 mg	1 day	Yes	01599001
Absorption:						
Repeat-dose PK	Rats / Sprague Dawley	Oral (gavage)	100, 200 mg/kg	7 days	Yes	49508 PSR
Repeat-dose PK	Rabbits / New Zealand White	IV	8 mg/kg	7 days	Yes	49509 PSL
Single-Dose Toxicity:						
Single-dose toxicity and toxicokinetics	Dog / Beagle	Intranasal	6, 12, 17 mg	1 day	No	20291735
Repeat-Dose Toxicity:						
Repeat-dose toxicity and toxicokinetics	Rat / Sprague Dawley	Intranasal	3, 6, 8.5 mg	7 days	No	20291733
Repeat-dose toxicity and toxicokinetics	Rat / Sprague Dawley	Intranasal	0, 1, 3, 8.5 mg	28 days	Yes	20291737
Repeat-dose toxicity and toxicokinetic	Dog / Beagle	Intranasal	0, 2, 6, 17 mg	28 days	Yes	20291738
Local Tolerance:						
Conducted as part of the Repeat-Dose Toxicity Studies						

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

None

4 Pharmacology

4.1 Primary Pharmacology

No primary studies were conducted with nalmefene by the Applicant. Nalmefene is an opioid receptor antagonist at mu and delta opioid receptors. In vitro and in vivo studies report that nalmefene is a partial agonist at human kappa opioid receptors (Remmers 1999, Bart 2005), although this has not been uniformly replicated (Toll 1998). It is well

accepted that the mechanism of action to reverse opioid overdose is the blockade of mu opioid receptors.

4.2 Secondary Pharmacology

No secondary pharmacology studies were conducted with nalmefene by the Applicant.

4.3 Safety Pharmacology

In addition to what is known about the safety pharmacology of nalmefene, the Applicant conducted a GLP safety pharmacology study to assess the potential acute effects of intranasal nalmefene on heart rate, arterial blood pressure, body temperature, lead II electrocardiogram (ECG), and respiratory parameters in conscious radiotelemetry-instrumented male Beagle dogs (Study 01599001) that received a single intranasal dose of vehicle control, 2 mg, 6 mg, or 17 mg nalmefene hydrochloride in a Latin square cross-over design. The findings from the study were limited to clinical observations of partly digested food, liquid brown material with particles, and foamy white material at 2 mg; mucoid feces and foamy white material at 6 mg; and partly digested food, mucoid brown material with particles, and foamy white material at 17 mg. There were no effects on hemodynamic, body temperature, ECG, or respiratory parameters at any dose level tested.

The 28-day repeat dose dog study also includes ECG assessment (refer to the study review for details).

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

The Applicant conducted PK studies to bridge to the reproductive and developmental toxicology data described in the label of the listed drug, (b) (4) (Revex-2006). These PK studies utilized the same doses, species, sex, and route of administrations as those described in the Revex labeling regarding reproductive and developmental toxicity (DART) studies so that the animal exposures can be compared to the clinical exposures achieved with the drug product at the MRHD. These studies included a rat (oral; 100 and 200 mg/kg/day) and a rabbit (intravenous; 8 mg/kg/day) GLP study, demonstrating approximately 9-fold (C_{max}) and 6-fold ($AUC_{0\text{-}inf}$) exposure margins in the rat study and approximately 96-fold (C_{max}) and 20-fold ($AUC_{0\text{-}inf}$) exposure margin in the rabbit study, calculated against the human exposures observed at the MRHD (see the table below).

Animal PK Bridging Studies	Doses	C_{max} Day 7 (ng/mL)	$AUC_{0\text{-}inf}$ Day 7 (ng*h/mL)	Exposure Margins at the MRHD (2 doses)	
				*C_{max} 22.3 ng/mL	*$AUC_{0\text{-}inf}$ 89.5 ng*h/mL

Oral PK study in Rats (Study 49508 PSR)	100 mg/kg	205	524	9.2	5.9
	200 mg/kg	NA	NA	NA	NA
IV PK study in Rabbits (Study 49509 PSL)	8 mg/kg	2150	1800	96.4	20.1

* At MRHD, the associated systemic exposures were C_{max} of 22.3 ng/mL and $AUC_{0\text{-}inf}$ of 89.5 ng*h/mL, which were reported in the human PK Study OPNT003-PK-002

Pharmacokinetic Study of Nalmefene Hydrochloride by the Oral (Gavage) Route in the Female Sprague-Dawley Rat (Study Number 49508 PSR; GLP)

Treatment
Twelve female Sprague-Dawley rats were treated with oral 100 mg/kg/day or 200 mg/kg/day nalmefene for 7 days (6/group).

Key results
All rats at 200 mg/kg/day were prematurely sacrificed on Day 2 due to the occurrence of severe and adverse clinical signs in all animals shortly after dosing on Day 1.

The PK data in rats are summarized in the Applicant's table below. There was a marked decrease in nalmefene hydrochloride plasma concentrations observed over the treatment period, which was considered, by the Applicant, related to a clearance auto-induction after repeated administrations.

		Day 1		Day 7	
Dose Level	**(mg/kg/day)**	**100**	**200**	**100**	**200[1]**
T_{max}	(h)	0.5	1	0.5	N/A
C_{max}	(ng/mL)	1440	3380	205	N/A
SE (C_{max})	(ng/mL)	531	436	83.0	N/A
C_{max}/Dose	(ng/mL)/(mg/kg/day)	14.4	16.9	2.05	N/A
T_{last}	(h)	24	24	24	N/A
AUC_{tlast}	(h*ng/mL)	2400	5720	501	N/A
SE (AUC_{tlast})	(h*ng/mL)	582	678	113	N/A
AUC_{tlast}/Dose	(h*ng/mL)/(mg/kg/day)	24.0	28.6	5.01	N/A
R_{AUC}		N/A	N/A	0.209	N/A
λ_z	(1/h)	0.182	0.173	0.112	N/A
$T_{1/2}$	(h)	3.81	4.00	6.20	N/A
$AUC_{(0\text{-}inf)}$	(h*ng/mL)	2400	5750	524	N/A
Cl/F	(mL/h/kg)	41600	34800	191000	N/A
V_z/F	(mL/kg)	229000	201000	1710000	N/A
AUC extrapolation	(%)	0.303	0.441	4.45	N/A
No. points λ_z		3	3	3	N/A
r^2		0.987	0.999	0.999	N/A

N/A = not applicable.

[1] no data from Females of Group 2 on Day 7, since animals underwent unscheduled euthanasia on Day 2 due to heavy clinical signs; R_{AUC}: accumulation ratio, calculated as AUC_{tlast} Day 7 /AUC_{tlast} Day 1

Note that the values highlighted in the red box were used to calcaulate exposure margins.

Pharmacokinetic Study of Nalmefene Hydrochloride by the Intravenous Route in the Female New Zealand White Rabbit (Study Number 49509 PSL; GLP)

Treatment
Three female New Zealand White rabbits were treated with IV, slow bolus, 8 mg/kg/day nalmefene for 7 days (3/group).

Key results
The PK parameters of nalmefene in rabbits are summarized in the Applicant's table below.

		Day 1	Day 7
Dose Level	**(mg/kg/day)**	**8**	**8**
$C_{(0)}$	(ng/mL)	1790 (11)	2150 (34)
AUC_{tlast}	(h*ng/mL)	1820 (6)	1790 (12)
T_{last}[1]	(h)	8 [4-8]	8 [8-8]
$AUC_{(0-8h)}$	(h*ng/mL)	1850 (9)	1790 (12)
R_{AUC}[1]		0.965	
λ_z	(1/h)	0.673 (32)	0.644 (14)
$T_{1/2}$[1]	(h)	1.03	1.08
$AUC_{(0-inf)}$	(h*ng/mL)	1850 (7)	1800 (12)
Cl	(mL/h/kg)	4340 (6)	4490 (12)
V_z	(mL/kg)	7030 (39)	7100 (21)

[1] Median [Min-Max] for T_{last}; harmonic mean for $T_{1/2}$ and geometric mean for R_{AUC}; R_{AUC}: Accumulation ratio, calculated as AUC(0-8h) Day 7 / AUC(0-8h) Day 1.

Note that the values highlighted in the red box were used to calculate exposure margins.

5.2 Toxicokinetics

Toxicokinetic data were collected in the repeat-dose toxicology studies (see below).

6 General Toxicology

6.1 Single-Dose Toxicity

A non-GLP study single-dose general toxicology study was conducted in dogs with intranasal administration of 6, 12, or 17 mg/day. The high dose selection was based on the maximum solubility of nalmefene HCl in the clinical vehicle. The Applicant states that there were no treatment-related effects noted during the study with the NOAEL considered to be the high dose of 17 mg/day.

6.2 Repeat-Dose Toxicity

Study Title: A 28-Day Study of Nalmefene Hydrochloride by Intranasal Administration in Rats with a 28-Day Recovery Period

Study no.:	20291737
Study report location:	Study Report Link
Conducting laboratory and location:	(b) (4)
Date of study initiation:	June 4, 2021
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Nalmefene hydrochloride Batch/Lot No: 1902000367 Purity: 95.2%

Key Study Findings

- Slight decreased body weight gains were noted in males administered ≥ MD, corresponding to a slight decrease of food consumption.

- Moderate to marked bilateral seminiferous tubule degeneration in testis were noted in 2 of 10 rats administered HD. The same animals also had secondarily, cellular debris and decreased sperm in the epididymites. There were no such findings observed at the end of the recovery phase. The findings are considered test article related and adverse by this Reviewer.

- Moderate lung hemorrhage was observed in one HD animal, which was not considered test article-related by the Applicant.

- In nasal cavity, minimal multifocal erosion/ulcer, slight acute focal hemorrhage or minimal to slight exudate were noted in one or two HD-treated animals, and minimal exudate was also noted in one MD animal. Minimal metaplasia was observed in one vehicle-treated male and one HD female, suggesting that the finding may be related to the vehicle, which consisted of the excipients of the drug product. Reversibility was not assessed.

- NOAEL for the systemic effects is the HD for the females and MD for the males due to the findings with testis and epididymis at the HD. NOAEL is not established for the local effects; but the local effects are not considered dose limiting given the findings are mild in general and clinically monitorable.

Methods

Doses: 0, 1 (LD), 3 (MD) and 8.5 mg (HD)
Frequency of dosing: Once daily
Route of administration: Intranasal instillation
Dose volume: 0.1 mL
Formulation/Vehicle: Vehicle and control article: (b) (4) mg benzalkonium chloride (b) (4) mg dodecyl maltoside, (b) (4) mg disodium edetate, (b) (4) mg sodium chloride in reverse osmosis deionized (RODI) water (per mL)
Species/Strain: Rat/Sprague-Dawley
Number/Sex/Group:

Text Table 1
Experimental Design – Main and Recovery

Group No.	Test Material	Dose Level[a] (mg)	Total Dose Volume[b] (mL)	Dose Concentration (mg/mL)	Adjusted Dose Concentration[c] (mg/mL)	No. of Animals			
						Main Study		Recovery Study	
						Males	Females	Males	Females
1	Control[d]	0	0.1	0	0	10	10	5	5
2	Nalmefene Hydrochloride	1	0.1	10	10.50	10	10	-	-
3	Nalmefene Hydrochloride	3	0.1	30	31.51	10	10	-	-
4	Nalmefene Hydrochloride	8.5	0.1	85	89.29	10	10	5	5

- = Not applicable.
[a] Dosed once daily from Days 1 to 28.
[b] The dose volume was administered to each animal with the total dose volume split equally between each nostril.
[c] The dose concentration was corrected for water based on a correction factor of 0.952.
[d] (b) (4) mg Benzalkonium chloride, (b) (4) mg Dodecyl maltoside, (b) (4) mg Disodium edetate (b) (4) mg Sodium chloride in reverse osmosis deionized (RODI) water (per mL).

Text Table 2
Experimental Design – Toxicokinetic

Group No.	Test Material	Dose Level[a] (mg)	Total Dose Volume[b] (mL)	Dose Concentration (mg/mL)	Adjusted Dose Concentration[c] (mg/mL)	No. of Animals	
						Toxicokinetic Study	
						Males	Females
1	Control[d]	0	0.1	0	0	3	3
2	Nalmefene Hydrochloride	1	0.1	10	10.50	6	6
3	Nalmefene Hydrochloride	3	0.1	30	31.51	6	6
4	Nalmefene Hydrochloride	8.5	0.1	85	89.29	6	6

Age: 8 weeks
Weight: Average body weight of 180 g at the initiation of dosing
Satellite groups: TK groups (see the table above)
Unique study design: None
Deviation from study protocol: No deviations were noted that would impact the results of the study.

Observations and Results

Dosing Solution Analysis

All study samples analyzed had mean concentrations within or equal to the acceptance criteria of ± 10% (individual values within or equal to ± 15%) of their theoretical concentrations. For homogeneity, the relative standard deviation (RSD) of concentrations for all samples in each group tested was within the acceptance criteria of ≤ 5%.

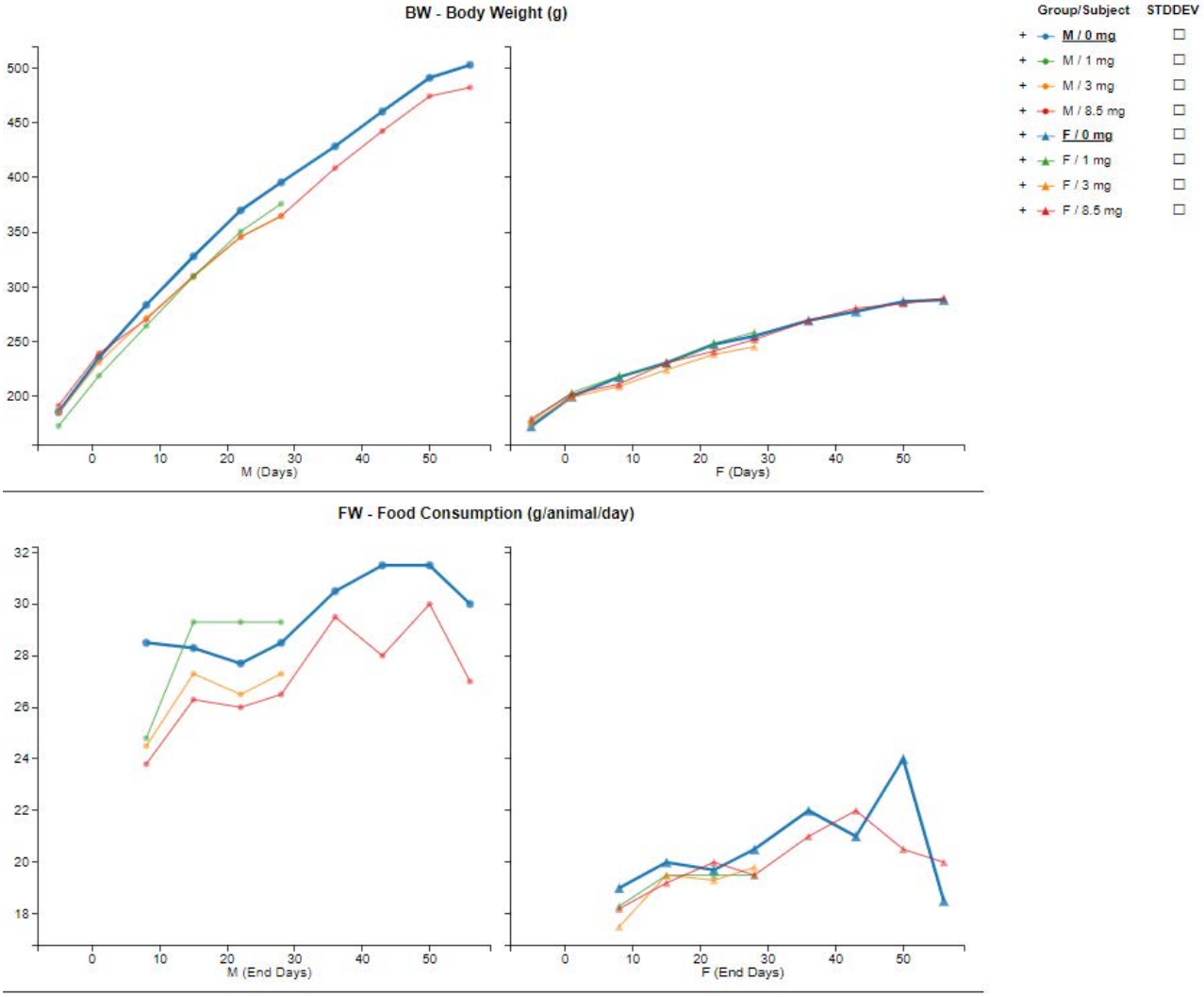
Mortality
There was no mortality in the study.

Clinical Signs
There were no test article-related clinical observations noted during the study.

Neurobehavioral Evaluations
There were no test article-related differences noted in neurobehavioral findings.

Body Weights and Food Consumption

- Slight decreased body weight gains were noted in males administered ≥ MD from Days 22 to 28 and from Days 1 to 28.
    - This decrease corresponded to a slight decrease in food consumption but was not considered adverse.
- Body weight gain in females administered ≥ MD was decreased from Days 1 to 8, but this decrease in body weight gain did not result in meaningful differences in mean body weight.
- During the recovery period, body weight gains in rats administered HD were comparable to those of controls.



Ophthalmoscopy
No test article-related changes were observed.

ECG
Not conducted.

Clinical Pathology Procedure

11.1. Sample Collection

Clinical Pathology Sample Collection

Group Nos.	Time Point	Hematology	Coagulation	Clinical Chemistry	Urinalysis
1 to 4[a]	Day 29	X	X	X	X
1 and 4 (Recovery study animals only)	Day 57	X	X	X	X
Unscheduled euthanasia (when possible)		X	X	X	-
Fasting[b]:		-	-	Min. 4 hours	Min. 4 hours
Method/Comments:		Venipuncture of the Vena Cava[c]	Venipuncture of the Vena Cava[c]	Venipuncture of the Vena Cava[c]	Urine will be collected by urine collection cages containing an alternate water source
Target Volume (mL)[d]:		2	1.8	2	-
Anticoagulant:		(K_2) EDTA	Sodium citrate	None	-
Special Requirements:		-	-	-	-
Processing:		None	Plasma	Serum	-

X = Sample to be collected; Min. = Minimum; - = Not applicable.
[a] Samples will only be collected from those animals scheduled for euthanasia on Day 29.
[b] For scheduled collection only.
[c] Will be collected under isoflurane anesthesia. On days of unscheduled euthanasia, blood may be collected under isoflurane anesthesia from the jugular or tail vein.
[d] Additional samples may be obtained (e.g., due to clotting of non-serum samples) if permissible sampling frequency and volume are not exceeded. Maximum obtainable is permissible for terminal samples.

11.2. Hematology

Hematology Parameters

Red blood cell count	White blood cell count
Hemoglobin concentration	Neutrophil count (absolute)
Hematocrit	Lymphocyte count (absolute)
Mean corpuscular volume	Monocyte count (absolute)
Red blood cell distribution width	Eosinophil count (absolute)
Mean corpuscular hemoglobin concentration	Basophil count (absolute)
Mean corpuscular hemoglobin	Large unstained cells (absolute)
Reticulocyte count (absolute)	Other cells (as appropriate)
Platelet count	

11.3. Coagulation

Coagulation Parameters

Activated partial thromboplastin time	Prothrombin time
Fibrinogen	Sample quality

11.4. Clinical Chemistry

Clinical Chemistry Parameters

Alanine aminotransferase	Total protein
Aspartate aminotransferase	Albumin
Alkaline phosphatase	Globulin (calculated)
Gamma-glutamyltransferase	Albumin/globulin ratio
Creatine kinase	Glucose
Total bilirubin[a]	Cholesterol
Urea nitrogen	Triglycerides
Creatinine	Sodium
Calcium	Potassium
Phosphorus	Chloride
	Sample quality

[a] When total bilirubin is > 0.5 mg/dL, direct bilirubin will be measured and indirect bilirubin will be calculated

11.5. Urinalysis

Urinalysis Parameters

Color	Protein
Appearance/Clarity	Glucose
Specific gravity	Bilirubin
Volume	Ketones
pH	Blood

Hematology
There were no test article-related changes.

Clinical Chemistry
There were no test article-related changes.

Urinalysis
There were no test article-related changes.

Terminal Procedures

Terminal procedures are summarized in the following table:

Replaced, Found Dead and Unscheduled Euthanasia Animals (Except Toxicokinetic Animals)

Group No.	Necropsy Procedures			Histology Processing	Microscopic Evaluation
	Necropsy	Tissue Collection	Organ Weights		
Replaced animals (prestudy)[a]	X	-	-	-	-
Replaced animals (after dosing start)	X	Full List[b]	-	-	-
Found dead or unscheduled euthanasia	X	Full List[b]	-	Full List[b]	Full List[b]

Main Study Animals

Group No.	No. of Animals		Scheduled Euthanasia Day	Necropsy Procedures			Histology Processing	Microscopic Evaluation
	M	F		Necropsy	Tissue Collection	Organ Weights		
1	10	10	29	X	Full List[b]	Full List[b]	Full List[b]	Full List[b]
2	10	10	29	X	Full List[b]	Full List[b]	Full List[b]	Full List[b]
3	10	10	29	X	Full List[b]	Full List[b]	Full List[b]	Full List[b]
4	10	10	29	X	Full List[b]	Full List[b]	Full List[b]	Full List[b]

Recovery Animals

Group No.	No. of Animals		Scheduled Euthanasia Day	Necropsy Procedures			Histology Processing	Microscopic Evaluation
	M	F		Necropsy	Tissue Collection	Organ Weights		
1	5	5	57	X	Full List[b]	Full List[b]	Full List[b]	Gross Lesions Target Tissues[c]
4	5	5	57	X	Full List[b]	Full List[b]	Full List[b]	Gross Lesions Target Tissues[c]

Toxicokinetic Animals

Group No.	Necropsy Procedures			Histology Processing	Microscopic Evaluation
	Necropsy	Tissue Collection	Organ Weights		
Found dead or unscheduled euthanasia	X[d]	-	-	-	-
Scheduled euthanasia	-	-	-	-	-

X = Procedure to be conducted; M = Males; F = Female; - = Not applicable.
Histology Processing = trimmed, embedded in paraffin, sectioned, mounted on glass slides, and stained with hematoxylin and eosin.

[a] In the case of mortality only, unless otherwise specified by the study director.
[b] See Tissue Weighing, Collection, Processing and Evaluation table for list of tissues applicable to each procedure.
[c] Any target tissues identified by the study pathologist during microscopic evaluation of full list animals will be communicated to the Study Director, then evaluated and reported in non-full list animals.
[d] Toxicokinetic animals that die on study or are euthanized for humane reasons will be subjected to a limited necropsy examination, consisting of an evaluation of the organs and tissues in the thoracic, abdominal, and pelvic cavities, with no tissues retained. Prior to euthanasia, a bioanalytical sample may be collected at the discretion of the Study Director.

In the final study report, it is stated that microscopic evaluation for the 28-day recovery period animals was limited to the testes and epididymides.

ATTACHMENT A

Tissue Weighing, Collection, Processing, and Evaluation Table

Organ	Weigh	Macroscopic Evaluation and Collection	Histology Processing	Microscopic Evaluation
Animal ID	-	X	-	-
Artery, aorta	-	X	X	X
Body cavity, nasal	-	X	X[d]	X[d]
Bone marrow, sternum	-	X	X	X
Bone marrow smear	-	X[a]	-	-
Bone, femur	-	X (1)	X (1)	X (1)
Bone, sternum	-	X	X	X
Brain	X	X	X	X
Epididymis	X (2)	X (2)[b]	X (2)	X (2)
Esophagus	-	X	X	X
Eye	-	X (2)[b]	X (2)	X (2)
Ganglion, dorsal root, lumbar	-	X	-	-
Gland, adrenal	X (2)	X (2)	X (2)	X (2)
Gland, clitoral	-	X (2)	-	-
Gland, lacrimal	-	X (2)	-	-
Gland, Harderian	-	X (2)	X (1)	X (1)
Gland, mammary	-	X	X	X
Gland, parathyroid	-	X (2)	X (2)	X (2)
Gland, pituitary	X	X	X	X
Gland, preputial	-	X (2)	-	-
Gland, prostate	X	X	X	X
Gland, salivary, submandibular	-	X (2)	X (1)	X (1)
Gland, salivary, sublingual	-	X (2)	-	-
Gland, salivary, parotid	-	X (2)	-	-
Gland, seminal vesicle	-	X (2)	X (2)	X (2)
Gland, thyroid	-	X (2)	X (2)	X (2)
Gland, thyroid/gland, parathyroid	X (2)	-	-	-
Gland, Zymbal's	-	X (2)	-	-
Gut-associated lymphoid tissue[c]	-	X	X	X
Heart	X	X	X	X
Joint, femorotibial	-	X (1)	X (1)	X (1)
Kidney	X (2)	X (2)	X (2)	X (2)
Large intestine, cecum	-	X	X	X
Large intestine, colon	-	X	X	X
Large intestine, rectum	-	X	X	X
Larynx	-	X[e]	-	-
Liver	X	X	X	X
Lung	-	X[f]	X[f]	X[f]
Lymph node(s) draining administration site(s): tracheobronchial	-	X	X	X

Organ	Weigh	Macroscopic Evaluation and Collection	Histology Processing	Microscopic Evaluation
Lymph node, mandibular	-	X (2)	X (1)	X (1)
Lymph node, mesenteric	-	X	X	X
Macroscopic abnormalities	-	X	X	X
Muscle, skeletal	-	X (2)	X (1)	X (1)
Nasopharynx	-	X	X	X
Nerve, optic	-	X (2)[b]	X (2)	X (2)
Nerve, sciatic	-	X (2)	X (1)	X (1)
Nerve, tibial	-	X (2)	-	-
Ovary	X (2)	X (2)	X (2)	X (2)
Oviduct	-	X (2)	-	-
Pancreas	-	X	X	X
Skin	-	X	X	X
Small intestine, duodenum	-	X	X	X
Small intestine, ileum	-	X	X	X
Small intestine, jejunum	-	X	X	X
Spinal cord	-	X	X	X
Spleen	X	X	X	X
Stomach	-	X	X	X
Testis	X (2)	X (2)[b]	X (2)	X (2)
Thymus	X	X	X	X
Tongue	-	X	X	X
Trachea	-	X	X	X
Ureter	-	X (2)	-	-
Urinary bladder	-	X	X	X
Uterus/Cervix	X	X	X	X
Vagina	-	X	X	X

X = Procedure to be conducted. - = Not applicable. (1) = 1 side. (2) = both sides.

[a] Two bone marrow smears will be collected from the femur at scheduled and unscheduled necropsies (for possible examination). Smears will not be collected from animals that are found dead or from animals that were euthanized moribund and then stored in the refrigerator prior to necropsy. Bone marrow smears are allowed to air dry and are not fixed in formalin. They are fixed in methanol as soon as practical after necropsy and stained.

[b] Eyes and optic nerves are preserved in Davidson's fixative. Testes and epididymides are preserved in modified Davidson's fixative.

[c] From small intestine: Peyer's patch or solitary lymphoid follicle.

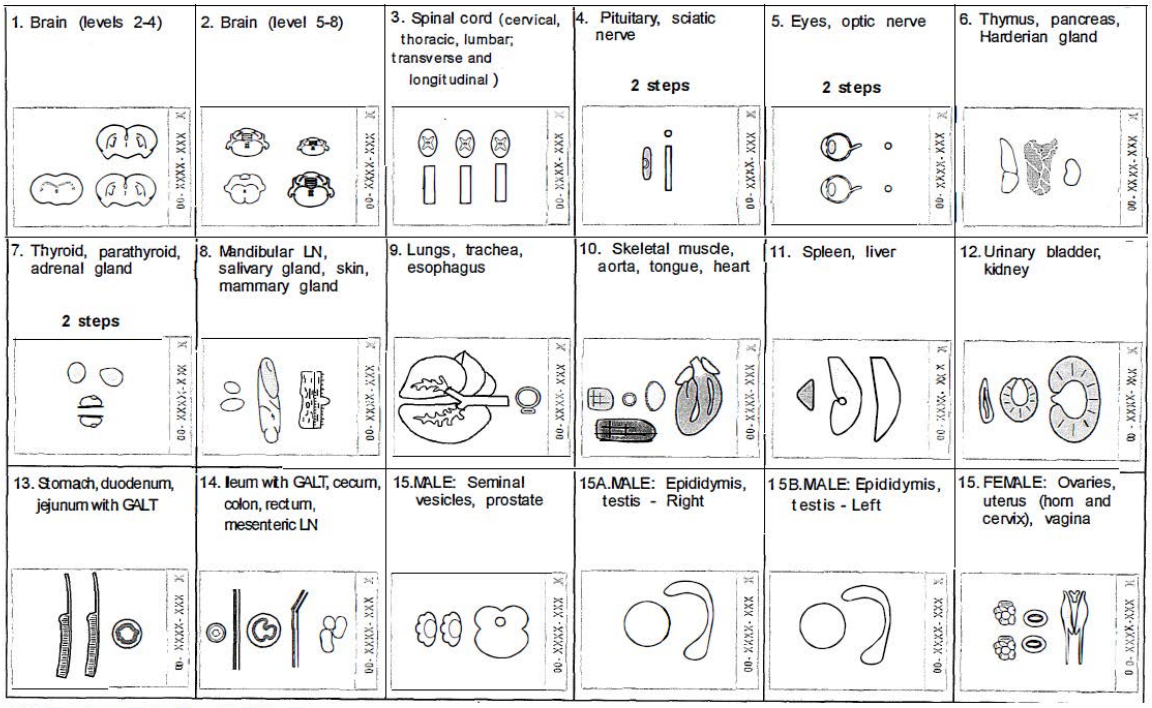
[d] Examine nasal cavity, at least 4 levels.

[e] Collect with ventral pouch.

[f] Collect with tracheal bifurcation (with mainstem brochi). Longitudinal section (LS) to include carina. Examine all lobes to include proximal and distal regions.

Reviewer's note: According to the Applicant's response to our IR, dated February 24, 2023, the Applicant has evaluated 7 brain slices and the connected tissues to the nasal cavity. The following details of the tissues examined were provided in the response to the IR:

Rodent Trimming & Embedding Scheme — SN: 20291737



GALT = gut associated lymphoid tissue

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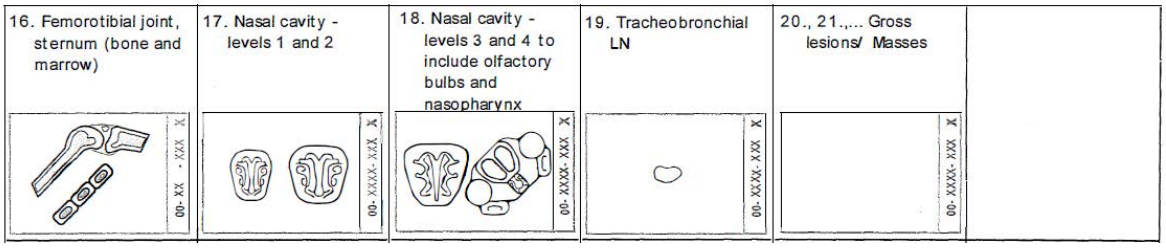
Rodent Trimming & Embedding Scheme — SN: 20291737



Gross Pathology

No test article-related gross findings were noted at terminal euthanasia. Two instances of dark focus were noted for thymus at LD and HD, which were considered incidental and unrelated to the test article.

Organ Weights

The Applicant noted that no test article-related organ weight changes were noted. This Reviewer noted that there was a slight reduction of mean organ weight of epididymis and testis at HD (see the table below).

Organ/Tissue	Specimen Laterality	Test	Unit	Male			
				Veh	LD	MD	HD

EPIDIDYMIS	BILATERAL	Organ to Body Weight Ratio	%	0.28907	-1.35%	5.05%	-4.90%
		Organ to Brain Weight Ratio		50.67071	-3.22%	0.92%	-7.37%
		Weight	g	1.048	-3.54%	2.46%	-10.42%
TESTIS		Organ to Body Weight Ratio	%	0.93245	0.04%	8.83%	-8.88%
		Organ to Brain Weight Ratio		163.81187	-2.19%	4.18%	-10.95%
		Weight	g	3.383	-2.21%	5.91%	-13.80%

Furthermore, the two HD male rats that had histopathology findings in testis and epididymis appear to have lower organ weight.

Histopathology

Adequate Battery:
Peer Review: Unknown

Male Reproductive Organs

As shown in the table below, moderate to marked bilateral seminiferous tubule degeneration were noted in 2 of 10 HD rats. The same animals also had cellular debris and decreased sperm in the epididymides, likely secondary findings, but were not observed at the end of the recovery phase.

Applicant's justification:

"Although the incidence was greater than is often observed in control populations, no evidence for degeneration occurred in the testes of the remaining rats of the same group or in males administered lower doses of Nalmefene Hydrochloride. The reproductive systems of the females administered Nalmefene Hydrochloride were also within normal limits. In an FDA review of Nalmefene as Revex Injection (Revex Injection FDA Review 1995), no evidence for impaired fertility was noted when Nalmefene was administered orally to rats or when administered orally or intravenously to rabbits. Nalmefene has been available for parenteral administration to humans for more than 20 years with no reported evidence for reproductive system toxicity. Therefore, male reproductive tissue findings in 2 rats administered Nalmefene Hydrochloride were considered incidental and unrelated to the test article."

***Reviewer's note:* This Reviewer considers the testis and epididymis findings test article-related, given that both occurred in two HD-treated animals that exceeded the incidence observed in the control groups.**

Lung

Moderate hemorrhage was noted in 1 HD animal. The finding was not considered test article-related by the Applicant.

Nasal Cavity

As shown in the tables below, the following findings were noted in nasal tissues at terminal sacrifice:

- Multifocal Erosion/ulcer: minimal in 1 HD male
- Focal Exudate: minimal in 1 MD female and 1 HD female; mild in 1 HD male
- Acute focal Hemorrhage: mild in 1 HD male
- Focal metaplasia: minimal in 1 veh male and 1 HD female

The Applicant did not consider these findings test article related. Recovery of the nasal tissues was not assessed.

Table 7: Summary of Histopathological Findings at Terminal Necropsy (Janus)

Organ	Finding	Finding Modifier	Severity	Male				Female			
				Veh	LD	MD	HD	Veh	LD	MD	HD
EPIDIDYMIS			# Animals Examined	10	10	10	10	0	0	0	0
	CELL DEBRIS		2 OF 5				2				
			Total				2				
	SPERM, DECREASED	bilateral; intraluminal	3 OF 5				2				
			Total				2				
BODY CAVITY, NASAL			# Animals Examined	10	10	10	10	10	10	10	10
	EROSION /ULCER	unilateral, MULTIFOCAL	1 OF 5				1				
			Total				1				
	EXUDATE	bilateral; unilateral,FOCAL	1 OF 5							1	1
		unilateral,FOCAL	2 OF 5				1				
			Total				1			1	1
	HEMORRHAGE	ACUTE,FOCAL	2 OF 5				1				
			Total				1				
	METAPLASIA	respiratory; unilateral,FOCAL	1 OF 5	1							1
			Total	1							1
GLAND, PROSTATE			# Animals Examined	10	10	10	10	0	0	0	0
	INFILTRATE	mononuclear cell,MULTIFOCAL	1 OF 5		2		1				
			2 OF 5	1							
			Total	1	2		1				
TESTIS			# Animals Examined	10	10	10	10	0	0	0	0
	DEGENERATION	bilateral; tubular, SEGMENTAL	3 OF 5				1				
			4 OF 5				1				
			Total				2				
LUNG	HEMORRHAGE		# Animals Examined	10	10	10	10	10	10	10	10
			3 OF 5				1				
			TOTAL				1				

1: minimal; 2: mild; 3: moderate; 4: marked; 5: severe

Toxicokinetics

Blood samples were collected on Days 1 and 28 according to the collection schedule in **Text Table 2**.

Text Table 2
TK Sample Collection Schedule

Group No.	Subgroup	No. of Animals (M/F)	Time Postdose on Day 1					
			0.167 hr (10 min)	0.5 hr	2 hr	4 hr	8 hr	24 hr
1	A	3/3	X	-	-	X	-	-
2	A	3/3	X	-	X	-	X	-
	B	3/3	-	X	-	X	-	X
3	A	3/3	X	-	X	-	X	-
	B	3/3	-	X	-	X	-	X
4	A	3/3	X	-	X	-	X	-
	B	3/3	-	X	-	X	-	X

X = Sample to be collected; M = Male; F = Female; - = Not applicable; min = minute; hr = hour.

Group No.	Subgroup	No. of Animals (M/F)	Time Postdose on Day 28						
			0 hr[a]	0.167 hr (10 min)	0.5 hr	2 hr	4 hr	8 hr	24 hr
1	A	3/3	X	-	-	-	X	-	-
2	A	3/3	X	-	X	-	X	-	X
	B	3/3	-	X	-	X	-	X	-
3	A	3/3	X	-	X	-	X	-	X
	B	3/3	-	X	-	X	-	X	-
4	A	3/3	X	-	X	-	X	-	X
	B	3/3	-	X	-	X	-	X	-

X = Sample to be collected; M = Male; F = Female; - = Not applicable; min = minute; hr = hour.
[a] Sample collected before dosing.

6.2.6. Incurred Sample Reanalysis

Twenty-six study samples were selected for reanalysis to evaluate the overall performance of the bioanalytical assay.

For the analytical method to be considered as acceptable for incurred samples reanalysis, 67% of the reanalyzed samples should have results within 20% utilizing the following calculation:

$$\frac{(repeat\ result - original\ result)}{((repeat\ result + original\ result)/2)} \quad x \quad 100\%$$

Incurred sample reanalysis (ISR) was successfully conducted in this study to support the method for the determination of Nalmefene in Sprague-Dawley rat plasma (K_2EDTA) by high performance liquid chromatographic mass spectrometric detection.

The TK results are summarized by the Applicant in the table below:

Table 7
Toxicokinetic Parameters for Nalmefene in Male and Female Rats following Intranasal Administration of Nalmefene Hydrochloride at 1, 3, or 8.5 mg

Analyte	Gender	Day	Dose (mg)	AUC_{tlast} (hr*pg/mL)	AUC_{tlast}/D	C_{max} (pg/mL)	C_{max}/D	t_{max} (hr)	t_{last} (hr)	R_{AUC} (RATIO)
Nalmefene	Male	1	1	63300	63300	38600	38600	0.167	24	NA
			3	218000	72800	244000	81200	0.167	24	NA
			8.5[a]	414000 [1710000]	48700 [201000]	265000	31200	0.167	24	NA
		28	1	41000	41000	33000	33000	0.167	24	0.648
			3	251000	83600	524000	175000	0.167	24	1.15
			8.5	509000	59900	1250000	147000	0.167	24	1.23
	Female	1	1[b]	143000 [2230000]	143000 [2230000]	119000 [701000]	119000 [701000]	0.167 [4]	24	NA
			3	368000	123000	482000	161000	0.167	24	NA
			8.5	668000	78500	451000	53000	0.167	24	NA
		28	1	61200	61200	50400	50400	0.167	24	0.429
			3	186000	61900	146000	48700	0.167	24	0.505
			8.5	333000	39200	272000	32000	0.167	24	0.499

Units for AUC_{tlast}/D are (hr*pg/mL)/(mg); units for C_{max}/D are (pg/mL)/(mg)
NA = Not applicable
[a] TK results shown excluding and [including] aberrant concentration at 8 hours postdose for Group 4 (8.5 mg) Male No. 4016.
[b] TK results shown excluding and [including] aberrant concentration at 4 hours postdose for Group 2 (1 mg) Female No. 2514.

Study title: A 28-Day Study of Nalmefene Hydrochloride by Intranasal Administration in Dogs with a 28-Day Recovery Period

Study no.:	20291738
Study report location:	Study Report Link
Conducting laboratory and location:	(b) (4) [redacted] United States
Date of study initiation:	June 1, 2021
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Nalmefene hydrochloride Batch/Lot No: 1902000367 Purity: 95.2%

Key Study Findings

- Minimal to mild microscopic findings were observed in the lung. These findings are either associated with nasal route of administration or background findings, as opposed to a direct effect by nalmefene treatment.
    - Minimal mixed cell infiltrate (alveolar and/or perivascular) across all treatment groups including the vehicle group
    - Mild mixed cell inflammation in bronchioloalveolar in one MD female

- Mild alveolar hemorrhage in one HD male
- Minimal alveolar granuloma was noted in one vehicle-treated female

- For nasal cavity, minimal transitional epithelium degeneration was noted in one vehicle-treated and one MD-treated female. No such a finding was observed in the recovery groups, indicating recovery.

- The HD is considered as the systemic and local NOAEL for the study. The findings in the lung and nasal cavity are likely vehicle related, as opposed to being related to nalmefene.

Methods

Doses: 0, 2 (LD), 6 (MD) and 17 mg (HD)
Frequency of dosing: Once daily
Route of administration: Intranasal
Dose volume: 0.2 mL
Formulation/Vehicle: Vehicle and control article: (b) (4) mg benzalkonium chloride, (b) (4) mg dodecyl maltoside, (b) (4) mg disodium edetate, (b) (4) mg sodium chloride in reverse osmosis deionized (RODI) water (per mL)
Species/Strain: Dog/Beagle
Number/Sex/Group:

Text Table 1
Experimental Design – Main and Recovery

Group No.	Test Material	Dose Level[a] (mg)	Total Dose Volume[b] (mL)	Dose Concentration (mg/mL)	Adjusted Dose Concentration[c] (mg/mL)	No. of Animals			
						Main Study		Recovery Study	
						Males	Females	Males	Females
1	Control[d]	0	0.2	0	0	3	3	2	2
2	Nalmefene Hydrochloride	2	0.2	10	10.50	3	3	-	-
3	Nalmefene Hydrochloride	6	0.2	30	31.51	3	3	-	-
4	Nalmefene Hydrochloride	17	0.2	85	89.29	3	3	2	2

- = Not applicable.
[a] Dosed once daily from Days 1 to 28.
[b] The dose volume was administered to each animal with the total dose volume split equally between each nostril (bilaterally).
[c] The dose concentration was corrected for water based on a correction factor of 0.952.
[d] (b) (4) mg Benzalkonium chloride (b) (4) mg Dodecyl maltoside, (b) (4) mg Disodium edetate, (b) (4) mg Sodium chloride in reverse osmosis deionized (RODI) water (per mL).

Age: 6-months at initiation of dosing
Weight: Average bodyweight of 7.1 kg at the initiation of dosing
Satellite groups: None
Unique study design: None
Deviation from study protocol: No deviations were noted that would impact the results of the study.

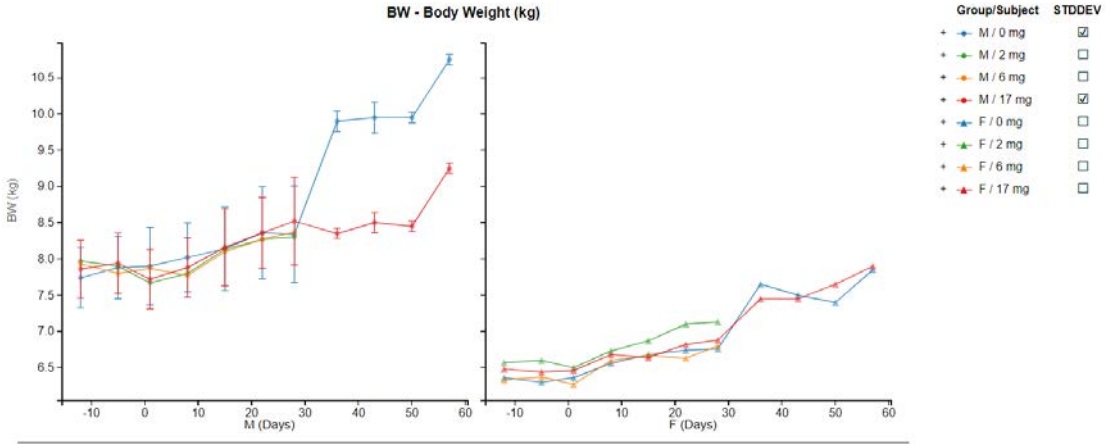
Observations and Results

Dosing Solution Analysis
All study samples analyzed had mean concentrations within or equal to the acceptance criteria of ± 10% (individual values within or equal to ± 15%) of their theoretical concentrations. For homogeneity, the relative standard deviation (RSD) of concentrations for all samples in each group tested was within the acceptance criteria of ≤ 5%.

Mortality
There was no mortality noted in the study.

Clinical Signs
Slight tremors were noted in 3 animals (1 male and 2 females) administered HD on Day 14. This finding was considered incidental as it appears sporadic.

Body Weights and Food Consumption
There were no test article-related effects noted on body weights or body weight gains or food consumption during the dosing phase. However, it appears that the males at HD had substantial less weight gain during the recovery phase (see the figure below from SEND EXPLORER).



Ophthalmoscopy
No test article-related findings were observed.

ECG
ECG evaluations were conducted on Day -9, prior to dosing and at 2-4 hours postdosing on Day 2 and Day 27 and during the last week of the recovery period.

No test article-related changes in ECG endpoints were observed.

Abnormal ECG waveform morphology results are presented in the following table:

Text Table 2
Abnormal ECG Waveform Morphology

Animal No.	Day	Time Point	Nalmefene Hydrochloride Dose Group (mg)				
			Predose	0	2	6	17
3002 (M)	2	Predose	-	-	-	PVC (1)	-
3502 (F)	27	Predose	-	-	-	AVB2M1 (1)	-

- = No significant finding noted; M = Male; F = Female.
AVB2M1 = Atrioventricular second degree block – Mobitz type 1
PVC = Premature ventricular contraction
( ) = Number of incidences for that particular finding

No changes in ECG waveform morphology were considered a result of Nalmefene Hydrochloride administration at any dose level tested as occurrences were not noted in a dose-dependent manner, occurred at a single time point, and/or in single animals (Atterson et al., 2009; Richig and Sleeper, 2018).

The percent changes from the control group for each significant time point are summarized in the Applicant's table below. Only time points with statistically significant changes were included. This Reviewer agrees with the Applicant that none of the changes appears test article related.

Text Table 3
Summary of Statistically Significant ECG Interval Data Expressed as Percent Change from Control (%)

Day	Interval	Sex	Heart Rate			PR			QRS			RR			QT			QTcV		
			Dose Level (mg)																	
			2	6	17	2	6	17	2	6	17	2	6	17	2	6	17	2	6	17
2	Predose	Male	-25.1	-	-29.5	-	-	-	-	-	-	32.4	-	41.3	-	-	-	-	-	-
		Female	-	-	-28.2	-	-	-	-	-	-	-	-	41.3	-	-	-	-	-	-
27	Predose	Male	-29.9	-	-	-	-	-	-	-	-	40.8	-	-	8.7	-	8.5	-	-	-

- = Not applicable.

Clinical Pathology Procedure

11.1. Sample Collection

Clinical Pathology Sample Collection

Group Nos.	Time Point	Hematology	Coagulation	Clinical Chemistry	Urinalysis
All animals	Week -1	X	X	X	X
1 to 4	Day 29	X	X	X	X[a]
1 and 4 (Recovery study animals only)	Day 58	X	X	X	X[a]
Unscheduled euthanasia (when possible)		X	X	X	X[b]
Fasting[c]:		-	-	Min. 4 hours	Min. 4 hours
Method/Comments:		Venipuncture of the Jugular Vein[d]	Venipuncture of the Jugular Vein[d]	Venipuncture of the Jugular Vein[d]	Urine will be collected overnight via cage pan drainage
Target Volume (mL)[e]:		2	1.8	2	-
Anticoagulant:		(K_2) EDTA	Sodium citrate	None	-
Special Requirements:		-	-	-	-
Processing:		None	Plasma	Serum	-

X = Sample to be collected; Min. = Minimum; - = Not applicable.

[a] If an adequate urine sample is not collected at scheduled euthanasia via the urine collection cage, then cystocentesis at gross necropsy may be used.

[b] Collect by cystocentesis at gross necropsy.

[c] For scheduled collection only.

[d] The cephalic vein may be used if necessary.

[e] Additional samples may be obtained (e.g., due to clotting of non-serum samples) if permissible sampling frequency and volume are not exceeded.

11.2. Hematology

Hematology Parameters

Red blood cell count	White blood cell count
Hemoglobin concentration	Neutrophil count (absolute)
Hematocrit	Lymphocyte count (absolute)
Mean corpuscular volume	Monocyte count (absolute)
Red blood cell distribution width	Eosinophil count (absolute)
Mean corpuscular hemoglobin concentration	Basophil count (absolute)
Mean corpuscular hemoglobin	Large unstained cells (absolute)
Reticulocyte count (absolute)	Other cells (as appropriate)
Platelet count	

One blood smear will be prepared from each hematology sample. The slide will be labeled, stained, and archived. Slide review will only be performed on samples that meet flagging criteria in order to confirm accurate hematology analyzer results. If additional examination of blood smears is deemed necessary, the smears may be subsequently evaluated at additional cost by protocol amendment.

11.3. Coagulation

Coagulation Parameters

Activated partial thromboplastin time	Prothrombin time
Fibrinogen	Sample quality

11.4. Clinical Chemistry

Clinical Chemistry Parameters

Alanine aminotransferase	Total protein
Aspartate aminotransferase	Albumin
Alkaline phosphatase	Globulin (calculated)
Gamma-glutamyltransferase	Albumin/globulin ratio
Creatine kinase	Glucose
Total bilirubin[a]	Cholesterol
Urea nitrogen	Triglycerides
Creatinine	Sodium
Calcium	Potassium
Phosphorus	Chloride
	Sample quality

[a] When total bilirubin is > 1.0 mg/dL, direct bilirubin will be measured and indirect bilirubin will be calculated

11.5. Urinalysis

Urinalysis Parameters

Color	Protein
Appearance/Clarity	Glucose
Specific gravity	Bilirubin
Volume[a]	Ketones
pH	Blood

[a] If urine is collected by cystocentesis, total volume will not be determined.

Hematology

No test article-related changes in ECG endpoints were observed.

Clinical Chemistry

No test article-related changes in clinical chemistry endpoints were observed.

Urinalysis

No test article-related changes in urinalysis endpoints were observed.

Terminal Procedures

13. TERMINAL PROCEDURES

Terminal procedures are summarized in the following table:

Replaced, Found Dead and Unscheduled Euthanasia Animals

Group No.	Necropsy Procedures			Histology Processing	Microscopic Evaluation
	Necropsy	Tissue Collection	Organ Weights		
Replaced animals (prestudy)[a]	X	-	-	-	-
Replaced animals (after dosing start)	X	Full List[b]	-	-	-
Found dead or unscheduled euthanasia	X	Full List[b]	-	Full List[b]	Full List[b]

Main Study Animals

Group No.	No. of Animals		Scheduled Euthanasia Day	Necropsy Procedures			Histology Processing	Microscopic Evaluation
	M	F		Necropsy	Tissue Collection	Organ Weights		
1	3	3	29	X	Full List[b]	Full List[b]	Full List[b]	Full List[b]
2	3	3	29	X	Full List[b]	Full List[b]	Full List[b]	Full List[b]
3	3	3	29	X	Full List[b]	Full List[b]	Full List[b]	Full List[b]
4	3	3	29	X	Full List[b]	Full List[b]	Full List[b]	Full List[b]

Recovery Animals

Group No.	No. of Animals		Scheduled Euthanasia Day	Necropsy Procedures			Histology Processing	Microscopic Evaluation
	M	F		Necropsy	Tissue Collection	Organ Weights		
1	2	2	58	X	Full List[b]	Full List[b]	Full List[b]	Full List[b]
4	2	2	58	X	Full List[b]	Full List[b]	Full List[b]	Full List[b]

X = Procedure to be conducted; M = Males; F = Female; - = Not applicable.
Histology Processing = trimmed, embedded in paraffin, sectioned, mounted on glass slides, and stained with hematoxylin and eosin.

[a] In the case of mortality only, unless otherwise specified by the study director.
[b] See Tissue Weighing, Collection, Processing and Evaluation table for list of tissues applicable to each procedure.
[c] Any target tissues identified by the study pathologist during microscopic evaluation of full list animals will be communicated to the Study Director, then processed, evaluated and reported in non-full list animals.

ATTACHMENT A

Tissue Weighing, Collection, Processing, and Evaluation Table

Organ	Weigh	Macroscopic Evaluation and Collection	Histology Processing	Microscopic Evaluation
Animal ID	-	X	-	-
Artery, aorta	-	X	X	X
Body cavity, nasal	-	X[e]	X[e]	X[e]
Bone marrow, sternum	-	X	X	X
Bone marrow smear	-	X[a]	-	-
Bone, femur	-	X (1)	X (1)	X (1)
Bone, sternum	-	X	X	X
Brain	X	X	X	X
Epididymis	X (2)	X (2)[b]	X (2)	X (2)
Esophagus	-	X	X	X
Eye	-	X (2)[b]	X (2)	X (2)
Gallbladder	-[d]	X	X	X
Ganglion, dorsal root, lumbar	-	X	-	-
Gland, adrenal	X (2)	X (2)	X (2)	X (2)
Gland, lacrimal	-	X (2)	-	-
Gland, mammary (females)	-	X	X	X
Gland, parathyroid	-	X (2)	X (2)	X (2)
Gland, pituitary	X	X	X	X
Gland, prostate	X	X	X	X
Gland, salivary, submandibular	-	X (2)	X (1)	X (1)
Gland, salivary, sublingual	-	X (2)	-	-
Gland, salivary, parotid	-	X (2)	-	-
Gland, thyroid	-	X (2)	X (2)	X (2)
Gland, thyroid/gland, parathyroid	X (2)	-	-	-
Gut-associated lymphoid tissue[c]	-	X	X	X
Heart	X	X	X	X
Joint, femorotibial	-	X (1)	X (1)	X (1)
Kidney	X (2)	X (2)	X (2)	X (2)
Large intestine, cecum	-	X	X	X
Large intestine, colon	-	X	X	X
Large intestine, rectum	-	X	X	X
Larynx	-	X[f]	X[f]	X[f]
Liver	-	X	X	X
Liver/gallbladder	X	-	-	-
Lung	-	X[g]	X[g]	X[g]
Lymph node(s) draining administration site(s): tracheobronchial	-	X	X	X
Lymph node, mandibular	-	X (2)	X (1)	X (1)
Lymph node, mesenteric	-	X	X	X

Organ	Weigh	Macroscopic Evaluation and Collection	Histology Processing	Microscopic Evaluation
Macroscopic abnormalities	-	X	X	X
Muscle, skeletal	-	X (2)	X (1)	X (1)
Nerve, optic	-	X (2)[b]	X (2)	X (2)
Nerve, sciatic	-	X (2)	X (1)	X (1)
Nerve, tibial	-	X (2)	-	-
Ovary	X (2)	X (2)	X (2)	X (2)
Oviduct	-	X (2)	-	-
Pancreas	-	X	X	X
Skin	-	X	X	X
Small intestine, duodenum	-	X	X	X
Small intestine, ileum	-	X	X	X
Small intestine, jejunum	-	X	X	X
Spinal cord	-	X	X	X
Spleen	X	X	X	X
Stomach	-	X	X	X
Testis	X (2)	X (2)[b]	X (2)	X (2)
Thymus	X	X	X	X
Tongue	-	X	X	X
Tonsils	-	X (2)	X (2)	X (2)
Trachea	-	X	X	X
Ureter	-	X (2)	-	-
Urinary bladder	-	X	X	X
Uterus/Cervix	X	X	X	X
Vagina	-	X	X	X

X = Procedure to be conducted. - = Not applicable. (1) = 1 side. (2) = both sides.

[a] Bone marrow smears will be collected from the 5th to 7th rib at scheduled and unscheduled necropsies (for possible examination). Smears will not be collected from animals that are found dead or from animals that were euthanized moribund and then stored in the refrigerator prior to necropsy. Bone marrow smears are allowed to air dry and are not fixed in formalin. They are fixed in methanol as soon as practical after necropsy and stained.

[b] Eyes and optic nerves are preserved in Davidson's fixative. Testes and epididymides are preserved in modified Davidson's fixative.

[c] From small intestine: Peyer's patch or solitary lymphoid follicle.

[d] Weigh with liver.

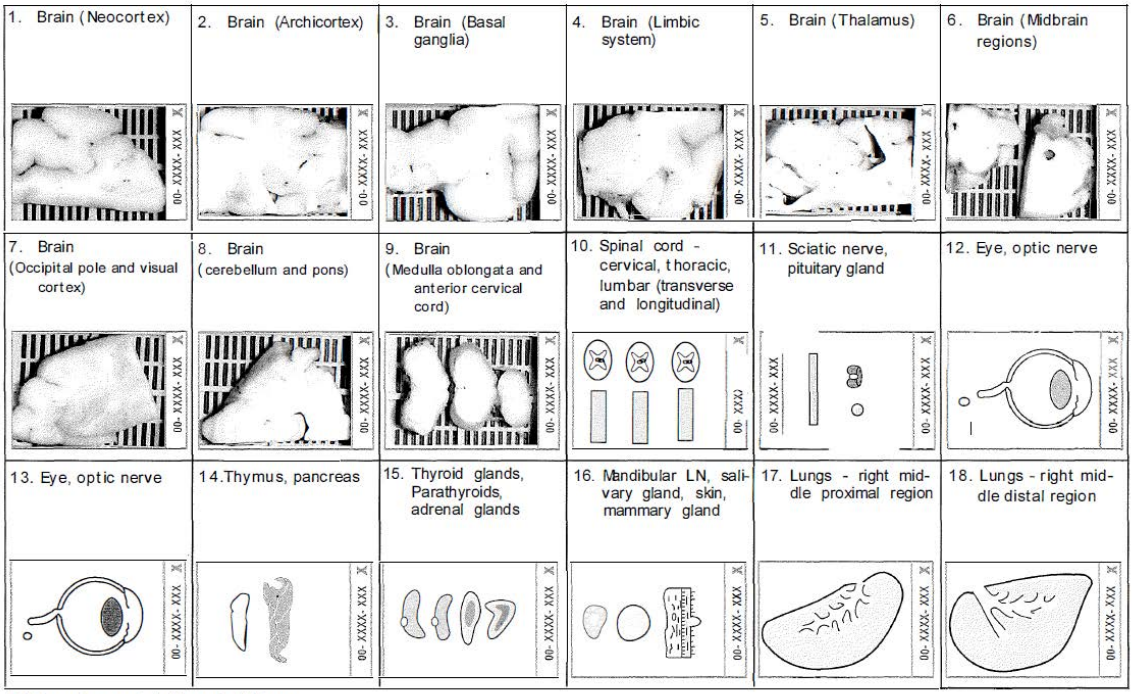
[e] Nasal cavities and nasopharynx with skull will be collected. Examine nasal cavity at least 4 levels and nasopharynx.

[f] Larynx will include at least 2 levels to include vestibular and vocal folds.

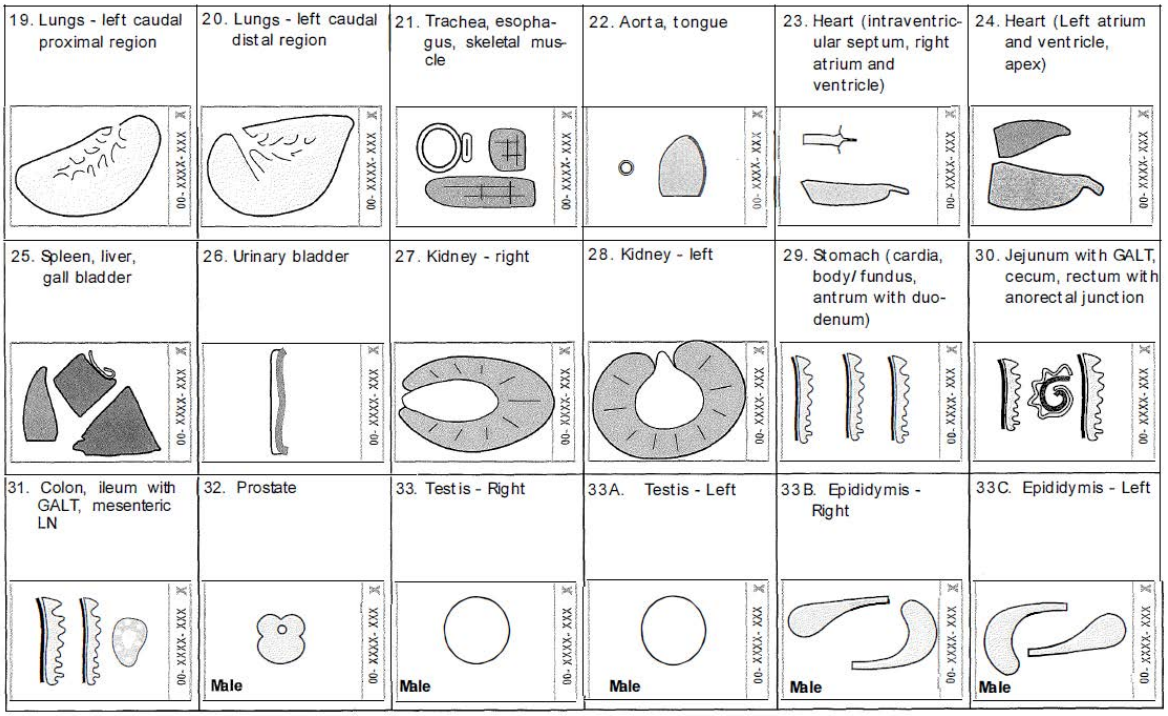
[g] Collect and retain all 7 lobes and tracheal bifurcation (with mainstem bronchi). Longitudinal section (LS) to include carina. Examine the right middle and left caudal lobes, to include proximal and distal regions.

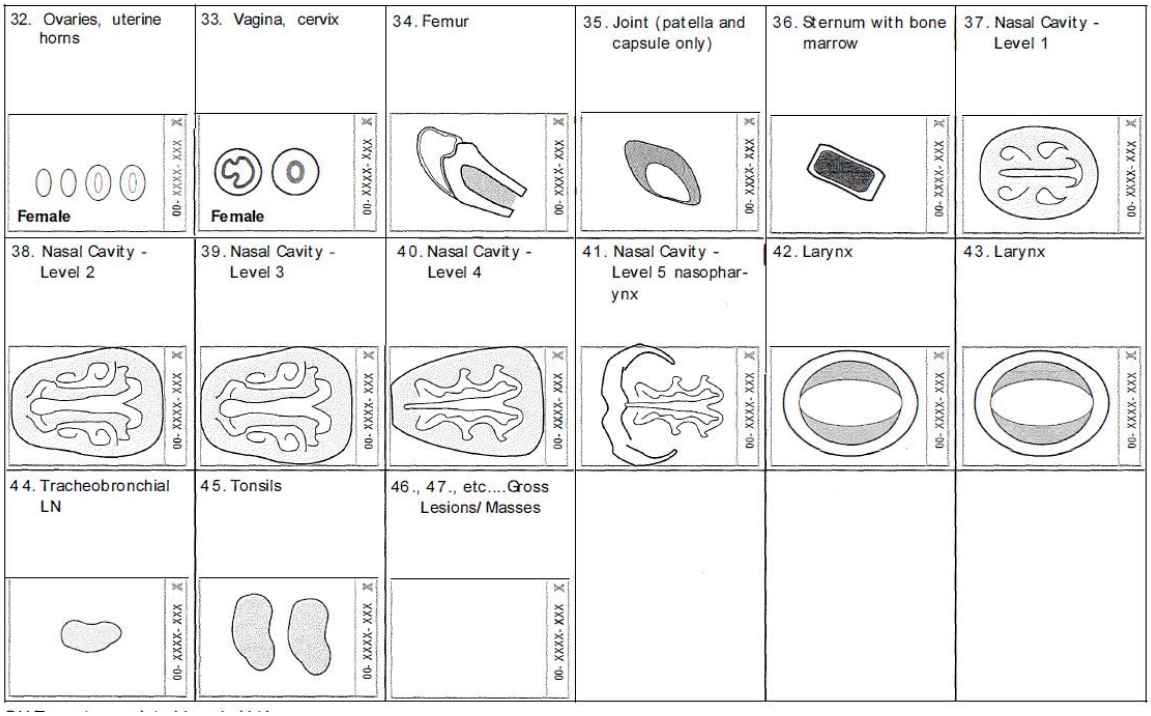
Reviewer's note: According to the Applicant's response to our IR, dated February 24, 2023, the Applicant has evaluated 6 brain slices and the connected tissues to the nasal cavity. The following details of the tissues examined were provided in the response to the IR:

Large Animal Trimming & Embedding Scheme — SN: 20291738



GALT = gut associated lymphoid tissue





Gross Pathology
No test article-related gross findings were noted.

Organ Weights
No test article-related organ weight changes were noted.

Histopathology

Adequate Battery: Yes

Peer Review: Unknown

The microscopic findings are summarized in the tables below.

<u>Lung</u>
At the terminal necropsy, the following findings were observed:

- Minimal mixed cell infiltrate (alveolar and/or perivascular) across all treatment groups including the vehicle group
- Mild mixed cell inflammation in bronchioloalveolar in one MD female
- Mild alveolar hemorrhage in one HD male
- Minimal alveolar granuloma was noted in one vehicle-treated female.

Following 4 weeks of recovery, minimal to mild alveolar mixed cell infiltrate was still noted across treatment groups.

Applicant's Justification:

Microscopic findings in the lungs have been reported as spontaneous lesions in vehicle-treated beagle dogs used for inhalation toxicity studies (Mukaratirwa et al., 2016) and/or background findings reported in beagles used in toxicity studies (Sato et al., 2012; Morishima et al., 1990). These included minimal mixed cell infiltration (alveolar and/or perivascular) in all groups, minimal alveolar granuloma in 1 control female (Animal No. 1502), mild bronchioloalveolar mixed cell inflammation in 1 female at 6 mg (Animal No. 3501), and mild pulmonary hemorrhage in 1 male at 17 mg (Animal No. 4002). These lesions tended to be focal, limited in distribution, and were non dose responsive. Therefore, these findings were considered incidental and unrelated to administration of Nalmefene Hydrochloride.

Reviewer's Note: This Reviewer agrees with the Applicant that the lung findings are likely not specifically related to the nalmefene treatment. See Section 11 for more discussion.

Nasal Cavity

Minimal transitional epithelium degeneration was noted in one vehicle-treated and one MD-treated female. Similar to the lung findings, this Reviewer considers the finding in nasal cavity drug product vehicle related as opposed to being related to nalmefene treatment. No such finding was observed in the recovery groups, indicating a recovery.

Table 8: Histopathological Findings at Terminal Necropsy (Janus)

Organ Tissue	Finding	Finding Modifier	Severity	Male				Female			
				Veh	LD	MD	HD	Veh	LD	MD	HD
LUNG			# Animals Examined	3	3	3	3	3	3	3	3
	GRANULOMA	alveolar,FOCAL	1 OF 5					1			
			Total					1			
	HEMORRHAGE	alveolar	2 OF 5				1				
			Total				1				
	INFILTRATE	mixed cell; alveolar	1 OF 5	2	2	3	3	3	2	2	3
			Total	2	2	3	3	3	2	2	3
	INFLAMMATION	mixed cell; bronchioloalveolar	2 OF 5							1	
			Total							1	
BODY CAVITY, NASAL			# Animals Examined	3	3	3	3	3	3	3	3
	DEGENERATION	transitional epithelium	1 OF 5					1		1	
			Total					1		1	
THYMUS			# Animals Examined	3	3	3	3	3	3	3	3
	HEMORRHAGE		3 OF 5							1	
			Total							1	

1: Minimal; 2: Mild; 3: Moderate; 4: Marked; 5: Severe

Table 9: Histopathological Findings at Recovery Necropsy (Janus)

Organ/Tissue	Finding	Finding Modifier	Severity	Male		Female	
				Veh	HD	Veh	HD
LUNG			# Animals Examined	2	2	2	2
	INFILTRATE	mixed cell; alveolar	1 OF 5	1	2	2	1
			2 OF 5	1			
			Total	2	2	2	1

1: Minimal; 2: Mild; 3: Moderate; 4: Marked; 5: Severe

Toxicokinetics

12.1. Bioanalytical Sample Collection

Bioanalytical Sample Collection

Group Nos.	Time Postdose on Days 1 and 28									
	0 hr[a]	0.083 hr (5 min)	0.17 hr (10 min)	0.5 hr	1 hr	2 hr	6 hr	8 hr	12 hr	24 hr
1	X	X	X	X	X	X	X	X	X	X
2	X	X	X	X	X	X	X	X	X	X
3	X	X	X	X	X	X	X	X	X	X
4	X	X	X	X	X	X	X	X	X	X
Unscheduled euthanasia (when possible)	Before euthanasia									
Method/Comments:	Venipuncture of the jugular vein. The cephalic vein may be used if necessary.									
Target Volume (mL):	1									
Anticoagulant:	K_2EDTA									
Special Requirements:	Tubes will be chilled after blood collection.									
Processing:	Plasma									

X = Sample to be collected; hr = hour; min = minute.

[a] Sample will be collected before dosing.

ISR was successfully conducted in this study to support the method for the determination of nalmefene in Beagle dog plasma (K_2EDTA) by high performance liquid chromatographic mass spectrometric detection.

The TK results are summarized by the Applicant in the table below:

Text Table 5
Mean ±SD Toxicokinetic Parameters for Nalmefene in Male and Female Dogs

Day	Dose (mg)	Sex	N	AUCtlast (hr*pg/mL)	AUC(0-24) (hr*pg/mL)	Cmax (pg/mL)	tmax[a] (hr)	tlast[a] (hr)	RAUC (RATIO)
1	2	Male	3	197000 ± 50900	198000 ± 50200	723000 ± 385000	0.083 (0.083 - 0.17)	12 (12 - 24)	NA
		Female	3	150000 ± 34700	150000 ± 34000	574000 ± 251000	0.083 (0.083 - 0.083)	24 (12 - 24)	NA
		Combined	6	173000 ± 46600	174000 ± 46300	649000 ± 302000	0.083 (0.083 - 0.17)	‡ (12 - 24)	NA
	6	Male	3	459000 ± 128000	459000 ± 128000	1240000 ± 440000	0.17 (0.083 - 0.17)	24 (24 - 24)	NA
		Female	3	524000 ± 184000	524000 ± 184000	2190000 ± 845000	0.083 (0.083 - 0.083)	24 (24 - 24)	NA
		Combined	6	491000 ± 146000	491000 ± 146000	1720000 ± 794000	0.083 (0.083 - 0.17)	24 (24 - 24)	NA
	17	Male	5	1420000 ± 510000	1420000 ± 510000	3470000 ± 1480000	0.083 (0.083 - 0.17)	24 (24 - 24)	NA
		Female	5	1500000 ± 598000	1500000 ± 598000	4150000 ± 2140000	0.083 (0.083 - 0.17)	24 (24 - 24)	NA
		Combined	10	1460000 ± 526000	1460000 ± 526000	3810000 ± 1770000	0.083 (0.083 - 0.17)	24 (24 - 24)	NA
28	2	Male	3	178000 ± 51900	178000 ± 51900	583000 ± 179000	0.083 (0.083 - 0.17)	24 (24 - 24)	0.970 ± 0.404
		Female	3	105000 ± 21800	105000 ± 21800	274000 ± 31400	0.083 (0.083 - 0.17)	24 (24 - 24)	0.744 ± 0.320
		Combined	6	142000 ± 53900	142000 ± 53900	428000 ± 205000	0.083 (0.083 - 0.17)	24 (24 - 24)	0.857 ± 0.349
	6	Male	3	503000 ± 181000	503000 ± 181000	1430000 ± 812000	0.17 (0.083 - 0.17)	24 (24 - 24)	1.17 ± 0.492
		Female	3	484000 ± 191000	484000 ± 191000	887000 ± 838000	0.083 (0.083 - 0.083)	24 (24 - 24)	0.932 ± 0.303
		Combined	6	494000 ± 167000	494000 ± 167000	1160000 ± 796000	0.083 (0.083 - 0.17)	24 (24 - 24)	1.05 ± 0.387
	17	Male	5	1190000 ± 621000	1190000 ± 621000	2920000 ± 1510000	0.17 (0.083 - 0.17)	24 (24 - 24)	0.886 ± 0.350
		Female	5	1130000 ± 441000	1130000 ± 441000	2900000 ± 1310000	0.17 (0.083 - 0.17)	24 (24 - 24)	0.852 ± 0.425
		Combined	10	1160000 ± 509000	1160000 ± 509000	2910000 ± 1330000	0.17 (0.083 - 0.17)	24 (24 - 24)	0.869 ± 0.367

NA = Not applicable
[a] Median (range) presented for tmax and tlast.
‡ Median time not an actual collection time.

7 Genetic Toxicology

As dodecylmaltoside (DDM) is a new excipient, the genotoxicity potential of this excipient should be addressed as outlined in the guidance for industry, *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*. To address the genetic toxicity potential of the excipient, the Applicant referenced the nonclinical data in DMF (b) (4)

The genotoxicity potential of dodecylmaltoside (DDM) was adequately evaluated. Refer to the nonclinical review of genotoxicity studies submitted under DMF (b) (4)

8 Reproductive and Developmental Toxicology

As dodecylmaltoside (DDM) is a new excipient, the reproductive and developmental toxicity potential of this excipient should be addressed as outlined in the guidance for industry, *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*. To address the reproductive and developmental toxicity potential of the excipient, the Applicant referenced the nonclinical data contained in DMF (b) (4) and submitted the study report for a preliminary embryofetal study in rats.

8.2 Embryonic Fetal Development

Study title: Dodecyl Maltoside: Pilot investigation of the tolerance by continuous intravenous (24 hours per day) infusion in the pregnant Wistar rat

Study no.:	AA99567
Study report location:	Study Report
Conducting laboratory and location:	(b) (4)
Date of study initiation:	July 18, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Dodecyl Maltoside (DDM) (1-O-n-Dodecyl-beta-D Maltopyranoside) Batch Number: P21/148/010 Purity: 99.6 %

Key Study Findings

Under the experimental conditions of the study, 24-hour continuous infusion of Dodecyl Maltoside to pregnant rats during organogenesis (Days 6 to 17 of gestation) at a dose level of 30 mg/kg/day was not associated with any maternal changes or embryo-fetal toxicity. The NOAEL (no observed adverse effect level) was considered to be 30 mg/kg/day.

Methods

Doses:	0 (Vehicle), 30 mg/kg/day
Frequency of dosing:	Daily from GD (Gestation Day) 6 to 17
Dose volume:	60 mL/kg/day
Route of administration:	IV continuous infusion (24 hours)
Formulation/Vehicle:	Vehicle: saline Test article was prepared in saline at 0.5 mg/mL.
Species/Strain:	Rats/Wistar
Number/Sex/Group:	8/female/group
Satellite groups:	None
Study design:	Only one treatment group was evaluated and not the standard three dosing groups that are generally tested. It is also noted that this study did not evaluate a maximum feasible dose.
Deviation from study protocol:	No significant deviation was noted that would impact the interpretation of data.

Observations and Results

Mortality

There was no mortality in the study.

Clinical Signs

There were no test article-related clinical signs.

Body Weight

No test article-related changes in body weight.

Food Consumption

No test article-related changes in food consumption.

Toxicokinetics

Not assessed.

Dosing Solution Analysis

Met acceptance criteria.

Necropsy

No macroscopic findings were noted for the adult females in any group.

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

All females were pregnant with viable fetuses in each group. The percentage pre- and post-implantation loss and the mean live litter size were comparable between the treated and control groups.

		Group 1 Control 0 mg/kg/day	Group 2 Treated 30 mg/kg/day
Pregnant	N	8	8
Dams with no Viable Fetuses	N	0	0
Dams with Viable Fetuses	N	8	8
Corpora Lutea	TOTAL	98	106
No. per animal	MEAN	12.3	13.3
	S.D.	1.0	2.1
Implantation Sites	TOTAL	90	96
No. per animal	MEAN	11.3	12.0
	S.D.	2.3	3.3
Preimplantation Loss	TOTAL	8	10
No. per animal	MEAN	1.0	1.3
	S.D.	2.1	2.1
% per animal	MEAN%	8.1	10.2
	S.D.	17.3	18.6
Live Fetuses	TOTAL	85	90
No. per animal	MEAN	10.6	11.3
	S.D.	2.1	3.5
Males	TOTAL	44	41
	MEAN%	51.6	49.2
	S.D.	10.4	16.7
Females	TOTAL	41	49
	MEAN%	48.4	50.8
	S.D.	10.4	16.7

		Group 1 Control 0 mg/kg/day	Group 2 Treated 30 mg/kg/day
Postimplantation Loss	TOTAL	5	6
No. per animal	MEAN	0.6	0.8
	S.D.	0.7	1.0
% implants per animal	MEAN%	5.2	7.3
	S.D.	6.2	9.1
Dead Fetuses	TOTAL	0	0
No. per animal	MEAN	0.0	0.0
	S.D.	0.0	0.0
% of implants per animal	MEAN%	0.0	0.0
	S.D.	0.0	0.0
Resorptions: Early	TOTAL	4	6
No. per animal	MEAN	0.5	0.8
	S.D.	0.5	1.0
% of implants per animal	MEAN%	4.2	7.3
	S.D.	4.5	9.1
Resorptions: Late	TOTAL	1	0
No. per animal	MEAN	0.1	0.0
	S.D.	0.4	0.0
% of implants per animal	MEAN%	1.0	0.0
	S.D.	2.9	0.0

Offspring (Malformations, Variations, etc.)

Mean fetal weight and fetal sex ratio was comparable between the treated and control groups.

SUMMARY OF CAESAREAN SECTION DATA

		Group 1 Control 0 mg/kg/day	Group 2 Treated 30 mg/kg/day
Fetal Body Weight (g)	MEAN	3.9	3.7
	S.D.	0.3	0.2
	N	8	8
Male Fetuses	MEAN	4.0	3.9
	S.D.	0.3	0.2
Female Fetuses	MEAN	3.7	3.6
	S.D.	0.3	0.3

Visceral Malformations and Variations:
No test article-related visceral malformations and variations were noted for any of the fetuses.

There was a single fetus from the control group (dam no. 4) with a malformed heart (both ventricular chambers were enlarged with thin walls). This isolated finding in the control group was spontaneous in origin. The incidences of other less severe visceral anomalies, principally including a convoluted ureter, were comparable in both groups.

Skeletal Malformations and Variations:
There was no fetus with a skeletal malformation in either group.

Occasional differences were noted in both the control and treated groups compared with the historical control data such as a higher incidence of incomplete ossification of the 2nd to 4th sternebrae in the control and of unossified caudal arches in the treated group.

- Applicant: In the absence of any consistent pattern in the changes, these minor differences were considered to reflect normal biological diversity, exacerbated by the small group sizes, rather than a drug effect, and of no toxicological significance.

Reviewer's Note: It is noted that this preliminary embryo-fetal development toxicity study evaluated only 8 pregnant females whereas in a definitive study, it is recommended that at least 16 pregnant females are included in the study design. Another deviation from a modern and standard design is that only a single treatment group was evaluated. Typically, 3 treatment groups along with a single control group are evaluated. The dose evaluated was deemed an acceptable high dose as this dose was at least 500-fold higher than in humans based on BSA, which is higher than the 25-fold exposure margin criteria outlined in ICH S5(R3) for high dose selection.

After review of the DMF and the submitted preliminary embryofetal study in rats, the fertility and early embryonic, embryofetal, and pre- and postnatal developmental endpoints have not been addressed to characterize the potential for DDM, to cause reproductive and developmental toxicity. However, given the

product is for a lifesaving indication and DDM did not show adverse effects in the preliminary GLP embryo-fetal toxicology study, the full battery of reproductive and developmental studies with the new excipient can be requested as a PMR.

9 Carcinogenicity

A carcinogenicity evaluation was not conducted and was not needed as the proposed product is for an acute use indication.

10 Special Toxicology Studies

This NDA submission seeks a marketing approval in patients who are 12 years or older. A deferral has been granted by the Agency for clinical studies assessing the pharmacokinetics and pharmacodynamics of nalmefene in patients < 12 years of age. (b) (4) [redacted] The Division disagreed (b) (4) [redacted]. Subsequently to receiving the Division's feedback on the iPSP, the Applicant proposed to conduct two JAS to address specific findings related to the API and the DDM excipient to support their pediatric studies as outlined in the agreed Pediatric Study Plan (PSP):

- Conduct a juvenile animal study in rats to support the initiation of clinical studies in pediatric patients from 3 to less than 12 years of age. This study will evaluate the effect of the drug on growth and development, specifically reproductive performance/sexual maturation, local tissues including the nasal and respiratory tract, immune capacity, and central nervous system histopathology and long-term behavioral effects.

- Conduct a juvenile animal study in rats to support the initiation of clinical studies in pediatric patients from birth to less than 3 years of age. This study will evaluate the effect of the drug on growth and development, specifically reproductive performance/sexual maturation, local tissues including the nasal and respiratory tract, immune capacity, and central nervous system histopathology and long-term behavioral effects.

11 Integrated Summary and Safety Evaluation

The regulatory pathway for the NDA submission is via 505(b)(2) with Revex as the listed drug; thus, no additional pharmacology studies were needed to support this NDA. Following the Division's recommendation in a PIND meeting, the Applicant conducted 28-day repeat-dose studies in rats and dogs to characterize the local effects and to support the systemic safety at exposure levels associated with the MRHD of 5.4 mg of nalmefene. These two studies were also designed to support the local and systemic safety of the excipient, dodecylmaltoside (DDM). Additionally, the Applicant conducted PK studies in rats and rabbits to bridge to the reproductive and developmental toxicology data described in REVEX label (Revex-2006).

Specifications for the drug substance and drug product impurity specifications are deemed acceptable. One drug substance impurity, (b) (4) was noted to exceed ICH Q3A(R2). However, (b) (4) is not a safety concern given that this impurity is controlled at an acceptable limit in the drug product. Residual solvent specifications are within the levels outlined in ICH Q3C(R8). Elemental impurities are below the control threshold of 30% as recommended in ICH Q3D. To support the safety of the container closure system, the Applicant provided an extractables and leachables evaluation. No leachable compounds were present over the 5 mcg/day qualification threshold and therefore there are no concerns with the safety of the container closure system.

General Toxicity Summary

The Applicant conducted a 28-day repeat-dose study in the rat (Study 20291737) that received daily intranasal administration with nalmefene hydrochloride at a dose of 0, 1, 3, or 8.5 mg (0, 10, 30, or 85 mg/mL) as well as a 28-day repeat-dose study in the dog (Study 20291738) that received daily intranasal dose of nalmefene hydrochloride at a dose of 0, 2, 6 or 17 mg (0, 10, 30 or 85 mg/mL). The key findings in the 28-day repeat-dose studies and corresponding exposure multiples have been summarized in the tables below.

Table 10: Nonclinical Findings of Potential Clinical Relevance

Toxicity/Finding	Studies	Reversible?	Effect Dose (mg)	Comments
Nasal cavity				
Erosion/ulcer, focal hemorrhage or exudate (minimal to slight)	28-day rat	Not examined	HD[a] (1 MD rat had minimal exudate)	Test article-related
Metaplasia (minimal)			Veh and HD	Vehicle-related
Epithelium degeneration (minimal)	28-day dog	Yes	Veh and MD[b]	Vehicle-related
Lung				
Hemorrhage (moderate)	28-day rat	Not examined	HD	Likely related to the nasal administration route
Mixed cell infiltrate, inflammation, alveolar hemorrhage or alveolar granuloma (minimal to mild)	28-day dog	Yes in general	All dose levels including veh; no dose dependency	
Testis				
Moderate to marked seminiferous tubule degeneration accompanied by cellular debris and decreased sperm in the **epididymides**	28-day rat	Yes	HD	Reviewer: Test article related and adverse

a: HD=high dose = 8.5 mg/day in the 28-day rat study
b: MD=mid dose = 6 mg/day in the 28-day dog study

Table 11: Exposure Margins Reached in the Nonclinical Studies Against Two Intranasal Human Doses

Animal						Human 2 doses		Local Exposure Margins (Concentration Comparison)
Animal Study		Dose (mg)	Sex	Exposure (ng*h/mL)		Exposure Margin*		
				$AUC_{(0\text{-}inf)}$ ng*h/mL	C_{max} ng/mL	$AUC_{(0\text{-}inf)}$ 89.5 ng*h/mL	C_{max} 22.2 ng/mL	
Rat	28-day (20291737)	1	M	41	33	0.5	1.5	0.4
			F	61.2	50.4	0.7	2.3	
		3	M NOAEL	251	524	2.8	23.6	1.2
			F	186	146	2.1	6.6	
		8.5	M	509	1250	5.7	56.3	3.3
			F NOALE	333	272	3.7	12.3	

Dog	28-day (20291737)	2	M/F	142	428	1.6	19.3	0.4
		6	M/F	494	1160	5.5	52.3	1.2
		17	M/F NOAEL	1160	2910	13.0	131.1	3.3

*Exposure margins are calculated based upon exposures in animal studies vs exposures achieved in humans at MRHD in Study Number OPNT003-PK-002.

Table 12: Exposure Margins Reached in the Nonclinical Studies Against Three and Four Intranasal Human Doses

Animal						Human 3 Doses		Human 4 Doses	
Animal Study		Dose (mg)	Sex	Exposure (ng*h/mL)		Exposure Margin*		Exposure Margin*	
				$AUC_{(0\text{-}inf)}$ ng*h/mL	Cmax ng/mL	AUC (0-inf) 123.9 ng*h/mL	Cmax 31.78 ng/mL	AUC (0-inf) 165 ng*h/mL	Cmax 37 ng/mL
Rat	28-day (20291737)	1	M	41	33	0.3	1.0	0.2	0.9
			F	61.2	50.4	0.5	1.6	0.4	1.4
		3	M NOAEL	251	524	2.0	16.5	1.5	14.2
			F	186	146	1.5	4.6	1.1	3.9
		8.5	M	509	1250	4.1	39.3	3.1	33.8
			F NOALE	333	272	2.7	8.6	2.0	7.4
Dog	28-day (20291737)	2	M/F	142	428	1.1	13.5	0.9	11.6
		6	M/F	494	1160	4.0	36.5	3.0	31.4
		17 NOAEL	M/F	1160	2910	9.4	91.6	7.0	78.6

*Exposure margins are calculated based upon exposures in animal studies vs simulated human exposures (FDA internal data).

Testes and epididymides

In the 28-day rat study, moderate to marked bilateral seminiferous tubule degeneration in testis were noted in 2 of 10 rats administered the high dose. The same animals also had secondarily, cellular debris and decreased sperm in the epididymides. These male reproductive organ findings were not observed at the end of the recovery phase. Although the Applicant deemed these findings as not test article related, this Reviewer disagree given that the incidence appears higher than that for the background findings, as stated by the Applicant; the testis and epididymides finding were bilateral and related and occurred at the high dose.

Lung

Moderate hemorrhage in the lung was observed in one high dose-treated rat. In the dog study, minimal to mild mixed cell infiltrate in the lung was observed across all groups at both terminal and recovery sacrifice; mild bronchioloalveolar inflammation (in one mid-dose dog), mild alveolar hemorrhage (in one high-dose dog) or minimal granuloma (in one vehicle-treated dog) were observed at the terminal sacrifice. The lung findings tended to be focal, limited in distribution without clear dose dependency, and several of these findings were also observed in the vehicle-treated group. Recoverability of lung findings has been demonstrated in the dog study. As stated by the Applicant, microscopic findings in the lung have been reported as spontaneous findings in vehicle-treated groups in inhalation toxicology studies or as background findings in beagle dogs. This Reviewer has observed a similar patten of findings in other intranasal toxicology studies. Based upon weight of evidence, this Reviewer agrees with the Applicant that the lung findings are likely related to the administration route. Given the low level of severity, low incidence for the majority of the findings, limited distribution of the findings in the lung and potential recoverability, and findings were observed after 28 days of repeat-dose treatment, this Reviewer does not consider the lung effects are significant safety concerns for this acute use drug product.

Nasal cavity

In nasal cavity, minimal to slight erosion/ulcer, focal hemorrhage or exudate; minimal metaplasia was observed in the rat study and minimal epithelium degeneration was observed in the dog study. Some of the local effects were also observed in the groups treated with vehicle that consisted of the drug excipients. These local effects are considered drug product related, and reversibility was demonstrated in the dog study. It is not uncommon to see these effects in animal studies with nasal administration. Furthermore, the dosing regimen in the animal studies was daily nasal administration, which is much more aggressive than the intended acute use in humans. Comparing to the clinical nalmefene hydrochloride concentration at 30 mg/mL, the nonclinical studies have tested concentrations up to 3.3 times higher. Therefore, this Reviewer concludes that the local safety of the drug product has been adequately characterized.

Taken together, the Applicant has conducted nonclinical studies to adequately characterize the local and systemic safety of nasal administration of nalmefene nasal spray. Juvenile animal studies to support evaluation of nalmefene nasal spray in a pediatric population less than 12 years of age as outlined in the agreed PSP will be issued as a postmarketing requirement. Given the lack of adequate reproductive and developmental data with the new excipient, DDM, the standard battery of reproductive and developmental toxicity studies may be issued as postmarketing requirement studies, at the discretion of the clinical review team’s benefit risk analysis and given the lack of adverse findings reported in the preliminary embryofetal study and taking into consideration that the drug product is for a life-threatening indication.

12 Appendix/Attachments

References

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