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APPLICATION NUMBER:

213978Orig1s000

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/BLA REVIEW AND EVALUATION

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PDUFA date:	10/17/2021
Product:	(b) (4) ™ (varenicline) Nasal Spray, 0.6 mg/mL
Indication:	Dry Eye Disease
Applicant:	Oyster Point Pharma
Review Division:	Division of Pharm/Tox for Rare Diseases, Pediatrics, Urologic and Reproductive Medicine/ Specialty Medicine (DPT-RPURM/SM) in support of Division of Ophthalmology
Reviewer:	Aling Dong, Ph.D., DABT
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Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

The Applicant, Oyster Point Pharma submitted NDA 213978 under the 505(b)(2) pathway for (b) (4) ™ [also known as: OC-01] (varenicline tartrate) nasal spray, 0.6 mg/mL, to treat dry eye disease, which included proposed labeling text to comply with the "Pregnancy and Lactation Labeling Rule" (PLLR).

This NDA provides original nonclinical data in support of the ocular (and nasal) safety of OC-01 and relies on the FDA's previous findings of safety and effectiveness for Chantix® (varenicline tartrate) Tablet, EQ 0.5 mg base, EQ 1 mg base, as the listed drug (LD), to support the systemic safety.

In order to bridge OC-01 to Chantix®, the Applicant has conducted a comparative bioavailability study in humans (Study #192007).

In the clinical study #192007, 22 healthy volunteers between 18-65 years of age were administered either a single 1 mg (MRHD) oral dose of Chantix® in Treatment A, or an intranasal dose of 0.12 mg OC-01 (50 µL 1.2 mg/mL OC-01 nasal spray, equivalent to 0.06 mg into each nostril) in Treatment B (7 days between Treatments A and B). Varenicline C_{max} and AUC_{inf} values were 0.34 ng/mL and 8.30 ng•h/mL following OC-01, compared to 4.63 ng/mL and 102.53 pg•h/mL following Chantix®. Thus, the systemic exposure to varenicline from OC-01 at a dose (0.12 mg; (b) (4) (b) (4),) higher than the currently proposed commercial clinical dose (0.06 mg, with the currently proposed commercial concentration 0.6 mg/mL) was less than the exposure from Chantix® at the MRHD, (note that the two OC-01 formulations are same, except for the API concentration, and both have been administered in clinical trials throughout the OC-01 development). As such, reliance on the LD Chantix® to support the systemic safety of OC-01 is scientifically justified.

1.2 Brief Discussion of Nonclinical Findings

- A chronic toxicity study was conducted in DB rabbits with OC-01 nasal spray at doses up to 8.0 mg/day BID (~8 hours apart) bilaterally with treatment duration for 6 months. The key findings include:
    - No systemic toxicity or test article-related ocular findings were reported.
    - Excessive scratching, sneezing and twitching were noted right after dosing and resolved within one (1) or two (2) minutes post dosing, with a dose-dependent increase in incidence from the first/second week of dosing through the treatment period. Microscopically, minimal focal granulomatous inflammation in nose was observed in 1 (of 4) male animal treated with the high dose (8.0 mg/day) at end of the treatment (Day 183). No clinical

findings were noted during the recovery period, nor microscopic findings at end of the recovery period (Day 211).

- As such, for OC-01, the ocular NOAEL in all animals, and intranasal NOAEL in female animals, was 8.0 mg/day, the highest dose tested. The exposure margin is ~ 67X for the intended clinical dosing regimen of OC-01, at 50 µL of 0.6 mg/mL nasal spray into each nostril, bilaterally, BID.
- The intranasal NOAEL of OC-01 in male animals was 2.0 mg/day. The exposure margin is ~ 17X for the intended clinical dosing regimen of OC-01.
- OC-01 was rapidly absorbed after intranasal instillation, with T_{max} at 5 minutes following each dose, and subsequently rapidly cleared with no clear trend of accumulation after repeated administration.
- There was a general trend for elevated systemic exposure in male rabbits over female rabbits after repeated administration. On Day 182, the highest tested dose of OC-01, 8.0 mg/day, resulted in a C_{max} of 250 ng/mL and AUC_{last} of 967 hr•ng/mL in males, and a C_{max} of 129 ng/mL and AUC_{last} of 658 hr•ng/mL in females.

- Changes in Sections 8.1, 8.2, 12.1 and 13 Applicant-proposed labeling text were made to comply with “Pregnancy and Lactation Labeling Final Rule”.

1.3 Recommendations

1.3.1 Approvability

Approval is recommended.

1.3.2 Additional Nonclinical Recommendations

None.

1.3.3 Labeling

This reviewer recommends the following editorial changes in Sections 8.1, 8.2, 12.1 and 13 according to “Pregnancy and Lactation Labeling Final Rule”.

(b) (4)

[redacted]

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this pag

(b) (4)

[redacted]

Reviewer Comments

- This reviewer edited the proposed label to be consistent with the language in the most recent label for the LD Chantix® (updated 07/12/2021).[1]

Table 1 Systemic Exposure Margins to Support Label Calculations

Clinical Exposure Margins (Based on Dose)			
Species/Type of Study	NOAEL or LOAEL (mg/kg/day)	HED (mg/kg/day)	Exposure Margins based on a MRHD of 0.12 mg/day = 0.002 mg/kg*
Rabbit EFD	LOAEL: 30	9.73	4864.86X

[1] https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f0ff4f27-5185-4881-a749-c6b7a0ca5696#data; updated July 12, 2021

Clinical Exposure Margins (Based on Dose)			
Species/Type of Study	NOAEL or LOAEL (mg/kg/day)	HED (mg/kg/day)	Exposure Margins based on a MRHD of 0.12 mg/day = 0.002 mg/kg*
Rabbit EFD	NOAEL: dose cannot be determined from LD labeling	--	cannot be calculated without a rabbit dose
Rat EFD	LOAEL: 15	2.43	1216X
Mouse Carcinogenesis	NOAEL: 20	1.62	810.81
Rat Carcinogenesis	LOAEL: 5	0.81	405.405
Rat Fertility	NOAEL: 15	2.43	1216X
Rat PPND	NOAEL: 3	0.4865	243.24X

NOAEL = no-observed-adverse-effect level
LOAEL = low-observed-adverse-effect level
MRHD = maximum recommended human dose
HED = human equivalent dose
* Assume 60 kg human adult

2 Drug Information

2.1 Drug

Generic Name
Varenicline tartrate; Varenicline

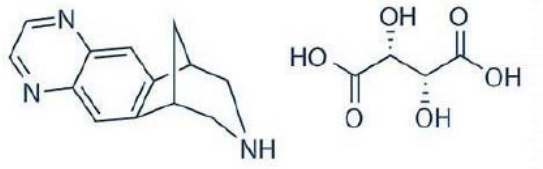
Code Name
OC-01; MED-201890/E

CAS Registry Number
375815-87-5

Chemical Name
7,8,9,10-tetrahydro-6H-6,10-methanoazepino[4,5-g]quinoxaline L-(+)-tartrate
7,8,9,10-Tetrahydro-6,10-methano-6H-pyrazino[2,3-h][3]benzazepine L-(+)-tartrate

Molecular Formula/Molecular Weight
$C_{13}H_{13}N_3 \cdot C_4H_6O_6$;
MW: 211.27 g/mol (free base); 361.35 g/mol (tartrate salt)

Structure or Biochemical Description



Pharmacologic Class
Nicotinic acetylcholine receptor (nAChR) agonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

- NDA 021928 [Chantix (varenicline tartrate) Tablet, EQ 0.5 mg base, EQ 1 mg base, by PF PRISM CV; approved 5/10/2006][2], which the Applicant plans to rely on via 505(b)(2) pathway.
- (b) (4)

2.3 Drug Formulation

- Varenicline Nasal Spray is a (b) (4) aqueous solution intended for multiple dose administration. Two concentrations of varenicline drug product were studied in the Phase 2b and Phase 3 clinical trials: 0.6 mg/mL (free base) and 1.2 mg/mL (free base).
- The proposed commercial strength is 0.6 mg/mL ((b) (4) (b) (4); the Applicant confirmed the 0.6 mg/mL as the commercial strength in SDN15 dated 6/16/2021), to be administered in a single 50 µL spray into each nostril.

[2] https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=021928

Table 2 Composition of Varenicline Nasal Spray 0.6 mg/mL (free base)

	1.0 mg mL tartrate salt which is equivalent to 0.6 mg/mL free base			Pharmaceutical Function	Quality Standards
	Quantity (mg) per Bottle	% w/v	mg/ 50 µL spray		
Active Ingredient					
Varenicline tartrate	(b) (4) mg of tartrate salt which is equivalent to (b) (4) mg of free base	(b) (4) % tartrate salt (b) (4) % free base	0.05 mg of tartrate salt is equivalent to 0.03 mg of free base	Active	Non-compendial[1] See Section 3.2.S.4.1 Specification
Inactive Ingredients					
Sodium Phosphate dibasic heptahydrate	(b) (4)			(b) (4)	USP
Monobasic sodium phosphate, anhydrous					USP
Sodium Chloride					USP
Sodium Hydroxide				pH adjuster	NF
Hydrochloric Acid				pH adjuster	NF
Water for Injection				(b) (4)	USP
Total	(b) (4)	100%			

[1] Varenicline tartrate is tested at (b) (4) for identity and assay as outlined in Section 3.2.S.2.1 Manufacturers

Table 3 Composition of Varenicline Nasal Spray 1.2 mg/mL (free base)

2.4 Comments on Novel Excipients

None.

2.5 Comments on Impurities/Degradants of Concern

- On 1/11/2021, CMC emailed P/T:

  "The drug substance is referenced in DMF (b) (4) *which is inadequate concerning* (b) (4) *impurities, it is controlled NMT* (b) (4) *ppm in the specifications below. Please let us know if the proposed level is acceptable from your perspective."*

Table 1: Specifications for Varenicline Tartrate

Test	Acceptance Criteria	Analytical Method
Description	White to off-white to slightly yellow powder	Visual
Identification -Test A (IR)	(b) (4)	USP <197K>
Identification -Test B (HPLC)		House method *
Specific Optical rotation		USP <781S>
Loss on drying		USP <731>
Residue on ignition		USP <281>
(b) (4)		House method
Assay		House method *
Residual solvents		House method
(b) (4)		House method
		House method
		(b) (4)

(*excerpted from internal email communication*)

- On 4/9/2021, CMC emailed P/T:

  "We will go with the decision by OGD/Division of Clinical Review that finds the limit of (b) (4) *ppm on the impurity* (b) (4) *to be acceptable in DMF* (b) (4) *for all referencing applications based on the ICH M7 lifetime exposure."*

Reviewer Comments

- As discussed in Section 1.1 of the current review, the current NDA adequately bridged/ justified systemic safety by relying upon the data in Chantix (NDA 021928), which included the DMF (b) (4).
- Per the DMF review by Dr. Deborah Johnson under DMF (b) (4), dated 02/03/2021:

  (b) (4) *is controlled in the DS at NMT* (b) (4) *ppm which is acceptable. We consider the DMF holder's proposed AI of NMT* (b) (4) *ng/day (NMT* (b) (4) *ppm) acceptable to monitor individual* (b) (4) *impurities… In general, for any* (b) (4) *above your proposed limit of* (b) (4) *ppm, reassess your control strategy such that the exposure to individual* (b) (4) *impurities does not exceed* (b) (4) *ng/day and that the total exposure to all* (b) (4) *impurities is kept at NMT* (b) (4) *ng/day, as described by FDA in "Control of* (b) (4) *Impurities in Human Drugs-Guidance for Industry".*

- This P/T reviewer verified that the above DMF recommendation is consistent with the current version of FDA Guidance for Industry "Control of [redacted] Impurities in Human Drugs" (published [redacted]), thus has no objections.
- As for ocular/nasal safety, the Applicant conducted a pivotal 6-Month toxicity study of OC-01 by intranasal instillation in DB Rabbits, using OC-01 nasal spray complete clinical formulation (lots # A-170268 and A-170271), and identified safe dose levels (NOAELs) for ocular/nasal safety over a 6-month period in rabbits.
- This reviewer verified that the impurity [redacted] specification in these tested lots were within the proposed limit of [redacted] ppm, per the Applicant-submitted batch analysis in Module 3.2.S.4.4 dated 5/28/2021:

Lot No.		A-170268	A-170271
Batch Size		(b) (4) kg	(b) (4) kg
Date of Manufacture		May 29, 2017	May 29, 2017
Site of Manufacture			(b) (4)
(b) (4) Drug Product Lot Number, strength (free base) and Use		181040 0.12 mg/mL Phase 2 Clinical batch	190728 0.6 mg/mL Phase 3 Clinical batch and Supportive Stability
		181044 1.2 mg/mL Phase 2 Clinical batch	200025 0.6 mg/mL Primary Stability
		181052 0.6 mg/mL Phase 2 Clinical batch	200028 1.2 mg/mL Primary Stability
		190729 1.2 mg/mL Phase 3 Clinical batch and Supportive Stability	
Test Method	**Proposed Specification**	**Result**	**Result**
			(b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

Per the proposed labeling:

- Indication: “for the treatment of signs and symptoms of dry eye disease”.
- Dosing Regimen: “Spray TRADENAME once in each nostril twice daily (approximately 12 hours apart).”

2.7 Regulatory Background

- On 12/17/2020, Oyster Point Pharma submitted the current NDA #213978 under the 505(b)(2) pathway, for OC-01 (varenicline tartrate) nasal spray, (b) (4), with proposed proprietary name of (b) (4) ™ to treat dry eye disease.
- On 3/10/2021, the Agency considered the proprietary name of (b) (4) ™ acceptable.
- On 6/16/2021, the Applicant confirmed (b) (4) ™ (varenicline tartrate) nasal spray, 0.6 mg/mL to be the proposed commercial product.
- (b) (4) ™ (varenicline tartrate) nasal spray, 0.6 mg/mL (b) (4), also called OC-01, have both been submitted (and reviewed) under IND #138645.

3 Studies Submitted

Study type/Species	Description	Study Number	Location (Module)
Primary pharmacodynamics			
Human nAChRs in Xenopus oocytes	Agonist and antagonist activity of OC-01 in nAChRs	200717	4.2.1.1
Intranasal Toxicology			
New Zealand White rabbits	7-day repeat-dose toxicity	14-03485-N1	4.2.3.2
Intranasal Toxicology and Toxicokinetics			
Sprague Dawley rats	7-day repeat-dose toxicity	TOX-OC-01-001 [a]	4.2.3.2
Dutch Belted rabbits	7-day repeat-dose toxicity	TOX-OC-01-002 [a]	4.2.3.2
Sprague Dawley rats	28-day repeat-dose toxicity	TOX-OC-01-003 [a]	4.2.3.2
Dutch Belted rabbits	28-day repeat-dose toxicity	TOX-OC-01-004 [a]	4.2.3.2
Dutch Belted rabbits	6-month repeat-dose toxicity	TOX-OC-01-005 [a]	4.2.3.2

nAChR=nicotinic acetylcholine receptor
[a] Toxicokinetic samples were also collected in this study.

3.1 Studies Reviewed

All Applicant-submitted studies have been reviewed.
In addition to the 6-month toxicity study which is being reviewed in the current review, all other nonclinical studies have been reviewed by this reviewer under IND #138645.

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

Nonclinical review by Dr. Aling Dong, dated 2/21/2019, under IND #138645.
Nonclinical review by Dr. Aling Dong, dated 6/18/2018, under IND #138645.

4 Pharmacology

4.1 Primary Pharmacology

Per label of Chantix:[3]

> *Varenicline binds with high affinity and selectivity at α4β2 neuronal nicotinic acetylcholine receptors… Electrophysiology studies in vitro and neurochemical studies in vivo have shown that varenicline binds to α4β2 neuronal nicotinic acetylcholine receptors and stimulates receptor-mediated activity, but at a significantly lower level than nicotine. Varenicline blocks the ability of nicotine to activate α4β2 receptors and thus to stimulate the central nervous mesolimbic dopamine system, believed to be the neuronal mechanism underlying reinforcement and reward experienced upon smoking. Varenicline is highly selective and binds more potently to α4β2 receptors than to other common nicotinic receptors (>500-fold α3β4, >3,500-fold α7, >20,000-fold α1βγδ), or to non-nicotinic receptors and transporters (>2,000-fold). Varenicline also binds with moderate affinity (Ki = 350 nM) to the 5-HT3 receptor.*

Drug activity related to proposed indication

- Dry eye disease is a multifactorial, age-related disorder of the ocular surface resulting in severe pain, visual impairment, tear film hyperosmolarity and instability, inflammation, and corneal wounding.
- The trigeminal-parasympathetic pathway is a well-established pathway by which nasal stimuli promote both resting basal and bolus tear secretion.
- Thus, stimulation of the trigeminal-parasympathetic pathway by OC-01 / varenicline may have therapeutic benefit in the treatment of diseases such as DED by activating nAChRs and increasing tear film production.

[3] https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=569f99b3-a52c-426a-b4f4-8d2399c4745e; Updated July 12, 2021

6 General Toxicology

6.2 Repeat-Dose Toxicity

Study title: A GLP 6-Month Toxicity Study of OC-01 by Intranasal Instillation in Dutch-Belted Rabbits with a 1-Month Recovery Period

Study no.:	TOX-OC-01-005
Study report location:	EDR Module 4.2.3.2
Conducting laboratory and location:	(b) (4) (b) (4) (b) (4) .
Date of study initiation:	January 21, 2019
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Varenicline Tartrate (Also known as OC-01), batch # A-170268, 98.6% pure (per Analysis Certificate on page 257 of the Study Report); batch # A-170271, 99.2% pure (per Analysis Certificate on page 259 of the Study Report)

Key Study Findings

- Intranasal instillation of OC-01 nasal spray at doses up to 8.0 mg/day to DB rabbits BID (~8 hours apart) bilaterally for 6 months was generally well-tolerated, with no systemic toxicity or test article-related ocular findings.
- Excessive scratching, sneezing and twitching were noted right after dosing and resolved within one (1) or two (2) minutes post dose, with dose-dependent increase in incidence from the first/second week of dosing through the treatment period. Microscopically, minimal focal granulomatous inflammation in nose was observed in 1 (of 4) male animal treated with high dose (8.0 mg/day) at end of the treatment (Day 183). No clinical findings were noted in recovery period, nor microscopic findings at end of the recovery period (Day 211).
- As such, for OC-01, the systemic and ocular NOAEL in all animals, and intranasal NOAEL in female animals was 8.0 mg/day, the highest dose tested. The NOAEL of OC-01 for intranasal safety in male animals was 2.0 mg/day.
- OC-01 was rapidly absorbed after intranasal instillation, with T_{max} at 5 minutes after each dose, and subsequently rapidly cleared with no clear trend of accumulation after repeated administration.
- There was a general trend for elevated systemic exposure in male rabbits over female rabbits after repeated administration. On Day 182, the highest tested dose of OC-01, 8.0 mg/day, resulted in a C_{max} of 250 ng/mL and AUC_{last} of 967 hr•ng/mL in males, and a C_{max} of 129 ng/mL and AUC_{last} of 658 hr•ng/mL in females.

Methods

Doses:	0 (vehicle), 0.4, 2.0 and 8.0 mg/day (0, 1, 5, 20 mg/mL OC-01)
Frequency of dosing:	Twice/day by intranasal instillation of both nostrils (~8 hours apart)
Route of administration:	Nasal
Dose volume:	100 µL/nostril/dose
Formulation/Vehicle:	OC-01 vehicle
Species/Strain:	Rabbit/ Dutch-Belted
Number/Sex/Group:	4 groups: 3 treated and 1 vehicle control: Vehicle group: 6 /sex/group; Low dose group: 4 /sex/group; Mid dose group: 4 /sex/group; High dose group: 6 /sex/group. See Table below for details.
Age:	6 months
Weight:	1.67 – 2.35 kg
Satellite groups:	Main:4 /sex/ satellite group; Recovery (Vehicle and highest dose groups): 2 /sex/ satellite group.
Unique study design:	See below Table 4 for details
Deviation from study protocol:	None considered to have an impact in the integrity of the data

Table 4 Study Design of 6-Month Toxicity Study of OC-01 by Intranasal Instillation in Rabbits with a 1-Month Recovery Period

Group No.	Treatment	Dose Level[a] (mg/day)	Dose Concentration (mg/mL)	Dose Volume (µL/nare /dose)	Animal No.			
					Main Study		Recovery	
					Male	Female	Male	Female
1	Vehicle	0	0	100	1001-1004	1501, 1504, 1505, 1602	1005, 1006	1503, 1506
2	OC-01	0.4	1	100	2001-2004	2501-2504	-	-
3	OC-01	2.0	5	100	3001-3004	3501-3504	-	-
4	OC-01	8.0	20	100	4001-4004	4501-4504	4005, 4006	4505, 4506

[a] The total daily dose was divided into 2 doses per day (administered 8 hours ±15 minutes on Days 1 and 182 and 8 hours ±30 minutes on all other days, based on the first animal dosed on each day) and each dose was split equally between the left and right naris.

Observations and Results

Mortality (Twice daily)

All animals survived to their scheduled necropsy.

Clinical Signs (Twice daily, detailed observations weekly)

Excessive scratching, sneezing and twitching were noted right after the dose and resolved within one or two minutes post dose, starting from the first or second week of dosing, with dose-dependent increase in incidence. The findings were not reported during the recovery period.

Table 5: Summary of Clinical Observations in 6-Month Toxicity Study of OC-01 by Intranasal Instillation in Rabbits with a 1-Month Recovery Period

mg/day	0	0.4	2.0	8.0
Excessive Scratching				
Males	0/0	102/4	68/4	352/6
Females	0/0	403/4	519/4	1032/6
Sneezing				
Males	14/5	325/4	483/4	824/6
Females	16/6	221/4	438/4	604/6
Twitching				
Males	0/0	728/4	658/4	1515/6
Females	1/1	516/4	892/4	1346/6
Number of times observed / Total number of animals affected				

Body Weights (Prestudy and weekly during study)

No test article-related effects.

Feed Consumption (Weekly)

No test article-related effects.

Ophthalmoscopy (Slit lamp biomicroscopy and indirect ophthalmoscopy; prestudy, once during Week 13, prior to the scheduled terminal and recovery necropsies)

No test article-related effects.

Intraocular Pressures (IOP; pretest, once during Week 13, and prior to the scheduled terminal necropsy)

No test article-related effects.

Electroretinography (ERG) (Scotopic and photopic; once prestudy, Week 4 of Treatment and End of Recovery period)

No test article-related effects.

Hematology (Pretest, once during Week 13, and prior to the scheduled terminal necropsy)

On Day 183, all females (animals # 4501- # 4506) at high dose (8.0 mg/day) had a minimal increase (~1.51x) in mean neutrophil count comparing with the vehicle control females. However, no microscopic correlates were observed.

Coagulation (Pretest, once during Week 13, and prior to the scheduled terminal necropsy)

No test article-related effects.

Clinical Chemistry (Pretest, once during Week 13, and prior to the scheduled terminal necropsy)

No test article-related effects.

Gross Pathology (Scheduled terminal and recovery necropsies: Days 183 and 211, respectively)

No test article-related macroscopic findings were observed.

Organ Weights

No test article-related alterations in organ weight parameters.

Histopathology

Adequate Battery – Yes.

Peer Review - No

Histological Findings
At end of the Main Study (Day 183), minimal focal granulomatous inflammation in nose was observed in 1 (of 4) male treated with high dose (8.0 mg/day). At the end of the recovery period (Day 211), no microscopic findings were reported.

Special Evaluation

Irritation in the Nasal Cavities (Pretest, Week 2, prior to the scheduled terminal and recovery necropsies; Draize scale for scoring skin irritation)
No changes in nasal cavity irritation assessment parameters.

Schirmer Tear Testing (Pretest, once during Week 13, and prior to the scheduled terminal necropsy)
No test article-related changes in Schirmer tear test parameters.

Toxicokinetics

- Blood samples for TK analysis were collected at predose, 0.083, 4, 7.75, 8.083, 12, 15.75 and 24 hrs post dose on Days 1 and 182 (n=6 /sex/group for vehicle and high dose groups; n=4 /sex/group for low dose and mid dose groups).
- OC-01 was rapidly absorbed after intranasal instillation, with T_{max} at 5 minutes after each dose, and subsequently rapidly cleared within the dose range evaluated with no clear trend of accumulation after 6-month repeated administration.
- There was a general trend for elevated systemic exposure in male rabbits over female rabbits after repeated administration and a trend for greater than dose proportional increases in exposure.
- On Day 182, the highest tested dose of OC-01, 8.0 mg/day, resulted in a C_{max} of 250 ng/mL and AUC_{last} of 967 hr•ng/mL in males, and a C_{max} of 129 ng/mL and AUC_{last} of 658 hr•ng/mL, in females.

Table 6 OC-01 Plasma Toxicokinetic Profiles in Male and Female DB Rabbits

Daily Dose*	Male		Female	
	AUC_{last} (h*ng/mL)	Cmax (ng/mL)	AUC_{last} (h*ng/mL)	Cmax (ng/mL)
Day 1 Toxicokinetics [mean ± standard deviation]				
0.4 mg/day	13.3±9.31	12.7±10.7	34.9±2.34	27.3±21.3
2.0 mg/day	292±241	81.5±52.2	680±970	294±426
8.0 mg/day	1110±876	312±283	601±269	122±46.5
Day 182 Toxicokinetics [mean ± standard deviation]				
0.4 mg/day	16.2±10.7	14.3±11.1	23.4±8.45	11.1±4.24
2.0 mg/day	208±170	67.2±63.6	144±55.6	46.4±11.1
8.0 mg/day	967±543	250±219	658±206	129±22.4

*Animals received a total of 2 applications/day (8 hours ± 30 minutes apart between each dose)

Dosing Solution Analysis –

Per the study report, the dosing formulations "were prepared weekly, and were stored refrigerated at 2°C to 8°C in amber glass bottles". And "all study samples analyzed had mean concentrations within the acceptance criteria of ± 10% (individual values within ± 15%) of their theoretical concentrations".

Per the Method Validation Report (Study # 2100763), stability of dose formulation samples (0.500 mg/mL – 30.0 mg/mL) was confirmed at "ambient room temperature for 1 day and in a refrigerator set to maintain 4°C for up to 10 days". Thus, this reviewer considers that its stability data supported the conditions of study use.

7 Genetic Toxicology

Genotoxicity studies have not been conducted with OC-01.
The Applicant is relying upon Chantix® (varenicline) tablets (NDA 021928) "prescribing information" for support regarding genotoxicity. Per the label of Chantix®:[4]

> *Varenicline was not genotoxic, with or without metabolic activation in the following assays: Ames bacterial mutation assay; mammalian CHO/HGPRT assay; and tests for cytogenetic aberrations in vivo in rat bone marrow and in vitro in human lymphocytes.*

8 Carcinogenicity

Carcinogenicity studies have not been conducted with OC-01.
The Applicant is relying upon Chantix® (varenicline) tablets (NDA 021928) prescribing information for support regarding carcinogenicity. Per the label of Chantix®:[5]

> *Lifetime carcinogenicity studies were performed in CD-1 mice and Sprague-Dawley rats. There was no evidence of a carcinogenic effect in mice administered varenicline by oral gavage for 2 years at doses up to 20 mg/kg/day (47 times the maximum recommended human daily exposure based on AUC). Rats were administered varenicline (1, 5, and 15 mg/kg/day) by oral gavage for 2 years. In male rats (n = 65 per sex per dose group), incidences of hibernoma (tumor of the brown fat) were increased at the mid dose (1 tumor, 5 mg/kg/day, 23 times the maximum recommended human daily exposure based on AUC) and maximum dose (2 tumors, 15 mg/kg/day, 67 times the maximum recommended human daily exposure based on AUC). The clinical relevance of this finding to humans has not been established. There was no evidence of carcinogenicity in female rats.*

9 Reproductive and Developmental Toxicology

No reproductive and developmental toxicity studies have been conducted with OC-01.
The Applicant is relying upon Chantix® (varenicline) tablets (NDA 021928) prescribing information for support regarding Reproductive and Developmental Toxicology.
Per the label of Chantix®:[6]

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[4] https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f0ff4f27-5185-4881-a749-c6b7a0ca5696#data; updated July 12, 2021
[5] https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f0ff4f27-5185-4881-a749-c6b7a0ca5696#data; updated July 12, 2021
[6] https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f0ff4f27-5185-4881-a749-c6b7a0ca5696#data; updated July 12, 2021

Pregnant rats and rabbits received varenicline succinate during organogenesis at oral doses up to 15 and 30 mg/kg/day, respectively. While no fetal structural abnormalities occurred in either species, maternal toxicity, characterized by reduced body weight gain, and reduced fetal weights occurred in rabbits at the highest dose (exposures 50 times the human exposure at the MRHD of 1 mg twice daily based on AUC). Fetal weight reduction did not occur in rabbits at exposures 23 times the human exposure at the MRHD based on AUC.

In a pre- and postnatal development study, pregnant rats received up to 15 mg/kg/day of oral varenicline succinate from organogenesis through lactation. Maternal toxicity, characterized by a decrease in body weight gain was observed at 15 mg/kg/day (36 times the human exposure at the MRHD based on AUC). However, decreased fertility and increased auditory startle response occurred in offspring at the highest maternal dose of 15 mg/kg/day.

There was no evidence of impairment of fertility in either male or female Sprague-Dawley rats administered varenicline succinate up to 15 mg/kg/day (67 and 36 times, respectively, the MRHD exposure based on AUC at 1 mg twice daily). Maternal toxicity, characterized by a decrease in body weight gain, was observed at 15 mg/kg/day. However, a decrease in fertility was noted in the offspring of pregnant rats who were administered varenicline succinate at an oral dose of 15 mg/kg/day. This decrease in fertility in the offspring of treated female rats was not evident at an oral dose of 3 mg/kg/day (9 times the MRHD exposure based on AUC at 1 mg twice daily).

11 Integrated Summary and Safety Evaluation

This NDA was submitted under the 505(b)(2) pathway. The listed drug (LD) is Chantix® (varenicline tartrate) Tablet, EQ 0.5 mg base, EQ 1 mg base (NDA #021928).

The Applicant has fulfilled the nonclinical regulatory requirements with original nonclinical studies, including two (2) pivotal 28-day toxicity studies in rats and rabbits and one (1) 6-month rabbit study which all used the complete clinical formulation of OC-01 nasal spray and included ocular (and nasal) toxicity evaluation, and by relied on previous findings of safety and efficacy of the LD for systemic safety, including genotoxicity, carcinogenicity, reproductive and developmental toxicity findings.

Exposure margins comparing NOAELs of 6-month pivotal nonclinical study and the maximum proposed clinical dose provide chronic safety support for intended clinical dosing regimen.

Table 7: Exposure Margins for Nasal Toxicities – Intranasal Instillation

Species	Toxicities	NOAEL / Total nasal dose (mg/day)	Margins of Exposure based on total dose (total animal dose divided by clinical dose)
			0.12 mg/day
Rabbit	None (female)	8.0	~ 66.67X
Rabbit	Minimal focal granulomatous inflammation in nose (male)	2.0	~ 16.67X

Systemic Safety

Table 8: Exposure Margins for Systemic Toxicities – Intranasal Instillation

Species	NOAEL (mg/day)	NOAEL (mg/m^2/day)	HED (mg/day)	Margins of Exposure based on total dose (HED divided by clinical dose)
				0.12 mg/ day
Rabbit	8.0	53#	86.49#	721X

#Assuming rabbit average weight = 1.8 kg, and a 60 kg human adult.

Minor format and language changes to adhere to PLLR guidance and provide consistency of language across paragraphs in Sections 8.1, 8.2, 12.1 and 13 were made to enhance readability of labeling.

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/s/

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