CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213978Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number	213978
Link to EDR	View submission in docuBridge
Submission Date	12/17/2021
Submission Type	NDA 505(b)(2); Standard
Brand Name	(b) (4)
Generic Name	Varenicline tartrate
Dosage Form and Regimen	Nasal spray, 0.05 mL per spray delivering 0.03 mg varenicline free base (0.6 mg/mL) administered as one spray in each nostril twice daily (approximately 12 hours apart)
Route of Administration	Intranasal
Proposed Indication	For the treatment of signs and symptoms of dry eye disease
Applicant	Oyster Point Pharma, Inc.
Associated IND	IND 138645
OCP Review Team	Amer Al-Khouja, Ph.D. M.H.S. Suneet Shukla, Ph.D.
OCP Final Signatory	Suresh Doddapaneni, Ph.D., Director (Acting), Division of Inflammation and Immune Pharmacology, Office of Clinical Pharmacology

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1 EXECUTIVE SUMMARY

Varenicline is a small molecule partial nicotinic agonist selective for the α4β2 nicotinic acetylcholine receptor. Varenicline tartrate oral tablets were initially approved in May 2006 as CHANTIX® for use in adults as an aid to smoking cessation treatment. The approved dosing regimen involves treatment for 12 weeks. In the first week, the dose is titrated up to reach a regimen of 1 mg twice daily, which is maintained for the remainder of the 12-week period. For patients with severe renal impairment (estimated creatinine clearance [CrCL] < 30 mL/min) and those with end-stage renal disease (ESRD) undergoing hemodialysis, the maximum dosing regimens are 0.5 mg twice daily and 0.5 mg once daily, respectively.

The Applicant, Oyster Point Pharma, Inc., has submitted a 505(b)(2) NDA to support the approval of a varenicline tartrate nasal spray (proposed trade name: (b) (4)) for the treatment of signs and symptoms of dry eye disease in adults. The proposed listed drug is CHANTIX® oral tablets. The activity of varenicline in dry eye disease is thought to be due to stimulation of the trigeminal parasympathetic pathway, which innervates the lacrimal functional unit, leading to increased tear film production.

For the nasal spray product, the Applicant initially proposed (b) (4) (b) (4) (b) (4) the proposed commercial strength and regimen have been updated to 0.6 mg/mL, given as one spray in each nostril BID. Each actuation of the 0.6 mg/mL spray delivers 0.05 mL containing 0.03 mg varenicline free base.

The clinical pharmacology submission includes one study, Study OPP-100 (ZEN), a phase 1, open-label, single-center, single-dose, randomized, two-way crossover study in healthy volunteers comparing the relative bioavailability of 0.12 mg intranasal varenicline (0.06 mg per nostril) using the 1.2 mg/mL strength, and 1 mg oral varenicline (CHANTIX® oral tablets) in the fasted state. Results from this study demonstrated that there is lower varenicline exposure following administration of 0.12 mg intranasal varenicline relative to 1 mg oral varenicline.

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Immune and Inflammation Pharmacology (OCP/DIIP) has reviewed the clinical pharmacology data submitted in support of NDA 213978 for the proposed varenicline nasal spray, 0.6 mg/mL and found the application acceptable to support approval from a clinical pharmacology perspective.

1.2 Post Marketing Requirement

None

2 SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

The clinical pharmacology assessment included a review of the relative bioavailability data from Study OPP-100, comparing the systemic exposure of 0.12 mg intranasal varenicline (0.06 mg per nostril) relative to 1 mg oral varenicline (CHANTIX®, varenicline oral tablets) in the fasted state. The results indicated that varenicline systemic exposure (AUC and Cmax) after dosing with the proposed intranasal dose was lower than the approved dose of orally administered listed drug, Chantix. Based on data from OPP-100, a PK bridge has been established between the proposed intranasal spray product and the listed drug (CHANTIX® oral tablets).

2.1 Pharmacology and Clinical Pharmacokinetics

In relative bioavailability Study OPP-100, the Applicant compared varenicline systemic exposure in healthy volunteers following administration of a single 0.12 mg bilateral intranasal dose of the proposed nasal spray product and a single 1 mg dose of the approved CHANTIX® oral tablets. After intranasal treatment, the median time to maximum concentration (T_{max}) of 2.00 hours was shorter than that following oral treatment, 3.00 hours. The mean [SD] elimination half-life ($t_{1/2}$) values following intranasal treatment was 18.9 [9.9] hours, which was similar to that following oral treatment, 19.6 [10.4] hours. The Applicant's assessment of relative bioavailability was based on a calculation of the geometric mean ratios (GMRs) and associated 90% confidence intervals (CIs) for human plasma C_{max}, AUC_{0-t}, and AUC_{0-inf}. The PK data shown in Table 1 indicate that varenicline exposure after intranasal dosing of 0.12 mg is 3.6-7.5% of that achieved after oral dosing of 1 mg.

Table 1. Geometric mean ratios (Nasal/Oral) [90% CIs] for plasma PK parameters of varenicline in Study OPP-100 .

PK Parameter	Geometric Mean Ratio (Nasal/Oral) [90% CI]
AUC_{0-t}	0.036 [0.026, 0.051]
AUC_{0-inf}	0.075 [0.060, 0.094]
C_{max}	0.070 [0.060, 0.082]

AUC_{0-t} = the observed area under the concentration-time curve from time zero to the time of last measureable concentration; AUC_{0-inf} = the extrapolated area under the concentration-time curve from time zero to time infinity; C_{max} = maximum concentration

Source: Data adapted from Table 11.4.2.3.2, page 55, Clinical Study Report for Study OPP-100, Module 5.3.1.2, NDA 213978 SDN 1, submitted Dec. 17, 2020

The data from OPP-100 indicate that varenicline exposure is lower after intranasal dosing relative to oral dosing. A PK bridge has been established between the proposed intranasal spray product and the listed drug, CHANTIX® varenicline oral tablets. This study was conducted using the 1.2 mg/mL nasal spray, a strength that is double that of the proposed 0.6 mg/mL commercial product. Thus, these results are still applicable and adequate from a clinical pharmacology perspective.

2.1.1 Dosing and Therapeutic Individualization

2.1.2 General Dosing

The recommended dose is 0.6 mg/mL administered as one spray per nostril BID to treat the signs and symptoms of dry eye disease in all patients. The clinical efficacy and safety of this dosing regimen was assessed in three studies: OPP-004 (phase 2), OPP-002 (phase 2b), and OPP-101 (phase 3) in adult patients with dry eye disease.

2.1.3 Therapeutic Individualization

The Applicant has not proposed any therapeutic individualization. The available clinical pharmacology information does not warrant a need for therapeutic individualization.

2.1.4 Outstanding Issues

None

2.1.5 Summary of Labeling Recommendations

The labeling review is ongoing at the time of this review.

3 COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

The proposed product is a varenicline tartrate nasal spray, 0.6 mg/mL (proposed trade name: (b) (4) for the treatment of the signs and symptoms of dry eye disease. Varenicline is a small molecule partial nicotinic agonist selective for the α4β2 nicotinic acetylcholine receptor. The activity of varenicline in dry eye disease is thought to be due to stimulation of the trigeminal parasympathetic pathway, which innervates the lacrimal functional unit, leading to increased tear film production.

The proposed product was evaluated under IND 138645. A summary of key clinical pharmacology-related discussions and correspondence with the Applicant are listed in Table 2 below.

Table 2. Summary of key clinical pharmacology-related communication with the Applicant

IND 138645, EOP2 (March 2019)	▪ The Agency agreed that no additional nonclinical studies would be needed beyond two 7-day and two 28-day intranasal toxicity studies in rats and rabbits, provided that an adequate bridge (e.g., via comparative PK data) can be established between the proposed product and the listed drug. ▪ Reliance upon the listed drug would be scientifically justified if exposure following intranasal administration of the to-be-marketed formulation is less than or equal to that of the listed drug at the approved dose and route of administration.

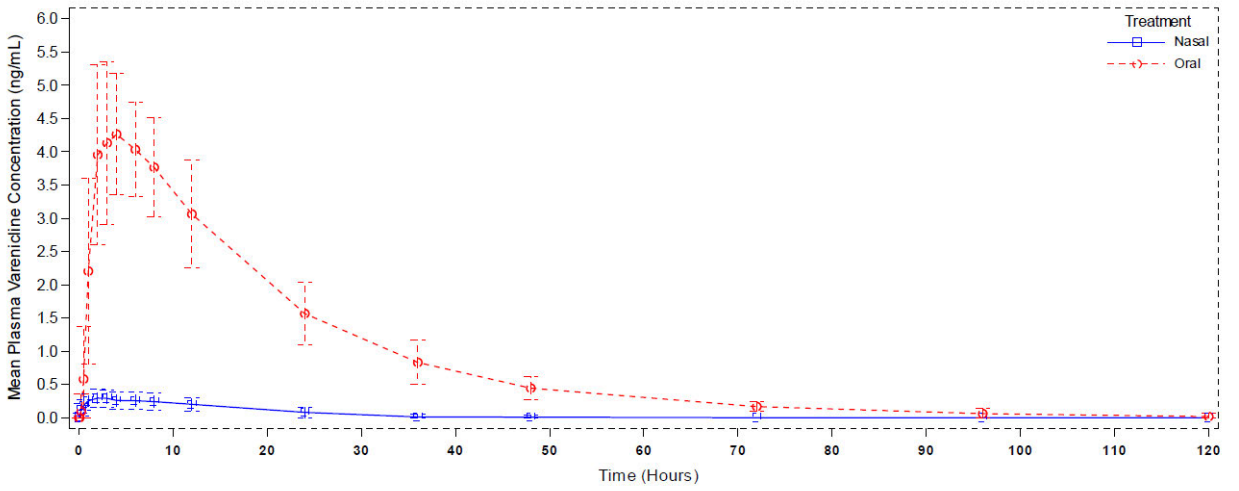
Source: Reviewer's summary based on meeting minutes located in DARRTS for IND 138645

3.2 General Pharmacology and Pharmacokinetic Characteristics

The Applicant conducted a two-way crossover relative bioavailability study in the fasted state comparing the systemic exposure of varenicline following a single dose of the 1.2 mg/mL nasal spray, defined as one spray in each nostril (0.06 mg per nostril, total dose of 0.12 mg), and the 1 mg oral tablets (CHANTIX®). The study enrolled 22 healthy volunteers who were randomized 1:1 to receive one of two treatment sequences (Oral-Nasal or Nasal-Oral). All participants who completed the study (n = 21) received both treatments.

PK analysis was conducted in 16/22 (72.7%) participants who completed both treatment periods and had sufficient data for calculation of PK parameters including $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max}. The mean concentration vs. time curves comparing nasal to oral treatment are shown in the linear scale in Figure 1. Calculated PK parameters are shown in Table 3.

Figure 1. Mean (±SD) varenicline concentration-time profiles in the linear scale following a single intranasal dose of 0.12 mg or a single oral dose of 1 mg.



Plasma concentration values below the LLOQ (0.1) are presented as '0' (zero) in the arithmetic mean calculations.
Treatment A: Single oral dose of 1 mg varenicline (Chantix®) administered orally;
Treatment B: Intranasal dose of 0.12 mg OC-01 (varenicline)- delivered as a 50 µL (0.06 mg) spray into each nostril.
Source: Figure 14.2.1.1 Source code: ...\OPP-100\Tables\Production\282_f_pc.sas (22NOV2019 9:43)

Source: Figure 11.4.2.3.1, page 51, Clinical Study Report for Study OPP-100, Module 5.3.1.2, NDA 213978 SDN 1, submitted Dec. 17, 2020)

Table 3. Summary of varenicline PK parameters following intranasal vs. oral dosing from Study OPP-100.

	Treatment B (Nasal)				Treatment A (Oral)			
Parameter (Unit)	**N**	**Mean**	**SD**	**CV%**	**N**	**Mean**	**SD**	**CV%**
AUC_{0-t} (h*ng/mL)	16	4.49	3.42	76.2	16	98.74	25.49	25.8
AUC_{0-inf} (h*ng/mL)	16	8.30	4.09	49.3	16	102.53	26.82	26.2
C_{max} (ng/mL)	16	0.34	0.13	37.6	16	4.63	0.93	20.2
$T_{1/2\ el}$ (h)	16	18.93	9.899	52.3	16	19.59	10.385	53.0
K_{el} (/h)	16	0.044	0.015	35.4	16	0.042	0.015	35.4
Parameter (Unit)	**N**	**Median**	**Min**	**Max**	**N**	**Median**	**Min**	**Max**
T_{max} (h)	16	2.00	0.3	3.0	16	3.00	1.0	6.0

N: Number of observations; SD: Standard Deviation; CV: Coefficient of variation; Min: Minimum; Max: Maximum.
Treatment A: Single oral dose of 1 mg varenicline (Chantix®) administered orally;
Treatment B: Intranasal dose of 0.12 mg OC-01 (varenicline)- delivered as a 50 µL (0.06 mg) spray into each nostril.
Data source: Table 14.2.2.1 and Listing 16.2.6.2

Source: Table 11.4.2.3.1, page 54, Clinical Study Report for Study OPP-100, Module 5.3.1.2, NDA 213978 SDN 1, submitted Dec. 17, 2020

The data in Figure 1 and Table 3 show reduced varenicline exposure following intranasal administration with the proposed nasal spray product relative to dosing with the approved oral tablets. After intranasal dosing, the median T_{max} was shorter than that for oral dosing, with calculated values of 2.00 and 3.00 hours, respectively. The mean [SD] elimination half-life, $t_{1/2}$, was consistent across treatments with values of 18.9 [9.9] hours and 19.6 [10.4] hours

determined after intranasal and oral dosing, respectively. The percent coefficient of variation (CV%) values for mean exposure parameters, including $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max}, were greater following intranasal relative to oral dosing, indicating greater intersubject variability after intranasal administration. In addition, the percent extrapolation required for the calculation of $AUC_{0\text{-}inf}$ was much greater for intranasal vs. oral treatment, as evidenced by a comparison of mean values for $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$. Therefore, with respect to intranasal dosing, $AUC_{0\text{-}inf}$ should be interpreted with caution.

Single-dose PK parameters determined for the listed drug in Study OPP-100 were consistent with the current approved labeling as well as previously determined PK parameters in studies conducted by the listed drug Sponsor. Per the approved labeling for CHANTIX® oral tablets, maximum plasma concentrations of varenicline were observed within 3-4 hours after administration and the elimination half-life was approximately 24 hours. In adult smokers aged 18-55 years receiving a single 1 mg dose of varenicline oral tablets (n = 51), the mean [SD] $AUC_{0\text{-}inf}$, C_{max}, and $t_{1/2}$ were 107 [21] ng·h/mL, 4.32 [0.78] ng/mL, and 19.2 [3.4] hours, respectively (Faessel HM, Obach RS, Rollema H, Ravva P, Williams KW, Burstein AH. *Clin Pharmacokinet.* 2010;49(12):799-816). These values are corroborated by those reported in the original clinical pharmacology review for CHANTIX® oral tablets (review by Dr. Srikanth Nallani, page 9, DARRTS date: Apr. 7, 2006).

Relative bioavailability was determined based on a calculation of the GMRs and associated 90% CIs for $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max}. The GMRs [90% CIs] comparing 0.12 mg intranasal varenicline vs. 1 mg oral varenicline for $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} were 0.036 [0.026, 0.051], 0.075 [0.060, 0.094], and 0.070 [0.060, 0.082], respectively. These data indicate that systemic exposure following administration of 0.12 mg intranasal varenicline is approximately 3.6-7.5% that observed after administration of 1 mg oral varenicline.

Results from Study OPP-100 also support the safety of the proposed nasal spray product relative to the approved listed drug oral tablets. Treatment-emergent adverse events (TEAEs) were observed in 13/21 (61.9%) participants after intranasal administration, and 9/22 (40.9%) participants after oral administration. The most commonly reported AEs after oral dosing were nausea (5/22, 22.7%), vomiting (4/22, 18.2%), and dizziness (5/22, 22.7%), all of which have previously been reported per the CHANTIX® approved labeling. The most commonly reported AEs after intranasal dosing were sneezing (7/21, 33.3%) and cough (6/21, 28.6%). Aside from one instance of vomiting that was deemed moderate in severity, all TEAEs were graded as mild in severity.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The only clinical pharmacology study submitted by the Applicant is Study OPP-100, a relative bioavailability study comparing 0.12 mg intranasal varenicline vs. 1 mg oral varenicline in healthy volunteers. Because the study was conducted in healthy volunteers, efficacy was not

assessed. The clinical pharmacology program therefore does not provide supportive evidence of effectiveness.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed strength and dosing regimen is a 0.6 mg/mL nasal spray, given as one spray in each nostril BID. Each actuation of the nasal spray delivers 0.05 mL containing 0.03 mg varenicline free base. In the Applicant's pivotal clinical studies, all doses were evaluated using only BID dosing regimens. (b) (4) (b) (4) In Study OPP-002 (ONSET-1) and Study OPP-101 (ONSET-2), improvement was shown among subjects receiving 0.6 mg/mL BID relative to those receiving placebo in the primary endpoints of change in Schirmer's Test Score from baseline to Day 28 and percent of subjects achieving ≥ 10 mm improvement in the study eye on Schirmer's Test Score from baseline to Day 28, respectively.

It should be noted that the Applicant initially recommended the (b) (4) (b) (4) (b) (4) the Applicant has updated the proposed commercial strength to 0.6 mg/mL. For additional details on the efficacy and safety of the proposed dosing regimen, refer to the clinical review by Dr. Jennifer Harris. From a clinical pharmacology perspective, the proposed dosing regimen appears appropriate to treat the signs and symptoms of dry eye disease in the general patient population.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

The varenicline nasal spray product is intended for use in adult patients and no alternative dosing regimens have been proposed for subpopulations based on intrinsic patient factors. The Applicant has not conducted any studies in subpopulations with variable intrinsic patient factors.

The current approved labeling for CHANTIX® indicates that there are no clinically meaningful differences in varenicline PK due to age, race, or gender. Varenicline PK is also expected to be unaffected in patients with hepatic impairment since varenicline undergoes minimal metabolism. However, dose adjustments are recommended in patients with severe renal impairment (CrCL < 30 mL/min) and those with ESRD undergoing hemodialysis, with reductions in the maximum dosing regimens from 1 mg twice daily to 0.5 mg twice daily and 0.5 mg once daily, respectively. Varenicline PK was unchanged in subjects with mild renal impairment (CrCL > 50 mL/min and ≤ 80 mL/min). In subjects with moderate (CrCL ≥ 30 mL/min and ≤ 50 mL/min) and severe (CrCL < 30 mL/min) renal impairment, varenicline exposure increased 1.5-fold and

2.1-fold, respectively, relative to subjects with normal renal function (CrCL > 80 mL/min). In subjects with ESRD undergoing hemodialysis receiving 0.5 mg varenicline once daily for 12 days, varenicline exposure increased 2.7-fold relative to subjects with normal renal function, although the plasma C_{max} and AUC were similar to those in healthy subjects receiving 1 mg twice daily.

Based on the results of Study OPP-100, the GMRs for AUC_{0-t}, AUC_{0-inf}, and C_{max} for 0.12 mg bilateral intranasal varenicline relative to 1 mg oral varenicline are approximately 0.036, 0.075, and 0.070, respectively. In addition, the proposed commercial strength of 0.6 mg/mL delivers half the quantity of varenicline that was evaluated in OPP-100. Taken together, this information supports the safe use of 0.06 mg intranasal varenicline in all patients with renal impairment. Alternative dosing regimens in patients with renal impairment are therefore not required.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The proposed varenicline nasal spray product is administered intranasally. Therefore, there are no clinically relevant food-drug interactions. The current approved labeling for CHANTIX® varenicline tartrate oral tablets describes results from *in vitro* and *in vivo* drug interaction studies, from which no clinically meaningful drug-drug interactions were identified. The proposed labeling submitted by the Applicant will indicate that (b) (4) (b) (4) (b) (4) No new data was submitted in this NDA regarding drug-drug interactions. Based on Study OPP-100, the Applicant has adequately established a bridge between their proposed product and the listed drug. Therefore, this is acceptable from a clinical pharmacology perspective.

4 APPENDICES

4.1 Clinical PK Assessment

4.1.1 Title: An Open-Label, Single-Center, Randomized, 2-way Crossover Study to Evaluate the Relative Bioavailability of Varenicline Administered as OC-01 Nasal Spray as Compared to Varenicline Administered Orally as CHANTIX® (The Zen Study) (Study OPP-100)

To establish a scientific bridge between the proposed varenicline nasal spray product and the listed drug, CHANTIX® oral varenicline tablets, the Applicant conducted Study OPP-100: "An open-label, single-center, randomized, 2-way crossover study to evaluate the relative bioavailability of varenicline administered as OC-01 nasal spray as compared to varenicline administered orally as CHANTIX® (The Zen Study)." The primary objective of this study was to assess the relative bioavailability of 0.12 mg intranasal varenicline administered bilaterally, (b) (4), as compared with varenicline administered orally at a dose of 1 mg, its highest oral tablet strength.

Healthy volunteers were randomized in Treatment Period 1 to receive either: 1) an intranasal dose of 0.12 mg varenicline nasal spray (0.05 mL spray of 0.06 mg into each nostril), or 2) a single 1 mg oral dose of CHANTIX®. Both products were self-administered by participants in the fasted state under direct supervision. After 14 days, participants returned for Treatment Period 2 to receive the alternate dose of varenicline not received in Treatment Period 1.

Study OPP-100 enrolled healthy males and females, between 18 and 65 years of age, inclusive, and a body mass index (BMI) between 18.0 and 32.0 kg/m^2, inclusive. Noteworthy exclusion criteria included: having had significant trauma to the nasal or sinus areas; having severe renal impairment (estimated CrCL < 30 mL/min); current concomitant use of cigarettes or any tobacco-containing products; current concomitant use, or previous use within 30 days, of a nicotinic acetylcholine receptor agonist; having clinically significant ECG or vital sign abnormalities; and enrollment in any investigational drug, biologic, or device study.

4.1.1.1 Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Blood samples for PK for each treatment were collected pre-dose, and post-dose at minutes 5, 15, and 30, and hours 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, and 120. Participants were confined in the Clinical Research Unit during the first 48 hours of sample collection. Remaining samples were collected on an outpatient basis. All samples were collected using tubes containing dipotassium ethylenediaminetetraacetic acid (EDTA K_2).

PK samples were analyzed using a validated electrospray ionization liquid chromatography-mass spectrometry-mass spectrometry (ESI-LC/MS/MS) method to determine the concentration of varenicline in human plasma with a lower limit of quantitation (LLOQ) of 0.100 ng/mL. Further details of the bioanalytical method and its validation are provided in a subsequent section.

The PK analysis population included all subjects who completed both treatment periods and had sufficient data for calculation of $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and C_{max}. PK parameters of varenicline in plasma, including $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, C_{max}, T_{max}, $t_{1/2}$, and K_{el}, were calculated using a non-compartmental method and summarized descriptively. For the primary analysis, log-transformed values of $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and C_{max} were compared with ANOVA using a linear mixed-effects model. Period, sequence, and treatment were considered fixed effects, while subject was considered a random effect. The GMR point estimates and associated 90% CIs were calculated for each of the three parameters.

4.1.1.2 Summary of Bioanalytical Method Validation

The Applicant submitted one validation report for the bioanalytical method used in Study OPP-100 entitled "The LC/MS/MS Quantitation of Varenicline in Human Plasma Between 0.100 and 50.0 ng/mL" (report number 12446.071519.1). Based on this report, this method for analysis of varenicline in human plasma has been adequately validated.

Varenicline concentrations in K_2EDTA human plasma were determined using an LC/MS/MS assay with a validated quantitation range between 0.100 and 50.0 ng/mL. The method relies on protein precipitation to extract varenicline (analyte) and varenicline-D_4 (internal standard) from 0.100 mL human plasma. Electrospray ionization mass spectrometry in positive ion mode was used for detection and quantification. Details of the HPLC system, including the mobile phases, flow rate, and sample gradient are provided in the tables below:

Name	***Parameter***
HPLC Model	AgieInt 1100 Series
Mobile Phase A	0.1% Formic Acid in Water
Mobile Phase B	0.1 % Formic Acid in Acetonitrile
Analytical Column	Atlantis dC18 HPLC column 3 µm,2.1 x 30 mm
Column Temperature	Ambient
Flow Rate	500 µL/min
Typical LC back pressure (at starting conditions)	~100 bar
Analysis Time (min)	4.5 min

Time (Min.)	Flow Rate (µL/min)	%A	%B
0.00	500	95	5
0.50	500	95	5
2.50	500	50	50
2.51	500	5	95
3.50	500	5	95
3.51	500	95	5
4.50	500	95	5

Source: pages 53-54, Bioanalytical Report Appendix A, Module 5.3.1.4, NDA 213978 SDN 1 submitted Dec. 17, 2020

The acquisition parameters for varenicline and varenicline-D_4 are provided in the table below. The typical retention times for varenicline and varenicline-D_4 are approximately 1.80 minutes.

Analyte/Internal Std	Precursor Ion	Product Ion	Dwell Time (msec)	Collision Energy (CE) (± 5eV)	Declustering Potential (DP) (± 30%)
Varenicline	212.1	169.1	100	33	70
[D_4]- Varenicline	216.1	169.1	100	33	70

Source: page 55, Bioanalytical Report Appendix A, Module 5.3.1.4, NDA 213978 SDN 1 submitted Dec. 17, 2020

Samples were quantified by obtaining the peak areas and determining the peak area ratio of analyte to internal standard.

Table 4. Bioanalytical method assessment

Information Requested	Data
Bioanalytical method validation report location	\\CDSESUB1\evsprod\NDA213978\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\opp-100-ba\varenicline-humanplasma-val-am1-finalreport.pdf
Analyte	Varenicline
Internal Standard (IS)	[D_4]-Varenicline
Limit of quantitation (pg/mL)	0.100 to 50.0 ng/mL
Average recovery of drug at each QC	LQC: 67.9 MQC: 69.7 HQC: 71.0
Average recovery of IS (%)	73.2

Standard curve concentrations (ng/mL)	0.100, .200, 1.50, 5.00, 10.0, 20.0, 40.0, 50.0
QC concentrations (µg/mL)	LLQC: 0.100 ng/mL LQC: 0.300 ng/mL MQC: 4.00 ng/mL HQC: 37.5 ng/mL
QC intraday (within-run) precision range (%CV)	1.41% to 11.1%
QC intraday (within-run) accuracy range (%bias)	-12.3% to 1.00%
QC interday (between-run) precision range (%CV)	2.15% to 10.9%
QC interday (between-run) accuracy range (%bias)	-7.00% to -0.750%
Bench-top stability (hrs)	21 hours (room temperature)
Stock stability (days)	154 days (-20 °C), and 19 hours (room temperature)
Processed stability (hrs)	94 hours (at 5 °C)
Freeze-thaw stability (cycles)	6 cycles (at -20 °C)
Long-term storage stability (days)	90 days at -20 °C and -80°C
Dilution Integrity	100-fold dilution (%CV = 1.65%, %Bias = -12.6%)
Selectivity	Mean matrix factor area ratio (plasma to control peak area ratios of analyte to IS) = 0.994. No interference from matrix components were observed at the retention times of analyte and IS

An information request was sent to the Applicant (DARRTS date: Apr. 30, 2021) to resolve a discrepancy between the validation report and the bioanalytical report, In the latter, it was indicated that the stability parameters of reinjection reproducibility and post-preparative stability (processed stability) were evaluated at ambient temperature. In contrast, the validation report suggests these parameters were evaluated at 5 °C. In a response dated May 5, 2021, the Applicant confirmed that the validation tests for reinjection reproducibility and post-preparative stability were run at 5 °C.

4.1.1.3 Bioanalytical Report Summary

The Applicant submitted one bioanalytical report detailing the performance of the PK sample analysis method used in Study OPP-100 entitled “Determination of Varenicline in Human Plasma Samples from Protocol OPP-100” (report number 14844.123119). Based on this report, the PK assay performed with acceptable precision and accuracy in Study OPP-100.

Overall, in relative bioavailability study OPP-100, 729 samples were analyzed. Samples were received between Aug. 31, 2019 and Sept. 25, 2019. Samples were analyzed between Sept. 11, 2019 and Oct. 17, 2019. All samples were kept at -20 °C. The interval between the first sample draw date to the last date of analysis is approximately 52 days and therefore falls within the validated time frame for long-term stability at -20 °C (90 days).

Eight-point calibration curves (linear regression; $1/X^2$ weighting) with concentrations ranging from 0.100 to 50.0 ng/mL were run in duplicate with each sample analysis run. Across all concentrations in all sample runs, the percent coefficient of variation (%CV) and absolute value of the percent bias (|% Bias|) were ≤ 6.14% and ≤ 0.600%, respectively.

QCs at concentrations of 0.300 ng/mL (LQC), 4.00 ng/mL (MQC), and 37.5 ng/mL (HQC) were run in duplicate with each sample analysis run. One LQC sample in a single run was found to be outside the acceptance criteria with a calculated concentration that was approximately 20% of the nominal concentration. Because the other LQC sample within that analytical run met acceptance criteria (comprising 50% of QCs per level), that run was still accepted. Across all QC values in all sample runs, excluding that value falling outside the acceptance range, the %CV and |% Bias| were ≤ 5.26% and ≤ 3.67%, respectively.

Incurred sample reanalysis (ISR) of 75 samples (approximately 10% of the total samples analyzed) yielded a passing rate of 98.7% (74/75) based on a maximum permitted deviation of 20% of the mean of the reference and repeat values. The Applicant's ISR evaluation is acceptable.

4.1.2 Impact of Sneezing on PK (Reviewer's Analysis)

Given that the proposed drug product is administered intranasally, it is possible that reported events of sneezing may have contributed to the high intersubject variability in exposure parameters as well as reductions in systemic varenicline exposure. Table 5 summarizes reported events of sneezing in individual subjects relative to the time of intranasal dosing and whether or not subjects were included in the PK analysis set. In all cases, all instances of sneezing occurred on the same day of intranasal dosing.

Table 5. Temporal relationship of sneezing to intranasal dose administration by subject.

Subject	Time of Intranasal Dosing	Reported Time of Sneezing	Included in PK Analysis Set?
(b) (6)	8:07 AM	8:19 AM	Y
	8:15 AM	8:16 AM	N
	9:00 AM	9:01 AM	Y
	9:15 AM	9:16 AM	N
	9:21 AM	9:27 AM	Y
	9:35 AM	9:35 AM	Y
	9:45 AM	9:45 AM	N

Source: Sections 16.2.7 and 16.2.5, Clinical Study Report for OPP-100, Module 5.3.1.2, NDA 213978 SDN 1, submitted Dec. 17, 2020

For all three subjects who were not included in the PK analysis set, plasma varenicline concentrations were below the limit of quantitation (BLQ) at all time points. For these three

subjects, sneezing occurred within one minute of intranasal dosing, although this was not a consistent predictor of decreased varenicline systemic exposure, as evidenced by the inclusion of subject (b) (6) in the PK analysis set. An exploratory analysis was conducted to compare PK parameters among those in the PK analysis set with (n = 4) and without (n = 12) reported sneezing. Results are shown in Table 6.

Table 6. Exploratory analysis assessing the impact of sneezing on PK parameters.

	Non-Sneezing Subset (N = 12)				Sneezing Subset (N = 4)			
Parameter (Unit)	**Mean**	**SD**	**%CV**	**Geometric Mean**	**Mean**	**SD**	**%CV**	**Geometric Mean**
AUC_{0-t} (h*ng/mL)	5.14	3.49	67.9	4.40	2.53	2.67	105.6	1.66
AUC_{0-inf} (h*ng/mL)	9.13	4.16	45.6	8.44	5.84	3.11	53.2	5.17
C_{max} (ng/mL)	0.37	0.12	32.4	0.35	0.26	0.14	52.9	0.24
$T_{1/2, el}$ (h)	18.20	6.95	38.2	--	21.12	17.44	82.6	--
K_{el} (h^{-1})	0.04	0.01	32.4	--	0.05	0.02	47.2	--

Source: Reviewer's analysis using ADPP Dataset with statistics calculated in JMP 13.0.0

Based on the data in Table 6, participants with reported sneezing had reductions in AUC_{0-t}, AUC_{0-inf}, and C_{max}, with geometric mean reductions of 62%, 39%, and 31%, respectively, relative to those without reported sneezing. The clinical significance of these decreases in PK parameters is unclear, although sneezing was commonly reported in later-phase trials, with rates of 80 to 95%. The proposed nasal spray drug product is locally-acting, so it is not clear whether reductions in systemic exposure to varenicline would impact overall efficacy. In an email communication with the clinical reviewer on Apr. 29, 2021, it was noted that the efficacy of the proposed 0.6 mg/mL strength was still demonstrated in later-phase trials irrespective of the high rates of sneezing.

Despite the observed changes in PK parameters, this analysis does not change the conclusion that varenicline exposure after an intranasal dose of 0.12 mg is lower than after an oral dose of 1 mg. A PK bridge has been adequately established between the proposed drug product and the listed drug.

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/s/

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