Original Research

A Phase I, Open-label, Randomized, 2-Way Crossover Study to Evaluate the Relative Bioavailability of Intranasal and Oral Varenicline

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ABSTRACT

Purpose: To estimate the systemic bioavailability of OC-01 (varenicline) nasal spray, an investigational treatment for dry eye disease, relative to oral varenicline approved for smoking cessation.

Methods: The Study to Evaluate the Relative Bioavailability of Varenicline Administered as OC-01 (Varenicline) Nasal Spray as Compared to Varenicline Administered Orally as Chantix (ZEN study) was a Phase I, open-label, randomized, single-center, 2-way crossover study. On day 1, 22 healthy participants were randomized 1:1 to a single intranasal dose of varenicline 0.12 mg in OC-01 nasal spray or a single oral dose of varenicline 1 mg. On day 15, all participants crossed over to receive a single dose of the alternate treatment. Plasma samples were collected for 6 days after each dose, and pharmacokinetic parameters were estimated using noncompartmental analysis. Tolerability was monitored throughout.

Findings: After a single dose of intranasal varenicline 0.12 mg in OC-01 nasal spray, peak systemic exposure (mean plasma C_{max}) was 0.34 ng/mL, which occurred at a median T_{max} of 2.0 hours. In comparison, mean plasma C_{max} after oral varenicline 1 mg was 4.63 ng/mL at a median T_{max} of 3.0 hours. On the basis of geometric mean ratio point estimates, peak exposure (C_{max}) and total exposure ($AUC_{0-\infty}$) after intranasal varenicline 0.12 mg were 7.0% and 7.5%, respectively, of the systemic exposure associated with oral varenicline 1 mg. Dose-normalized C_{max} and $AUC_{0-\infty}$ for intranasal varenicline remained 39% and 33% lower versus oral varenicline, respectively. No new or unexpected tolerability signals were detected.

Implications: At its highest intended single dose in OC-01 nasal spray, intranasal varenicline delivered less drug to the systemic circulation than oral varenicline at its highest approved single dose. ClinicalTrials.gov identifier: NCT04072146. (*Clin Ther.* 2021;43:1595–1607.)

Key words: Bioavailability, Dry eye disease, OC-01 nasal spray, Phase I study, Varenicline.

INTRODUCTION

Dry eye disease is a chronic disorder of the ocular surface, characterized by a loss of tear film homeostasis and accompanied by eye pain, discomfort, and visual disturbances that are detrimental to quality of life.[1,2] Dry eye disease is multifactorial in its etiology and pathophysiology, and its symptoms are often attributed to tear film instability, hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities.[1] Approximately 16 million people have been diagnosed with dry eye disease in the United States alone, with approximately 6 million more estimated to have undiagnosed dry eye symptoms.[3] Although dry eye disease is more common among women and in the aging population, annual prevalence and incidence rates have increased over time, irrespective of demographic profile.[3,4]

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Common treatment strategies for dry eye disease aim to replace and/or supplement the natural tear film or reduce the inflammation caused by tear film instability.[5–8] Over-the-counter ocular lubricants (artificial tears) are currently considered the mainstay of treatment,[5–8] whereas US Food and Drug Administration (FDA)–approved cyclosporine and lifitegrast reduce chronic inflammation associated with dry eye disease.[9–11] Although these strategies may provide relief from the signs and symptoms of dry eye disease, they do not address the underlying loss of tear film homeostasis[5] and may in fact exacerbate tear film instability and inflammation as an adverse event (AE) of added antimicrobial preservatives.[12] Moreover, eye drop formulations are often associated with ocular burning, reduced visual acuity, and dysgeusia, whereas anti-inflammatory therapies typically have a slow onset of action (˜3–6 months), which may further impact patient adherence.[9–11] Thus, there is a significant unmet need for efficacious, tolerable, and fast-acting therapies to reestablish the natural tear film in patients with dry eye disease.

Endogenous tear production is mediated by the glands and cells of the lacrimal functional unit, comprising the main lacrimal gland, ocular surface (cornea, conjunctiva, accessory lacrimal glands, and meibomian glands), and interconnecting sensory and motor neurons.[13] Parasympathetic activation of the lacrimal functional unit stimulates the coordinated secretion of mucin from conjunctival goblet cells, aqueous components from lacrimal glands, and lipid from meibomian glands onto the ocular surface.[13] As such, this neural pathway may represent a new therapeutic target to reestablish tear film homeostasis in dry eye disease. For example, oral pilocarpine and cevimeline are muscarinic acetylcholine receptor agonists used to treat dry mouth in patients with Sjögren's syndrome,[14,15] and although there is evidence that they may also improve dry eye symptoms in Sjögren's syndrome,[16–20] neither is approved by the FDA for the treatment of dry eye disease. Although these agents are delivered systemically to bind to receptors in close apposition to target glands, this mode of administration is frequently associated with off-target parasympathomimetic effects, such as sweating, nausea, rhinitis, diarrhea, frequent urination, flushing, and asthenia.[14,15]

OC-01 (varenicline) is a preservative-free, aqueous, 50-μL nasal spray in clinical development for the treatment of dry eye disease. Varenicline is a highly selective nicotinic acetylcholine receptor (nAChR) agonist that, when delivered as OC-01 nasal spray, binds to nAChRs located on the trigeminal nerve within the anterior nasal cavity. Activation of the trigeminal parasympathetic pathway by intranasal varenicline ultimately stimulates tear secretion from the meibomian glands, lacrimal glands, and goblet cells comprising the lacrimal functional unit; therefore, OC-01 nasal spray may reestablish tear film homeostasis via a new mechanism that does not require drug administration directly onto the ocular surface. The tolerability and efficacy of OC-01 (varenicline) nasal spray in dry eye disease has been assessed in 3 randomized, placebo-controlled trials: the Phase II MYSTIC study (Clinical Trial to Evaluate the Chronic Efficacy of OC-01 Nasal Spray on Signs of Dry Eye Disease),[21] the Phase IIb ONSET-1 study (Clinical Trial to Evaluate the Efficacy of OC-01 Nasal Spray on Signs and Symptoms of Dry Eye Disease),[22] and the Phase III ONSET-2 study (Clinical Trial to Evaluate the Efficacy and Safety of OC-01 (Varenicline) Nasal Spray on Signs and Symptoms of Dry Eye Disease).[23,24]

An oral formulation of varenicline was approved by the FDA as a smoking cessation treatment in 2006.[25] The metabolism, disposition, pharmacokinetic properties, clinical efficacy, and tolerability of oral varenicline have been extensively characterized and reviewed.[25–28] Briefly, varenicline tartrate is highly soluble in water, with a recommended oral dose of 0.5 to 1 mg twice daily that exhibits linear pharmacokinetic properties. Systemic bioavailability is high (˜90%) and unaffected by food, peak plasma concentration typically occurs within 3 to 4 hours, and with ongoing use, steady state occurs within 4 days. Varenicline exhibits low plasma protein binding ($\leq$20%) and is cleared with a t½ of approximately 24 hours. It is almost exclusively excreted unchanged in the urine, primarily via glomerular filtration, with an additional component of active tubular secretion via the organic cation transporter 2. Given that renal function can lead to interindividual variability in varenicline exposure, a maximum dose of 0.5 mg twice daily is indicated for patients with severe renal impairment. Varenicline does not inhibit or induce the major cytochrome P450 enzymes, and in the absence of significant hepatic metabolism, pharmacokinetic parameters should be unchanged for patients with hepatic impairment. There are no clinically meaningful

differences in the pharmacokinetic properties of varenicline across patient demographic characteristics of age, race, sex, use of concomitant medications, or smoking status.

Although the pharmacokinetic and pharmacodynamic properties of oral varenicline at its highest approved single dose (1 mg free base) have previously been examined, the systemic bioavailability of intranasal varenicline at its highest intended single dose based on efficacy in Phase II/III studies[21–24] (0.12 mg free base, delivered as one 50-μL spray of OC-01 1.2 mg/mL into each nostril) has not been characterized. Here we describe the Phase I ZEN study, which sought to estimate the systemic bioavailability of intranasal varenicline in OC-01 nasal spray relative to that of oral varenicline in healthy participants. We hypothesized that systemic exposure to varenicline in OC-01 nasal spray is no greater than that currently approved for varenicline administered orally.

PARTICIPANTS AND METHODS

Study Design

The ZEN study (ClinicalTrials.gov identifier NCT04072146) was a Phase I, open-label, randomized, single-center, 2-way crossover study designed to compare the systemic bioavailability of varenicline administered intranasally with that of varenicline administered orally.[29] This study was conducted at Syneos Health, Inc. (Miami, Florida) and sponsored by Oyster Point Pharma, Inc. (Princeton, New Jersey). The study adhered to the tenets of the Declaration of Helsinki, International Council for Harmonisation E6 Guidelines for Good Clinical Practice, US Health Insurance Portability and Accountability Act, and applicable local, state, and federal regulations. The ZEN study protocol and associated documents were approved by the Advarra institutional review board (Columbia, Maryland) before study commencement, and all participants provided written informed consent.

Study Population

Healthy men and nonpregnant women, 18 to 65 years of age with a body mass index of 18.0 to 32.0 kg/m^2, were enrolled in this study. Health was assessed by an experienced physician during a screening visit within 28 days before study entry, and those deemed healthy based on medical history, vital signs, physical examination, 12-lead ECG, intranasal examination, and laboratory tests (serology, hematology, clinical chemistry, and urinalysis) were eligible to participate. Key exclusion criteria were prior nasal or sinus surgery (including nasal cautery) or significant trauma to these areas; a vascularized polyp, severely deviated septum, chronic recurrent nosebleeds, severe nasal airway obstruction, or active nasal infection at the screening visit; current treatment with nasal continuous positive airway pressure; concomitant use of snuff, chewing tobacco, e-cigarettes, or cigarettes; concomitant use of nAChR agonists (eg, nicotine, cytisine, or varenicline); or any labeled contraindication to varenicline. Participants with severe renal impairment (estimated creatinine clearance <30 mL/min), a history of alcohol or drug abuse within 6 months before screening, or who donated plasma within 30 days before first treatment were also excluded.

Randomization, Treatment, and Follow-up

After screening, eligible participants were randomized 1:1 to treatment sequence A or B (Figure 1). Each participant was randomly allocated a unique participant number during screening, which corresponded to their assigned treatment sequence using a randomization schedule generated by Firma Clinical Research (Hunt Valley, Maryland) in SAS software, version 9.4 (SAS Institute Inc, Cary, North Carolina).

On day 1 (start of treatment period 1), participants randomized to treatment sequence A received a single intranasal dose of varenicline 0.12 mg free base in OC-01 nasal spray (delivered as one 50-μL spray of OC-01 1.2 mg/mL into each nostril), and those randomized to treatment sequence B received a single oral dose of varenicline 1 mg free base (delivered as one 1-mg Chantix oral tablet[25]). Pharmacokinetic samples were collected for 6 days after study drug administration (ie, days 1–6), then all patients entered an 8-day washout period from days 7 to 14. On day 15 (start of treatment period 2), all participants crossed over to receive a single dose of the alternate varenicline treatment that was delivered during treatment period 1, and pharmacokinetic samples were collected for 6 days thereafter (ie, days 15–20). Varenicline treatments were administered on days 1 and 15 after a supervised overnight fast, and all participants fasted for at least 3 to 4 hours after each dose. Participants were monitored on an inpatient basis for at least 48 hours after receiving OC-01 nasal spray or oral varenicline (ie, days 1–3 and days 15–17) and on an outpatient basis for the remainder of each treatment period (ie, days

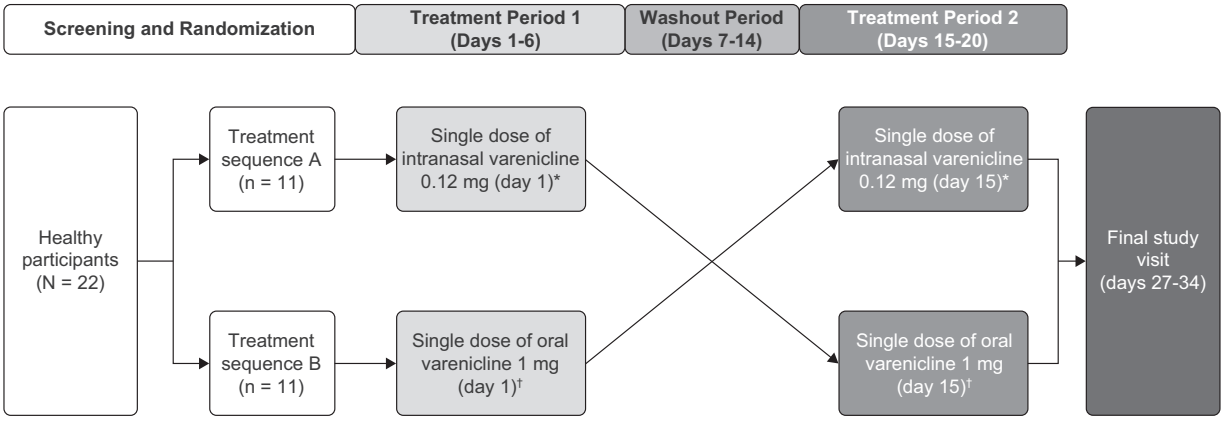

Figure 1. ZEN study design schematic. *Intranasal varenicline was a single dose of varenicline 0.12 mg free base, delivered as one 50-μL spray of OC-01 1.2 mg/mL into each nostril. †Oral varenicline was a single dose of varenicline 1 mg free base, delivered as one 1-mg Chantix oral tablet.

4–6 and days 18–20). A final study visit occurred approximately 7 to 14 days after the end of treatment period 2 (ie, days 27–34).

Outcomes

The primary objective of the ZEN study was to determine the systemic bioavailability of intranasal varenicline at its highest intended single dose, relative to oral varenicline at its highest labeled single dose. To assess this outcome, blood samples for pharmacokinetic analysis were collected from each participant before receiving varenicline on days 1 and 15 and at prespecified time points after each dose (5, 15, and 30 minutes and 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, and 120 hours).

The plasma varenicline concentration of each sample was quantified using a validated LC-MS/MS method, which used a Sciex API 4000 mass spectrometry system (AB Sciex LLC, Framingham, Massachusetts), Agilent 1100 Series pump (Agilent Technologies, Inc., Santa Clara, California), Atlantis C18 HPLC column (2.1 × 30 mm; particle size, 3 μm; Waters Corporation, Milford, Massachusetts), and varenicline-d4 as an internal standard. Briefly, 100 μL of K_2-EDTA anticoagulated plasma was extracted with 0.6 mL of acetonitrile and 50 μL of a 10 ng/mL internal standard working solution. The solution was vortexed for 1 minute and centrifuged for 5 minutes, then 0.5 mL of the supernatant was evaporated to dryness and reconstituted in 0.1 mL of the starting mobile phase (described below). The extracted samples were kept at 5°C in an autosampler until injected into an ambient temperature HPLC column and analyzed by LC-MS/MS in positive ion mode. The HPLC method used 0.1% formic acid in water for mobile phase A, 0.1% formic acid in acetonitrile for mobile phase B, and a flow rate of 0.5 mL/min. Samples were eluted using 95:5 mobile phase A:B for 0.5 minutes, which was then linearly graded to 50:50 mobile phase A:B until 2.5 minutes. With this method, the retention time for varenicline was approximately 1.8 minutes, and plasma varenicline was detectable within the concentration range of 0.1 to 50 ng/mL.

Pharmacokinetic parameters for intranasal and oral varenicline in plasma (AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, $t_{½}$, and k_e) were estimated for each participant using noncompartmental analysis in SAS software. AUC values were calculated with actual time points using the linear-log trapezoidal (linear-up log-down) method.

The secondary objective of this study was to evaluate the clinical and laboratory tolerability of intranasal and oral varenicline. Tolerability was assessed through vital signs, physical and intranasal examinations, 12-lead ECG, and laboratory tests (hematology, clinical chemistry, and urinalysis) conducted before the patient received intranasal or oral varenicline on days 1 and 15, 2 hours after each dose, and/or at the final study visit. AEs were monitored throughout the study period and coded using *Medical Dictionary for Regulatory Activities*, version 22.0.

Statistical Analysis

The ZEN study was not designed or powered to perform hypothesis testing. A sample size of ≥18 participants was required to evaluate the systemic bioavailability of intranasal varenicline relative to oral varenicline, assuming an 80% probability of no type II error, 5% probability of type I error, and 20% intraparticipant variability for pharmacokinetic parameters of systemic exposure.

All participants who were randomized and received ≥1 dose of varenicline were included in the safety analysis population. Baseline demographic and clinical characteristics were based on the safety analysis population and summarized using descriptive statistics by treatment sequence. Tolerability analyses compared the incidence of treatment-emergent AEs (TEAEs) associated with intranasal and oral varenicline, defined as any AE that occurred up to 5 days after treatment, or a preexisting event or condition that worsened after receiving varenicline and within its duration of residual effect. The severity of TEAEs (mild, moderate, or severe) and the incidence of other serious or significant AEs throughout the study period (eg, AEs leading to study withdrawal, hospitalization, or death) were also assessed.

Participants who completed both treatment periods and had sufficient data to calculate AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} for intranasal and oral varenicline in plasma were included in the pharmacokinetic analysis population. Plasma varenicline concentrations over time and associated pharmacokinetic parameters were described for each treatment using descriptive statistics (eg, mean, SD, CV, geometric mean, geometric CV, median, and/or range). Plasma varenicline concentrations below the lower limit of quantitation (ie, <0.1 ng/mL) were reported as 0 ng/mL in arithmetic mean calculations. Because varenicline exhibits linear pharmacokinetic properties at doses ≤1 mg, pharmacokinetic parameters for intranasal varenicline 0.12 mg (AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}) were dose normalized for equivalence with oral varenicline 1 mg. Pharmacokinetic analyses were based on observed data, with no imputation for missing values.

Log-transformed AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} for intranasal and oral varenicline administration were compared with an ANOVA using a linear mixed-effects model. The fitted model (log scale) for each parameter included period, sequence, and treatment as fixed effects and participant as a random effect. Each fitted model was used to derive point estimates and associated 90% CIs for the adjusted mean difference (log scale) between intranasal and oral varenicline, which were then exponentiated to obtain the adjusted geometric mean ratio (GMR) point estimates and associated 90% CIs. Intraparticipant variation was measured by the geometric CV and derived as $100 \times \sqrt{(e^{S2} - 1)}$, where S2 was the residual variation from the log-transformed linear mixed-effects model.

RESULTS

Study Population

A total of 42 healthy participants were screened for eligibility, and 25 were enrolled in the ZEN study. Of these, 22 participants were randomized to treatment sequence A (n = 11) or treatment sequence B (n = 11) and were included in the safety analysis population (Figure 2). Participants completed treatment period 1 from August 26 to 31, 2019 (ie, days 1–6); completed treatment period 2 from September 9 to 14, 2019 (ie, days 15–20); and attended a final study visit between September 21 and October 9, 2019.

Of the 22 participants in the safety analysis population, 21 completed both treatment periods. One participant was randomized to treatment sequence B (oral-nasal) and completed treatment period 1 with oral varenicline, but was discontinued from the study before dosing in treatment period 2 because of AEs unrelated to study treatment (headache and increased blood pressure). Among those who completed both treatment periods, 16 participants had sufficient data to calculate AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} for intranasal and oral varenicline in plasma and were subsequently included in the pharmacokinetic analysis population (Figure 2).

Baseline demographic and clinical characteristics of the safety analysis population are summarized in Table 1. Mean age at baseline was 42 years, 45% of participants were women, 86% were Hispanic or Latino, and mean body mass index was 26.5 kg/m^2. Baseline characteristics were generally balanced between participants randomized to treatment sequence A (nasal-oral) and treatment sequence B (oral-nasal).

Pharmacokinetic Analysis

Mean plasma concentration-time curves for intranasal and oral varenicline are presented in Figure 3, and associated pharmacokinetic parameters are summarized in Table 2. Intranasal varenicline 0.12 mg in

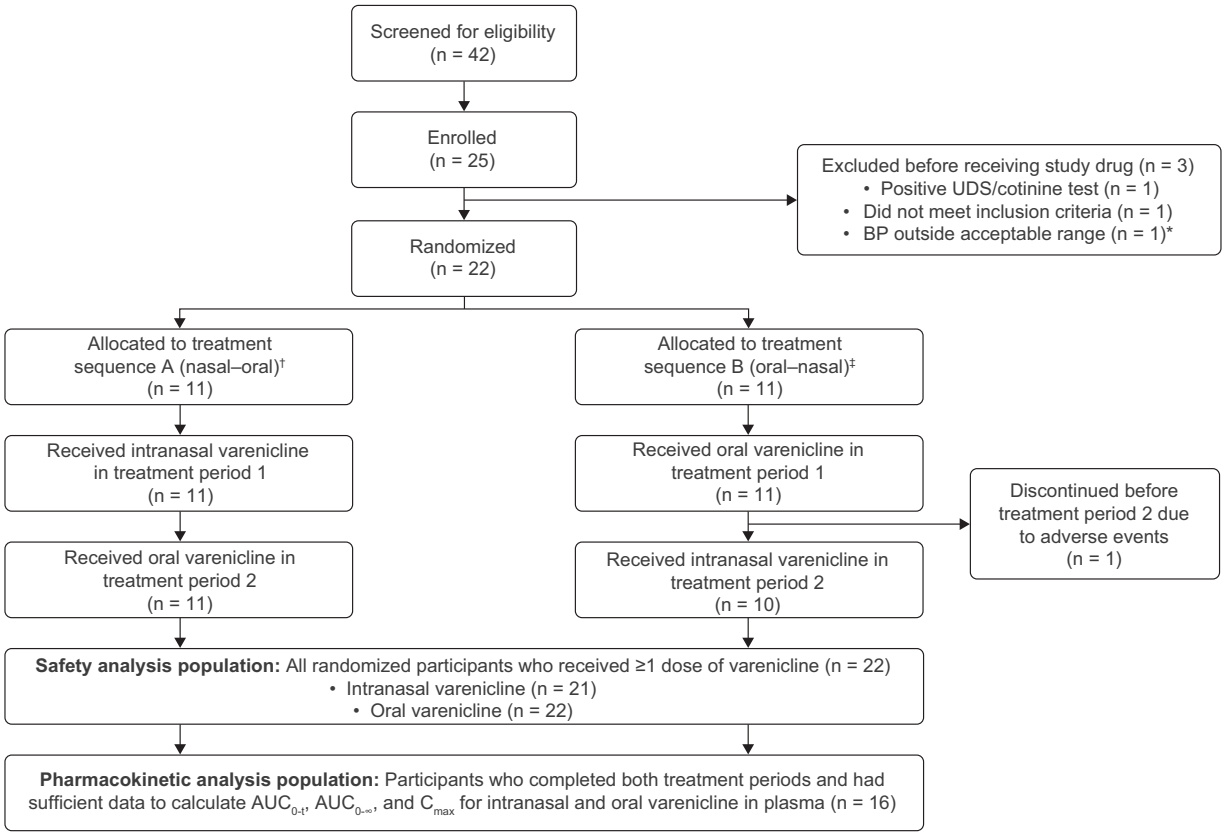

Figure 2. ZEN study participant selection. *Participants with systolic blood pressure (BP) <90 mm Hg or >140 mm Hg or with diastolic BP <50 mm Hg or >90 mm Hg were excluded. †Participants randomized to treatment sequence A received a single intranasal dose of varenicline 0.12 mg free base (delivered as one 50-μL spray of OC-01 1.2 mg/mL into each nostril) on day 1 and a single oral dose of varenicline 1 mg free base (delivered as one 1-mg Chantix oral tablet) on day 15. ‡Participants randomized to treatment sequence B received a single oral dose of varenicline 1 mg free base (delivered as one 1-mg Chantix oral tablet) on day 1 and a single intranasal dose of varenicline 0.12 mg free base (delivered as one 50-μL spray of OC-01 1.2 mg/mL into each nostril) on day 15. UDS = urine drug screen.

OC-01 nasal spray was rapidly absorbed and detected in plasma within 5 minutes, and reached a mean plasma C_{max} of 0.34 ng/mL at a median T_{max} of 2.0 hours. In comparison, oral varenicline 1 mg was first detected in plasma after 15 minutes and reached a mean plasma C_{max} of 4.63 ng/mL at a median T_{max} of 3.0 hours. The mean $t_{½}$ estimated for intranasal and oral varenicline was comparable between the 2 treatments (18.93 vs 19.59 hours, respectively).

The relative bioavailability of OC-01 (varenicline) nasal spray at its highest intended single dose of 0.12 mg (delivered as one 50-μL spray of OC-01 1.2 mg/mL into each nostril) was lower than that of oral varenicline at its highest labeled single dose of 1 mg (Table 3). Nondose-normalized adjusted GMRs for intranasal versus oral varenicline were 3.6% (90% CI, 2.6%–5.1%) for log-transformed AUC_{0-t}, 7.5% (6.0%–9.4%) for log-transformed $AUC_{0-\infty}$, and 7.0% (6.0%–8.2%) for log-transformed C_{max}. Therefore, based on GMR point estimates, peak exposure (C_{max}) and total exposure ($AUC_{0-\infty}$) after intranasal varenicline 0.12 mg in OC-01 nasal spray were 7.0% and 7.5%, respectively, of the systemic exposure associated with oral varenicline 1 mg administered in the fasted state. Similarly, when pharmacokinetic parameters for varenicline were dose normalized to 1

Table 1. Baseline demographic and clinical characteristics (safety analysis population).

Characteristic	Treatment Sequence		Total (N = 22)
	A (Nasal-Oral)* (n = 11)	B (Oral-Nasal)† (n = 11)	
Age, y			
Mean (SD)	39.5 (10.6)	44.5 (14.0)	42.0 (12.4)
Median (range)	41 (23–56)	47 (25–63)	43.5 (23–63)
Female, No. (%)	3 (27.3)	7 (63.6)	10 (45.5)
Race, No. (%)			
White	8 (72.7)	9 (81.8)	17 (77.3)
Black or African American	3 (27.3)	2 (18.2)	5 (22.7)
Other	0	0	0
Ethnicity, No. (%)			
Hispanic or Latino	10 (90.9)	9 (81.8)	19 (86.4)
Non-Hispanic or Latino	1 (9.1)	2 (18.2)	3 (13.6)
Weight, kg			
Mean (SD)	79.0 (10.3)	73.3 (13.3)	76.1 (12.0)
Median (range)	78.6 (63.0–94.7)	67.7 (62.2–105.2)	73.0 (62.2–105.2)
Height, cm			
Mean (SD)	172.6 (6.5)	165.4 (10.0)	169.0 (9.0)
Median (range)	175 (162–184)	163 (151–188)	169 (151–188)
BMI, kg/m^2			
Mean (SD)	26.5 (2.6)	26.6 (2.5)	26.5 (2.5)
Median (range)	25.4 (23.2–30.7)	26.1 (23.1–29.8)	25.7 (23.1–30.7)

BMI = body mass index.

* Participants randomized to treatment sequence A received a single intranasal dose of varenicline 0.12 mg free base (delivered as one 50-μL spray of OC-01 1.2 mg/mL into each nostril) on day 1 and a single oral dose of varenicline 1 mg free base (delivered as one 1-mg Chantix oral tablet) on day 15.

† Participants randomized to treatment sequence B received a single oral dose of varenicline 1 mg free base (delivered as one 1-mg Chantix oral tablet) on day 1 and a single intranasal dose of varenicline 0.12 mg free base (delivered as one 50-μL spray of OC-01 1.2 mg/mL into each nostril) on day 15.

mg, mean C_{max} and $AUC_{0-\infty}$ were 39% and 33% lower via the intranasal route versus the oral route (Table 2).

Tolerability Analysis

In total, 42 TEAEs were reported by 15 participants (68.2%) in the safety analysis population (Table 4). All TEAEs were related to study treatment except for 2 events (scratch and nasal congestion), each reported by 1 participant receiving oral varenicline. Fewer TEAEs were associated with OC-01 nasal spray than oral varenicline (16 vs 26 events, respectively); however, the incidence of TEAEs was higher among participants receiving intranasal versus oral varenicline (13 participants [61.9%] vs 9 participants [40.9%]). The most common TEAEs associated with intranasal varenicline in OC-01 nasal spray were sneezing and coughing (7 participants [33.3%] and 6 participants [28.6%], respectively); both events were temporally related to the route of administration and resolved shortly after each dose. The most common TEAEs associated with oral varenicline were nausea and dizziness (5 participants each [22.7%]), vomiting (4 participants [18.2%]), and somnolence (3 participants [13.6%]), all of which are consistent with Chantix prescribing information.[25] One participant experienced vomiting of moderate severity with oral varenicline; otherwise, all other TEAEs associated with intranasal and oral varenicline were mild. No other serious

Table 2. Summary of pharmacokinetic parameters for intranasal and oral varenicline (pharmacokinetic analysis population).

Parameter	Intranasal Varenicline 0.12 mg* (n = 16)	Oral Varenicline 1 mg† (n = 16)
AUC_{0-t}, ng·h/mL		
Mean (SD)	4.49 (3.42)	98.74 (25.49)
Dose-normalized mean (SD)‡	37.41 (28.52)	
CV, %	76.2	25.8
$AUC_{0-\infty}$, ng·h/mL		
Mean (SD)	8.30 (4.09)	102.53 (26.82)
Dose-normalized mean (SD)‡	69.20 (34.12)	
CV, %	49.3	26.2
C_{max}, ng/mL		
Mean (SD)	0.34 (0.13)	4.63 (0.93)
Dose-normalized mean (SD)‡	2.84 (1.07)	
CV, %	37.6	20.2
T_{max}, median (range), h	2.0 (0.3–3.0)	3.0 (1.0–6.0)
$t_{½}$, h		
Mean (SD)	18.93 (9.90)	19.59 (10.39)
CV, %	52.3	53.0
k_e, h^{-1}		
Mean (SD)	0.044 (0.015)	0.042 (0.015)
CV, %	35.4	35.4

* Participants received a single intranasal dose of varenicline 0.12 mg free base, delivered as one 50-μL spray of OC-01 1.2 mg/mL into each nostril.
† Participants received a single oral dose of varenicline 1 mg free base, delivered as one 1-mg Chantix oral tablet.
‡ Pharmacokinetic parameters for intranasal varenicline 0.12 mg were dose normalized to 1 mg for equivalence with oral varenicline.

Table 3. Relative bioavailability of intranasal versus oral varenicline (pharmacokinetic analysis population).

Parameter	Adjusted Geometric Mean*		Adjusted GMR (Intranasal-Oral) (90% CI), %	Intraparticipant Variability, %†
	Intranasal Varenicline 0.12 mg	Oral Varenicline 1 mg		
AUC_{0-t}, ng·h/mL	3.45	96.03	3.6 (2.6–5.1)	59.3
$AUC_{0-\infty}$, ng·h/mL	7.46	99.67	7.5 (6.0–9.4)	37.0
C_{max}, ng/mL	0.32	4.55	7.0 (6.0–8.2)	25.6

GMR = geometric mean ratio.
* Exponentiated value of the least squares means from the mixed-effects model of log-transformed data.
† Intraparticipant variability was measured by the geometric CV and derived as $100 \times \sqrt{(e^{S2} - 1)}$, where S2 was the residual variation from the log-transformed linear mixed-effects model.

Table 4. Summary of TEAEs (safety analysis population).

TEAE	Intranasal Varenicline, No. (%)* (n = 21)	Oral Varenicline, No. (%)† (n = 22)	Total, No. (%) (N = 22)
Total TEAEs	16	26	42
Participants with any TEAE	13 (61.9)	9 (40.9)	15 (68.2)
Mild	13 (61.9)	8 (36.4)	14 (63.6)
Moderate	0	1 (4.5)	1 (4.5)
Severe	0	0	0
Participants with any serious TEAE‡	0	0	0
Participants with any TEAE leading to study withdrawal	0	0	0
Participants with any TEAE leading to death	0	0	0
TEAEs reported by >1 participant			
Gastrointestinal disorders	0	6 (27.3)	6 (27.3)
Nausea	0	5 (22.7)	5 (22.7)
Vomiting	0	4 (18.2)	4 (18.2)
Nervous system disorders	1 (4.8)	8 (36.4)	8 (36.4)
Dizziness	0	5 (22.7)	5 (22.7)
Somnolence	1 (4.8)	3 (13.6)	3 (13.6)
Respiratory, thoracic, and mediastinal disorders	13 (61.9)	2 (9.1)	14 (63.6)
Sneezing	7 (33.3)	0	7 (31.8)
Cough	6 (28.6)	0	6 (27.3)

TEAE = treatment-emergent adverse event.

*Participants received a single intranasal dose of varenicline 0.12 mg free base, delivered as one 50-μL spray of OC-01 1.2 mg/mL into each nostril.

†Participants received a single oral dose of varenicline 1 mg free base, delivered as one 1-mg Chantix oral tablet.

‡Serious TEAEs were defined as those resulting in death, a life-threatening adverse event, inpatient hospitalization or prolonged hospitalization, persistent or significant incapacity or substantial disruption to normal life functions, a congenital anomaly or birth defect in an offspring, or any other medically important event that could jeopardize the participant and require medical intervention to prevent such an outcome.

or significant AEs were reported, and no clinically significant abnormalities in laboratory samples, vital signs, 12-lead ECG, or intranasal examinations were observed.

DISCUSSION

OC-01 (varenicline) nasal spray is an investigational treatment for dry eye disease that leverages the parasympathetic nervous system to promote natural tear film production. The MYSTIC,[21] ONSET-1,[22] and ONSET-2[23,24] trials examined the tolerability of OC-01 (varenicline) nasal spray in patients with dry eye disease, and its potential to improve the signs and symptoms associated with this condition. Meanwhile, the Phase I ZEN study sought to compare the bioavailability of intranasal varenicline in OC-01 nasal spray with oral varenicline in healthy participants. This study confirmed our hypothesis that systemic exposure to intranasal varenicline at its highest intended single dose in nasal spray is lower than that of oral varenicline at its highest single dose approved for smoking cessation.

Our results are consistent with others that have estimated pharmacokinetic parameters for oral varenicline in plasma. In previous studies of healthy smokers 18 to 55 years of age, peak plasma concentrations (mean C_{max}) of 4.3 to 5.1 ng/mL were observed after a single oral dose of varenicline 1 mg, all of which occurred at a median T_{max} of 3.0 hours.[27] Moreover, total systemic exposure to oral varenicline (mean $AUC_{0-\infty}$)

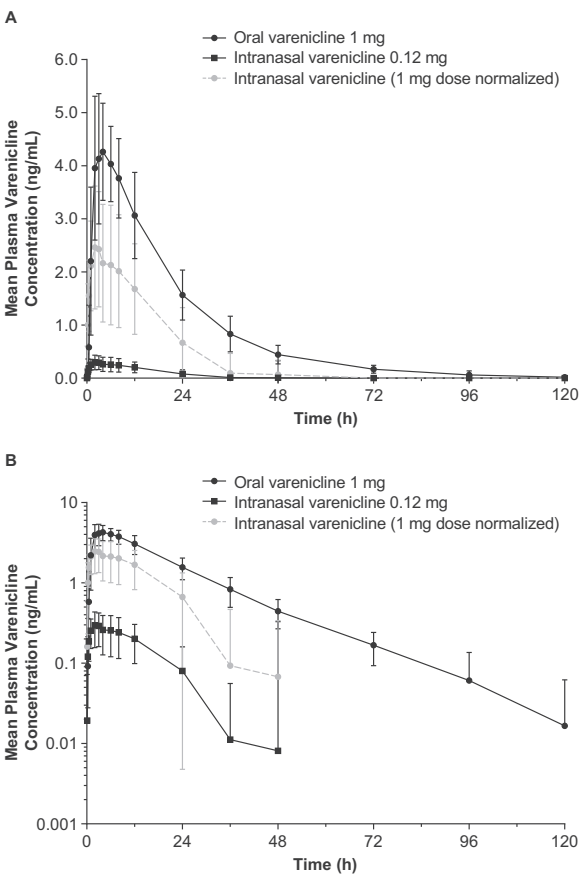

Figure 3. Mean (SD) plasma concentration-time profile of intranasal and oral varenicline in the pharmacokinetic analysis population (n = 16) on a (A) linear scale and (B) semi-log scale. Intranasal varenicline was a single dose of varenicline 0.12 mg free base, delivered as one 50-μL spray of OC-01 1.2 mg/mL into each nostril; oral varenicline was a single dose of varenicline 1 mg free base, delivered as one 1-mg Chantix oral tablet. Plasma concentrations of intranasal varenicline 0.12 mg were dose normalized to 1 mg for equivalence with oral varenicline. Plasma varenicline concentrations below the lower limit of quantitation (<0.1 ng/mL) were reported as 0 ng/mL in arithmetic mean calculations; pharmacokinetic analyses used observed data, with no imputation for missing values.

was estimated at 91 to 107 ng·h/mL across studies, and mean $t_{½}$ ranged from 15.2 to 19.2 hours.[27] In the present study of healthy nonsmokers between 18 and 65 years of age, corresponding estimates for C_{max}, T_{max}, $AUC_{0-\infty}$, and $t_{½}$ after a single oral dose of varenicline 1 mg were 4.6 ng/mL, 3.0 hours, 102.5 ng·h/mL, and 19.6 hours, respectively. The similarity and reproducibility of these parameters across studies lend validity to both the pharmacokinetic parameters of oral varenicline observed in the ZEN study, and the comparatively low systemic bioavailability of intranasal varenicline in OC-01 nasal spray.

After a single dose of intranasal varenicline 0.12 mg in OC-01 nasal spray, we found that varenicline was rapidly absorbed into the systemic circulation, with a low mean plasma C_{max} of 0.34 ng/mL occurring at a median T_{max} of 2.0 hours. To account for differences between varenicline at its highest intended clinical dose in OC-01 nasal spray (0.12 mg) and its highest labeled oral dose (1 mg), pharmacokinetic parameters for intranasal varenicline were dose normalized to 1 mg; however, dose-normalized C_{max} and $AUC_{0-\infty}$ for plasma varenicline remained 39% and 33% lower via the intranasal route versus the oral route, respectively. These findings collectively indicate that varenicline administered intranasally provides less drug to the systemic circulation than that provided by the oral route. Greater interparticipant variability in pharmacokinetic parameters (ie, AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}) was observed among participants receiving intranasal versus oral varenicline; however, mean $t_{½}$ was not considered clinically different between the 2 routes of administration.

Systemic exposure to intranasal varenicline is distinct from exposure at the site of action. After a single dose of varenicline 0.12 mg in OC-01 nasal spray, we estimated a peak systemic exposure (mean plasma C_{max}) of 0.34 ng/mL (˜1.6 nM); however, local concentrations of varenicline in the nasal airway surface liquid have been estimated at approximately 100 μM, assuming a nasal cavity surface area of 80 cm^2 and mucous thickness of 20 μm.[30–32] At this concentration, varenicline, which has high affinity for relevant nAChR subtypes ($K_i \leq 0.1$ μM),[33] binds to target nAChRs in the anterior nasal cavity and stimulates endogenous tear secretion, as evidenced by statistically significant improvements in natural tear film production seen in MYSTIC, ONSET-1, and ONSET-2.[21–24,34] Thus, unlike oral varenicline, intranasal administration of

OC-01 nasal spray delivers a relatively high concentration of varenicline directly to afferent neurons in the trigeminal parasympathetic pathway, while delivering a relatively low concentration to the systemic circulation. The results of the ZEN study also indicate that the lower bioavailability of intranasal varenicline in OC-01 nasal spray may translate to reduced risk of systemic AEs compared with oral varenicline.

Overall, intranasal and oral varenicline were well tolerated, with no unexpected or clinically significant events detected. All TEAEs except 1 (moderate vomiting with oral varenicline) were mild, no serious TEAEs were reported, and no TEAEs led to study withdrawal. Most TEAEs associated with intranasal varenicline were transient respiratory events that resolved shortly after each dose; in comparison, most TEAEs with oral varenicline were gastrointestinal and nervous system disorders. Varenicline is also an agonist of the 5-hydroxytryptamine$_3$ receptor,[35] and the nausea and vomiting events observed with oral varenicline are consistent with previous studies and Chantix prescribing information.[25,36] Relative to oral varenicline 1 mg, the lower incidences of nervous system and gastrointestinal events with intranasal varenicline 0.12 mg were likely attributable to both the lower dose of varenicline in OC-01 nasal spray and the lower systemic exposure associated with intranasal administration. For example, previous studies have found that nervous system (eg, insomnia, headache, and abnormal dreams) and gastrointestinal (eg, nausea) events with oral varenicline 0.3 mg were lower than with oral varenicline 1 mg and/or comparable with placebo,[37] whereas the systemic exposure estimated for oral varenicline 0.3 mg in healthy adults (mean C_{max}, 1.9–2.4 ng/mL; mean $AUC_{0-\infty}$, 31.4–37.9 ng·h/mL)[36] remains several-fold higher than that estimated for intranasal varenicline 0.12 mg in the ZEN study (mean C_{max}, 0.34 ng/mL; mean $AUC_{0-\infty}$, 8.3 ng·h/mL). Importantly, there were no ocular TEAEs associated with intranasal varenicline in OC-01 nasal spray, suggesting that its unique route of administration and mechanism of action may also avoid ocular events that commonly impact patient adherence to eye drop therapies for dry eye disease.

The ZEN study was not designed or powered to perform hypothesis testing. As such, additional studies may seek to determine whether observed differences in dose-normalized pharmacokinetic parameters and tolerability profiles between intranasal and oral varenicline are statistically significant. The effect of participant demographic and clinical characteristics (eg, race or concomitant nasal pathological conditions, such as allergic rhinitis) on the systemic bioavailability and tolerability of intranasal varenicline were not evaluated in the ZEN study and warrant further investigation in future research.

CONCLUSIONS

The Phase I ZEN study found that intranasal varenicline, when administered at its highest intended single dose of 0.12 mg in OC-01 nasal spray, delivers less drug to the systemic circulation compared with oral varenicline administered at its highest approved single dose of 1 mg. Specifically, it was estimated that the peak systemic exposure (C_{max}) and total systemic exposure ($AUC_{0-\infty}$) after a single intranasal dose of varenicline 0.12 mg were both <8% of the systemic exposure associated with oral varenicline 1 mg. In conjunction with randomized controlled Phase II and III trials, the ZEN study provides important pharmacokinetic and tolerability data to inform the value of OC-01 (varenicline) nasal spray as a new treatment strategy to reestablish tear film homeostasis and improve outcomes for patients with dry eye disease.

DISCLOSURE

Dr Nau is the president and chief executive officer of Oyster Point Pharma, Inc. Dr Wyatt and Mr Crean have served as consultants for Oyster Point Pharma, Inc. Dr Rollema is a consultant for Oyster Point Pharma, Inc., is a former employee of Pfizer Inc. (manufacturer of varenicline), and has served as a consultant for Astraea Therapeutics LLC, Pfizer Inc., and Redpin Therapeutics, Inc., outside the submitted work. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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