Ophthalmol Ther (2023) 12:355–364
https://doi.org/10.1007/s40123-022-00607-7

ORIGINAL RESEARCH

Does Menopausal Status Affect Dry Eye Disease Treatment Outcomes with OC-01 (Varenicline Solution) Nasal Spray? A Post Hoc Analysis of ONSET-1 and ONSET-2 Clinical Trials

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Received: September 23, 2022 / Accepted: October 21, 2022 / Published online: November 18, 2022

ABSTRACT

Introduction: This study sought to compare the efficacy of OC-01 (varenicline solution) nasal spray for treatment of dry eye disease (DED) in postmenopausal women (PM+) versus women who were not postmenopausal (PM−).

Methods: This was a post hoc subgroup analysis of data integrated from two prior randomized controlled clinical trials, ONSET-1 and ONSET-2. Women randomized to treatment with OC-01 (varenicline solution) nasal spray 0.03 mg or vehicle control (VC) whose self-reported menopausal status (PM+ versus PM−) was known were included. Outcomes included the treatment difference (the OC-01 [varenicline solution] nasal spray change from baseline [CFB] minus VC CFB) in Schirmer test score (STS, mm) with anesthesia and the eye dryness score (EDS) measured on a 100-mm visual analog scale (0 = no discomfort, 100 = maximal discomfort). Least-squares mean treatment differences were derived from analysis of covariance (ANCOVA) models.

Results: Overall, 449 female participants in the ONSET-1 and ONSET-2 trials randomized to the OC-01 (varenicline solution) nasal spray 0.03 mg or VC groups were included in this analysis. The treatment–menopausal status interaction terms in the STS and EDS ANCOVA and logistic regression models were not statistically significant ($p > 0.05$), indicating consistency of treatment effect between the PM− and PM+ groups. The treatment difference in STS was similar in the PM− and PM+ groups (6.7 and 5.5 mm, respectively). The treatment difference in EDS was similar in the PM− and PM+ groups (− 5.5 and − 4.1, respectively).

Conclusions: OC-01 (varenicline solution) nasal spray demonstrated similar efficacy in promoting natural tear production and improving symptoms in both PM− and PM+ groups. As menopausal-related hormonal changes may be associated with more severe DED, these results may support OC-01 (varenicline solution) nasal spray as an effective treatment for DED in women regardless of presenting menopausal status.

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Trial Registration: Post hoc subgroup analysis of data integrated from ONSET-1 (ClinicalTrials.gov identifier NCT03636061) and ONSET-2 (ClinicalTrials.gov identifier NCT04036292).

Keywords: Dry eye disease; Menopause; OC-01 (varenicline solution) nasal spray; Trigeminal-parasympathetic pathway; Tyrvaya

Key Summary Points

Why carry out this study?

Women are disproportionately impacted by dry eye disease, and this is known to be further exacerbated by menopause. There is an unmet need for effective dry eye disease treatments in the postmenopausal population.

OC-01 (varenicline solution) nasal spray is a potent partial agonist of nicotinic acetylcholine receptors, which is believed to activate the trigeminal-parasympathetic pathway, promoting endogenous production of the tear film.

Because postmenopausal women have potentially diminished tear film production, this study was conducted to assess the treatment effect of OC-01 (varenicline solution) nasal spray in postmenopausal women versus women who were not yet postmenopausal.

What was learned from this study?

In this post hoc analysis of 449 female participants, the treatment effect for OC-01 (varenicline solution) as compared to vehicle control was not statistically significantly different ($p > 0.05$), demonstrating similar efficacy in both the postmenopausal and the non-postmenopausal subgroups.

These data suggest that OC-01 (varenicline solution) nasal spray is effective for the treatment of dry eye disease in women regardless of presenting menopausal status.

INTRODUCTION

Dry eye disease (DED) is a common ocular disorder characterized by an unstable and/or deficient tear film resulting in symptoms ranging from mild discomfort to vision loss [1]. DED is highly prevalent, with estimates ranging from 5% to 50% in various studies [2]. Risk factors include female sex, advancing age, and environmental influences [2–4]. Women are impacted by DED at a disproportionate rate, are diagnosed at an earlier age, and generally suffer more pronounced symptoms as compared with men [5]. Additionally, DED is known to be associated with both menopause and pregnancy [6], suggesting that changes in hormone levels may result in disruption of ocular surface homeostasis.

Hormonal imbalance has been recognized as one of the factors associated with the development of DED [7]. It is well established that sex hormones—primarily including estrogens, androgens, and progestogens—exert an influence on the lacrimal and meibomian glands, both key elements of the lacrimal functional unit (LFU) [8–11]. Androgens in particular seem to be responsible for much of the sex-related disease susceptibility of the LFU [10]. Changes in the balance of estrogens and androgens that occur in the menopausal and postmenopausal age group may impact production of all components of the tear film including aqueous and mucins from the lacrimal gland, lipids from the meibomian glands, and mucins from the conjunctival goblet cells [12–15]. Some preclinical data suggest androgen, estrogen, and/or progesterone mRNAs have been detected in the LFU tissues [16]. Diminished androgen levels have been associated with lacrimal gland dysregulation resulting in aqueous tear deficiency [17, 18], and women are prone to such diminished levels during menopause [19]. In a similar capacity, the acinar epithelial cells within meibomian glands contain receptors that are regulated by androgens [20]. Reduced levels of 5α-dihydrotestosterone, a potent androgen, may lead to attenuated glandular activity, size, and lipid release [20]; this may serve to further

destabilize the tear film, giving rise to evaporative dry eye disease.

The impact of menopause on DED is also evident clinically. In a recent observational study of nearly 2000 peri- or postmenopausal women aged 45–79 years, the prevalence of DED as measured by the Ocular Surface Disease Index© [OSDI©] was 79%, of whom 38% had severe DED; additionally, postmenopausal women had poorer vision-related quality of life compared to perimenopausal women [21]. In contrast, only 5.7% of women under the age of 50 were found to have DED in the Women's Health Study [4].

OC-01 (varenicline solution) nasal spray 0.03 mg (TYRVAYA®; Oyster Point Pharma®) is a new treatment for DED. Approved by the US Food and Drug Administration (FDA) in 2021 [22], OC-01 (varenicline solution) nasal spray is a potent partial agonist of nicotinic acetylcholine receptors (nAChRs) [23] along the trigeminal nerve branches in the nasal mucosa [24, 25]. Application of OC-01 (varenicline solution) nasal spray activates the trigeminal-parasympathetic pathway by binding to nAChRs of the anterior ethmoid nerve in the nasal mucosa which in turn promotes endogenous production of the essential layers of the precorneal tear film: aqueous and mucins from the lacrimal gland, lipids from the meibomian glands, and mucins from conjunctival goblet cells [26–30]. Randomized, vehicle-controlled clinical trials demonstrated the efficacy and safety of OC-01 (varenicline solution) nasal spray for the treatment of DED [26–28]. Because postmenopausal women are known to have more severe DED and potentially diminished endogenous production of the essential layers of the tear film, it is important to assess the efficacy of OC-01 (varenicline solution) nasal spray treatment in women on the basis of menopausal status. In this post hoc analysis of pooled data from the phase 2b ONSET-1 trial [27] and phase 3 ONSET-2 trial [26], we compare the treatment effect of OC-01 (varenicline solution) nasal spray to vehicle control in the subgroup of postmenopausal women (PM+) versus women who were not yet postmenopausal (PM−).

METHODS

This was a post hoc subgroup analysis of the integrated data from the phase 2b ONSET-1 trial and the phase 3 ONSET-2 trial characterizing the efficacy and safety of OC-01 (varenicline solution) nasal spray versus vehicle control on the signs and symptoms of DED, both of which have been reported previously [26, 27]. For both trials, institutional review board (Alpha IRB, San Clemente, CA) approval was obtained and the study was conducted in compliance with the ethical principles of the Helsinki Declaration of 1964 and International Council for Harmonisation Good Clinical Practice. All patients provided written informed consent before participation. Both trials randomized patients with DED (key eligibility criteria included Schirmer test score [STS] $\leq$ 10 mm and OSDI© score $\geq$ 23) to receive OC-01 (varenicline solution) nasal spray in various concentrations or vehicle control in each nostril twice daily. Also, subjects in both studies were permitted to use artificial tears as desired in conjunction with the prescribed treatment, in order to simulate real-world conditions. Key endpoints included mean changes from baseline in STS and eye dryness score (EDS) as well as the percentage of eyes achieving a $\geq$ 10 mm improvement from baseline in STS, all assessed at week 4. In both trials, STS was performed with anesthesia in standard fashion and assessed after 5 min. The EDS was obtained by asking participants to rate their eye dryness symptoms on a 100-mm visual analog scale (0 = no discomfort, 100 = maximal discomfort).

The purpose of this analysis was to compare key outcomes in female participants of the ONSET-1 and ONSET-2 trials as defined by baseline menopausal status. The data set for this analysis consisted of female subjects randomized to receive OC-01 (varenicline solution) nasal spray 0.03 mg (the FDA approved dose) or vehicle control from the two pivotal ONSET trials. After exclusion of self-reported surgically sterile women (to eliminate potential confounding effects of concurrent oophorectomy), women who self-reported being not of childbearing potential because of menopause were

included in the PM+, and all other women were included in the PM− group. Data from both trials were integrated.

This analysis follows the recommended methodology for the reporting of subgroup analyses in clinical trials, namely that treatment–vehicle control *p* values were not calculated as subgroups and were not prespecified [31]. Results are reported as 95% confidence intervals. The consistency of treatment effect was explored for three outcomes from the primary and secondary measures in the ONSET-1 and ONSET-2 pivotal studies from baseline to week 4: (1) mean change in STS (primary outcome measure in ONSET-1); (2) proportion of patients achieving ≥ 10 mm on STS (primary outcome measure in ONSET-2), and; (3) mean change in EDS. STS data were analyzed from one eye per participant; the study eye was the qualifying eye or, if both qualified, the eye with worse DED at baseline. EDS was a patient-reported outcome. For each of these three outcomes, the consistency of treatment effect, or no interaction, was explored across subgroups using interaction terms in models employing the full data sets. The term "no interaction" is defined as follows: no statistically significant ($p > 0.05$) difference in the treatment effect, i.e., OC-01 (varenicline solution) nasal spray 0.03 mg treatment outcome minus vehicle control outcome, between the PM+ and the PM− subgroups. Exploratory post hoc evaluated subgroups are not powered for statistical significance testing; therefore, differences in treatment effects on tests for interaction will be presented.

Least-squares (LS) mean changes from baseline in STS and EDS were analyzed with analysis of covariance (ANCOVA) models that included baseline STS, EDS, inferior corneal fluorescein staining (ICFS), age, and race as covariates. The odds of achieving a ≥ 10 mm improvement in STS was assessed using logistic regression modeling with the same covariates. Treatment–subgroup interaction terms were included in models to test treatment effect consistency. The level of significance for interaction was $p > 0.05$. Separately in PM− and PM+ groups, LS mean treatment–vehicle control differences in STS and EDS were estimated, as were odds ratios for ≥ 10 mm STS improvement, and 95% confidence intervals (95% CI) constructed around these point estimates. In order to evaluate the influence of hormone replacement therapy (HRT) on outcomes, sensitivity analyses were conducted using the same models with the addition of HRT as a covariate. The small sample size of HRT users precluded any meaningful analysis of HRT effects.

RESULTS

Overall, 449 female participants in the ONSET-1 and ONSET-2 trials randomized to treatment with OC-01 (varenicline solution) nasal spray 0.03 mg or vehicle control were included in this analysis: 242 (53.9%) in the PM+ group and 207 (46.1%) in the PM− group. Demographic and baseline DED severity data are provided in Table 1 for each group. Women in the PM− group were younger than women in the PM+ group, and had higher mean baseline STS. No other notable differences between the groups were observed.

The treatment–menopausal status interaction term in the STS ANCOVA model was not statistically significant ($p > 0.05$), indicating consistency of the OC-01 (varenicline solution) nasal spray treatment effect [OC-01 (varenicline solution) − vehicle control] was demonstrated between the PM+ and PM− subgroups. As this was a post hoc subgroup analysis, statistical significance (i.e., *p* values) will not be reported; instead treatment effects on tests for interaction will be presented along with effect estimates (95% confidence intervals). Mean STS at baseline, mean change from baseline (CFB), and the LS mean treatment–vehicle control difference in CFB are provided for both groups by treatment in Table 2.

The proportion of subjects achieving STS improvements of ≥ 10 mm from baseline to week 4 is shown in Fig. 1. In the PM+ group, this outcome was achieved by 46.2% of OC-01 (varenicline solution) nasal spray-treated women and 24.6% of vehicle control-treated women; in the PM− group, corresponding rates were 58.0% and 30.4%, respectively. The odds (odds ratio [95% confidence interval]) of

Table 1 Subject demographics and baseline ocular characteristics by group

	Postmenopausal (PM+) (*n* = 242)	**Not postmenopausal (PM−) (*n* = 207)**
Age (years), mean (SD)	63.7 (8.7)	55.5 (14.6)
Ethnicity, *n* (%)		
White	213 (88.0)	176 (85.0)
Nonwhite	29 (12.0)	31 (15.0)
STS (mm), mean (SD)	4.6 (2.9)	5.2 (2.9)
EDS, mean (SD)	60.3 (21.1)	58.9 (21.9)
ICFS, mean (SD)	1.7 (0.7)	1.8 (0.6)
Treatment assignment, *n* (%)		
OC-01 (varenicline solution) nasal spray 0.03 mg	120 (49.6)	102 (49.3)
Vehicle control	122 (50.4)	105 (50.7)

Table 2 STS and EDS outcomes at week 4 by treatment in the PM+ and PM− subgroups

	Postmenopausal (PM+) (*n* = 242)			**Not postmenopausal (PM−) (*n* = 207)**		
	Baseline	**CFB**	**Treatment–vehicle control difference[a] in CFB, LSM (95% CI)**	**Baseline**	**CFB**	**Treatment–vehicle control difference[a] in CFB, LSM (95% CI)**
STS (mm), mean (SD)						
OC-01	4.5 (2.9)	10.6 (9.8)	5.5 (3.3, 7.7)	5.1 (2.7)	13.7 (10.2)	6.7 (4.1, 9.3)
Vehicle	4.6 (2.9)	5.5 (6.9)		5.2 (3.0)	7.2 (8.3)	
EDS, mean (SD)						
OC-01	61.8 (20.6)	− 21.0 (29.1)	− 4.1 (− 10.6, 2.5)	57.7 (22.4)	− 18.6 (29.5)	− 5.5 (− 12.3, 1.3)
Vehicle	58.8 (21.7)	− 14.7 (28.3)		60.0 (21.5)	− 13.5 (25.1)	

CFB change from baseline, *CI* confidence interval, *EDS* eye dryness score, *ICFS* inferior corneal fluorescein staining score, *LSM* least-squares mean, *STS* Schirmer test score

[a]Treatment–vehicle control difference from ANCOVA models; all treatment–subgroup interaction terms in ANCOVA models were insignificant ($p > 0.05$)

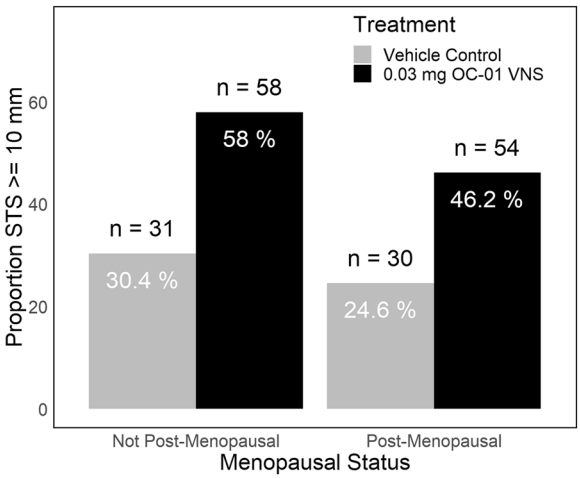

Fig. 1 Proportion of PM− and PM+ eyes in each treatment group that achieved ≥ 10 mm improvement in STS at week 4. Intent to treat population. Odds of ≥ 10 mm increase change from baseline Schirmer's test score from logistic regression model. Data presented with imputation using last observation carried forward (LOCF) for missing assessments. All comparisons made to vehicle control groups within subgroups. Post hoc analysis. Odds of achieving ≥ 10 mm increase in Schirmer's test score (treatment–vehicle control difference) in non-menopausal cohort (PM−) 3.45 (95% CI 1.90, 6.40), and in menopausal cohort (PM+) 3.25 (95% CI 1.83, 5.90). All treatment–subgroup interaction terms in ANCOVA models were insignificant ($p > 0.05$)

achieving a ≥ 10 mm improvement in STS with OC-01 (varenicline solution) nasal spray versus vehicle control treatment were 3.3 (1.8, 5.9) in the PM+ group and 3.5 (1.9, 6.4) in the PM− group.

In the EDS analysis, the treatment–menopausal status interaction term in the ANCOVA model was not statistically significant ($p > 0.05$), indicating no difference in treatment effect between the PM+ and PM− groups. Mean EDS at baseline, mean CFB, and the LS mean treatment difference (OC-01 [varenicline solution] nasal spray minus vehicle control) in CFB are provided for both groups by treatment in Table 2. The CFB treatment difference in EDS was similar in the PM+ and PM− groups (− 5.5 and − 4.1, respectively). Nineteen PM+ women and 10 PM− women reported HRT use, but inclusion of HRT as a covariate in models for EDS and STS did not alter any findings (data not shown).

DISCUSSION

As has been well established, the most significant risk factors for DED are age and being of female sex. Though women have a greater prevalence of DED than men in the literature, differences become significant only with age, which is known to induce profound systemic changes as well as impact to the LFU. The lacrimal gland itself is affected by aging, with tear abnormalities increasing from the fourth to eighth decade of life and having a greater prevalence in women than in men during this time [2–4, 32–35]. Among women, menopause is an additional risk factor for more severe DED, as alterations in serum levels of hormones are thought to play an etiological role in DED in this population [12, 36, 37]. The effect of HRT on DED symptoms in postmenopausal women has not been consistent among various studies and meta-analyses [14, 38, 39].

It has been postulated that an estrogen imbalance contributes to the dry eye disease etiology, and histological evidence supports that estrogen receptors are observed within glandular tissues of human lacrimal and meibomian glands, as well as the cornea and the conjunctiva [40–42]. However, recent phase 2 evidence with a topical estradiol ophthalmic formulation in postmenopausal women with moderate-to-severe dry eye disease did not meet its primary endpoint of improving Schirmer's II test score (with anesthesia) at day 90 compared to placebo [43]. Additionally, a recent systematic review of HRT use in postmenopausal women with dry eye disease did not demonstrate significance in tear breakup time outcomes at 3 and 6 months [39]. These together may indicate that an optimal hormonal balance of estrogen and androgen following either topical ophthalmic estrogen therapy or systemic hormonal therapy provides no clear benefit in achieving improvements for unstable or deficient tear film in DED. Additional research employing randomized controlled trials is needed to elucidate any benefit with HRT in the management of dry eye disease. Therefore, an unmet need remains in treating patients with worsened dry eye disease as

related to menopausal status. Therapies that demonstrate consistency in improvement in the clinical signs and symptoms of dry eye disease regardless of menopausal status are needed.

This post hoc analysis of integrated data from the phase 2b ONSET-1 and phase 3 ONSET-2 trials indicates OC-01 (varenicline solution) nasal spray was equally effective in women with DED who were and were not postmenopausal at the time of study participation. Considering age, sex, and menopause status as risk factors for DED as previously established, it is important to note that the post hoc analysis subject population included approximately 80% female enrolled subjects with a mean age of 60 years. Baseline characteristics were similar between the two groups, with the exceptions of age and baseline STS. Age difference was expected given that onset of menopause is highly correlated with age. A difference in baseline STS (indicating less severe disease in the PM− group) may suggest that these women had less to gain from therapy, although this was not observed in this analysis. Outcomes of this post hoc analysis suggest improvements were demonstrated in women regardless of menopausal status and are similar to outcomes reported in the pivotal phase 2b ONSET-1 and phase 3 ONSET-2 trials [26, 27]. Although postmenopausal women generally exhibit more severe DED compared to their premenopausal counterparts at clinical presentation, these findings may support the benefits of OC-01 (varenicline solution) nasal spray use for women across the spectrum of menopausal status.

This post hoc subgroup analysis is subject to inherent limitations and did not account for all possible comorbidities that could impact dry eye disease (i.e., autoimmune diseases). The analyses inform on tear production (STS with anesthesia) and symptom efficacy measure outcomes (EDS) that were assessed as primary and secondary endpoints in the pivotal studies. As a result of the confounding factors of numerous efficacy measurements at the same visit, the studies were not designed to inform on other parameters (i.e., tear breakup time, tear meniscus height). The analysis is strengthened by utilizing a large, robust data set collected in two controlled, prospective, randomized trials. Baseline imbalances in both age and STS between the PM+ and PM− groups were expected and observed, but inclusion of these variables in the ANCOVA and logistic regression models controlled for these inequalities. The impact of such baseline imbalances is likely not clinically significant given the similarity of treatment effect in both groups. The small number of HRT users precluded evaluation of effect modification by HRT use in this patient population.

CONCLUSION

OC-01 (varenicline solution) nasal spray demonstrated similar efficacy as assessed by the dry eye disease sign and symptom measures in the overall pivotal trial study design, illustrating an increase in natural tear film production (STS with anesthesia) and improvement in symptoms (EDS) in both postmenopausal women and women who were not postmenopausal. As menopause-related hormonal changes may be associated with more severe DED, these data suggest OC-01 (varenicline solution) nasal spray is effective for the treatment of DED in women regardless of presenting menopausal status.

ACKNOWLEDGEMENTS

Funding. Oyster Point Pharma, Inc. (Princeton, NJ). The sponsor participated in the study design, execution of the study, data collection, management, and interpretation; sponsored third-party writing assistance; and funded the journal's Rapid Service Fees.

Medical Writing and Other Assistance. The authors acknowledge that assistance in preparing this manuscript was provided by Hypotony Holdings LLC (Tony Realini, MD, MPH), with funding from Oyster Point Pharma, Inc. Additionally, the authors offer their utmost thanks and appreciation to those individuals who served as study participants in these pivotal clinical trials.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. Lisa M. Nijm, Dagny Zhu, Mandy Hemphill, Gretchen Blemker, Laura Hendrix, Alan G. Kabat, and Andrea Gibson made substantial contributions to the conception, design, acquisition, and/or interpretation of data. Additionally, all authors participated in the drafting and revising of this manuscript for important intellectual content, and approved the final version to be published. Data analysis was performed by Laura Hendrix and Andrea Gibson.

Prior Presentation. Portions of these data were presented at the following: (1) Women in Ophthalmology Annual Meeting, August 25–28, 2022 in Monterey, CA, USA; (2) World Cornea Congress, September 28–29, 2022 in Chicago, IL, USA, and; (3) American Academy of Ophthalmology Annual Meeting, September 30-October 3, 2022 in Chicago, IL, USA.

Disclosures. Lisa Nijm declares that she is a consultant and speaker for Oyster Point Pharma, Inc. Dagny Zhu declares that she has no competing interests. Mandy Hemphill, Gretchen Blemker, Laura Hendrix, Alan G. Kabat and Andrea Gibson are employees and shareholders of Oyster Point Pharma, Inc.

Compliance with Ethics Guidelines. The authors acknowledge Institutional Review Board (Alpha IRB, San Clemente, CA) approval of these trials, which were conducted in accordance with the Helsinki Declaration of 1964 and its later amendments. All subjects provided informed consent to participate in the study.

Data Availability. The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Tsubota K, Pflugfelder SC, Liu Z, et al. Defining dry eye from a clinical perspective. Int J Mol Sci. 2020;21:9271.

2. Stapleton F, Alves M, Bunya VY, et al. TFOS DEWS II epidemiology report. Ocul Surf. 2017;15:334–65.

3. Schaumberg DA, Dana R, Buring JE, Sullivan DA. Prevalence of dry eye disease among US men: estimates from the Physicians' Health Studies. Arch Ophthalmol. 2009;127:763–8.

4. Schaumberg DA, Sullivan DA, Buring JE, Dana MR. Prevalence of dry eye syndrome among US women. Am J Ophthalmol. 2003;136:318–26.

5. Matossian C, McDonald M, Donaldson KE, et al. Dry eye disease: consideration for women's health. J Womens Health (Larchmt). 2019;28:502–14.

6. Asiedu K, Kyei S, Adanusa M, et al. Dry eye, its clinical subtypes and associated factors in healthy pregnancy: a cross-sectional study. PLoS ONE. 2021;16: e0258233.

7. Huang R, Su C, Fang L, et al. Dry eye syndrome: comprehensive etiologies and recent clinical trials. Int Ophthalmol. 2022. https://doi.org/10.1007/s10792-022-02320-7.

8. Pontelli RCN, Rocha BA, Garcia DM, et al. Endocrine disrupting chemicals associated with dry eye syndrome. Ocul Surf. 2020;18:487–93.

9. Nuzzi R, Caselgrandi P. Sex hormones and their effects on ocular disorders and pathophysiology: current aspects and our experience. Int J Mol Sci. 2022;23(6):3269.

10. Sullivan DA, Rocha EM, Aragona P, et al. TFOS DEWS II sex, gender, and hormones report. Ocul Surf. 2017;15:284–333.

11. Rapoport Y, Singer JM, Ling JD, et al. A comprehensive review of sex disparities in symptoms, pathophysiology, and epidemiology of dry eye syndrome. Semin Ophthalmol. 2016;31:325–36.

12. Sriprasert I, Warren DW, Mircheff AK, Stanczyk FZ. Dry eye in postmenopausal women: a hormonal disorder. Menopause. 2016;23:343–51.

13. Peck T, Olsakovsky L, Aggarwal S. Dry eye syndrome in menopause and perimenopausal age group. J Midlife Health. 2017;8:51–4.

14. Liu C, Liang K, Jiang Z, Tao L. Sex hormone therapy's effect on dry eye syndrome in postmenopausal women: a meta-analysis of randomized controlled trials. Medicine (Baltimore). 2018;97:e12572.

15. Paulsen F, Langer G, Hoffmann W, Berry M. Human lacrimal gland mucins. Cell Tissue Res. 2004;316:167–77.

16. Wickham LA, Gao J, Toda I, et al. Identification of androgen, estrogen and progesterone receptor mRNAs in the eye. Acta Ophthalmol Scand. 2000;78:146–53.

17. Versura P, Giannaccare G, Campos EC. Sex-steroid imbalance in females and dry eye. Curr Eye Res. 2015;40:162–75.

18. Truong S, Cole N, Stapleton F, Golebiowski B. Sex hormones and the dry eye. Clin Exp Optom. 2014;97:324–36.

19. Yasui T, Matsui S, Tani A, et al. Androgen in postmenopausal women. J Med Invest. 2012;59:12–27.

20. Sullivan DA, Sullivan BD, Evans JE, et al. Androgen deficiency, meibomian gland dysfunction, and evaporative dry eye. Ann NY Acad Sci. 2002;966:211–22.

21. Garcia-Alfaro P, Garcia S, Rodriguez I, Verges C. Dry eye disease symptoms and quality of life in perimenopausal and postmenopausal women. Climacteric. 2021;24:261–6.

22. Drugs@FDA: TYRVAYA. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/213978Orig1s000ltr.pdf. Accessed 28 Oct 2021.

23. Rollema H, Chambers LK, Coe JW, et al. Pharmacological profile of the alpha4beta2 nicotinic acetylcholine receptor partial agonist varenicline, an effective smoking cessation aid. Neuropharmacology. 2007;52:985–94.

24. Alimohammadi H, Silver WL. Evidence for nicotinic acetylcholine receptors on nasal trigeminal nerve endings of the rat. Chem Senses. 2000;25:61–6.

25. Thuerauf N, Markovic K, Braun G, et al. The influence of mecamylamine on trigeminal and olfactory chemoreception of nicotine. Neuropsychopharmacology. 2006;31:450–61.

26. Wirta D, Vollmer P, Paauw J, et al. Efficacy and safety of OC-01 (varenicline) nasal spray on signs and symptoms of dry eye disease: the ONSET-2 phase 3, randomized trial. Ophthalmology. 2022;129:379–87.

27. Wirta D, Torkildsen G, Boehmer B, et al. ONSET-1 phase 2b randomized trial to evaluate the safety and efficacy of OC-01 (varenicline solution) nasal spray on signs and symptoms of dry eye disease. Cornea. 2022;41:1207–16.

28. Quiroz-Mercado H, Hernandez-Quintela E, Chiu KH, et al. A phase II randomized trial to evaluate the long-term (12-week) efficacy and safety of OC-01 (varenicline solution) nasal spray for dry eye disease: the MYSTIC study. Ocul Surf. 2021;24:15–21.

29. clinicaltrials.gov. Efficacy of OC-01 nasal spray on goblet cell and meibomian gland stimulation. https://www.clinicaltrials.gov/ct2/show/study/NCT03688802. Accessed 23 Mar 2022.

30. Dieckmann G, Cox SM, Lopez MJ, et al. A single administration of OC-01 (varenicline solution) nasal spray induces short-term alterations in conjunctival goblet cell in patients with dry eye disease. Ophthalmol Ther. 2022;11:1551–61.

31. Wang R, Lagakos SW, Ware JH, et al. Statistics in medicine—reporting of subgroup analyses in clinical trials. N Engl J Med. 2007;357:2189–94.

32. Bukhari AA, Basheer NA, Joharjy HI. Age, gender, and interracial variability of normal lacrimal gland volume using MRI. Ophthalmic Plast Reconstr Surg. 2014;30:388–91.

33. El-Fadaly AB, El-Shaarawy EA, Rizk AA, et al. Age-related alterations in the lacrimal gland of adult

albino rat: a light and electron microscopic study. Ann Anat. 2014;196:336–51.

34. Nasu M, Matsubara O, Yamamoto H. Post-mortem prevalence of lymphocytic infiltration of the lacrymal gland: a comparative study in autoimmune and non-autoimmune diseases. J Pathol. 1984;143:11–5.

35. Obata H, Yamamoto S, Horiuchi H, Machinami R. Histopathologic study of human lacrimal gland. Statistical analysis with special reference to aging. Ophthalmology. 1995;102:678–86.

36. Golebiowski B, Badarudin N, Eden J, et al. Does endogenous serum oestrogen play a role in meibomian gland dysfunction in postmenopausal women with dry eye? Br J Ophthalmol. 2017;101:218–22.

37. Ablamowicz AF, Nichols JJ, Nichols KK. Association between serum levels of testosterone and estradiol with meibomian gland assessments in postmenopausal women. Invest Ophthalmol Vis Sci. 2016;57:295–300.

38. Hao Y, Xiaodan J, Jiarui Y, Xuemin L. The effect of hormone therapy on the ocular surface and intraocular pressure for postmenopausal women: a systematic review and meta-analysis of randomized controlled trials. Menopause. 2020;27:929–40.

39. Dang A, Nayeni M, Mather R, Malvankar-Mehta MS. Hormone replacement therapy for dry eye disease patients: systematic review and meta-analysis. Can J Ophthalmol. 2020;55:3–11.

40. Rocha EM, Wickham LA, da Silveira LA, et al. Identification of androgen receptor protein and 5alpha-reductase mRNA in human ocular tissues. Br J Ophthalmol. 2000;84:76–84.

41. Esmaeli B, Harvey JT, Hewlett B. Immunohistochemical evidence for estrogen receptors in meibomian glands. Ophthalmology. 2000;107:180–4.

42. Schirra F, Suzuki T, Dickinson DP, et al. Identification of steroidogenic enzyme mRNAs in the human lacrimal gland, meibomian gland, cornea, and conjunctiva. Cornea. 2006;25:438–42.

43. Schmidl D, Szalai L, Kiss OG, et al. A phase II, multicenter, randomized, placebo-controlled, double-masked trial of a topical estradiol ophthalmic formulation in postmenopausal women with moderate-to-severe dry eye disease. Adv Ther. 2021;38:1975–86.