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Lotilaner Ophthalmic Solution, 0.25%, for the Treatment of *Demodex* Blepharitis: Results of a Prospective, Randomized, Vehicle-Controlled, Double-Masked, Pivotal Trial (Saturn-1)

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Purpose: The purpose of this study was to evaluate the safety and efficacy of lotilaner ophthalmic solution, 0.25%, compared with vehicle for the treatment of *Demodex* blepharitis.

Methods: In this prospective, randomized, controlled, double-masked, phase 2b/3 clinical trial, 421 patients with *Demodex* blepharitis were randomly assigned in a 1:1 ratio to receive either lotilaner ophthalmic solution, 0.25% (study group), or vehicle without lotilaner (control group) bilaterally, twice daily for 43 days. Patients were evaluated at days 8, 15, 22, and 43. Outcome measures were complete collarette cure (collarette grade 0), clinically meaningful collarette cure (grade 0 or 1), mite eradication (0 mites/lash), erythema cure (grade 0), composite cure (grade 0 for collarettes/erythema), and drop comfort. Adverse events were also evaluated.

Results: At day 43, the study group achieved a statistically significantly higher proportion of patients with clinically meaningful collarette cure (81.3% vs. 23.0%; $P < 0.0001$), complete collarette cure (44.0% vs. 7.4%; $P < 0.0001$), mite eradication (67.9% vs. 17.6%; $P < 0.0001$), erythema cure (19.1% vs. 6.9%; $P = 0.0001$), and composite cure (13.9% vs. 1.0%; $P < 0.0001$) than the control group. Nearly 92.0% of patients rated the study drop as neutral to very comfortable. All ocular adverse events in the study group were mild, with the most common being instillation site pain.

Conclusions: Twice-daily treatment with a novel lotilaner ophthalmic solution, 0.25% for 43 days, is safe and effective for the treatment of *Demodex* blepharitis compared with the vehicle control.

Key Words: Demodex blepharitis, lotilaner, lotilaner ophthalmic solution, 0.25%, collarettes, cylindrical dandruff, TP-03, lid margin disease

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Demodex mites are the most common ectoparasite found on the human skin.[1–3] The mites are associated with dermatologic and ocular diseases including blepharitis.[4–6] Reports in the literature suggest that 45% of patients with blepharitis have concomitant *Demodex* infestation or pathologic overgrowth of *Demodex* mites in the eyelid tissue.[7] In a recent observational study (Titan), the prevalence of collarettes, the pathognomonic sign of *Demodex* blepharitis, among patients seeking eye care for any reason was reported as 58%.[8] This could mean that as many as 25 million U.S. adults of the 45 million who visit eye care professionals annually have *Demodex* blepharitis.[9] Despite its high prevalence, *Demodex* mite infestation is often overlooked as a cause of blepharitis.[7,10,11]

In *Demodex* blepharitis, mites inhabit the eyelash follicles, where they cause damage through mechanical, chemical, and bacterial mechanisms. First, because the mites feed on sebum, they cause microscopic epithelial abrasions, resulting in epithelial hyperplasia and reactive hyperkeratinization.[1,4,12] Second, digestive enzymes and debris left behind by the mites can provoke an inflammatory response.[13–16] Finally, bacteria carried by the mites or transferred from the skin during eye rubbing to relieve blepharitis itch contribute to higher microbial counts in eyes with *Demodex* blepharitis, which then leads to an undesirable inflammatory response.[15,17–19]

Mite overgrowth, with all abovementioned mechanisms of damage, results in the formation of collarettes (also known as cylindrical dandruff), the pathognomonic sign for *Demodex* blepharitis.[10,20–23] Collarettes composed of undigested material, keratinized cells, eggs, and dead mites and may even contain embedded, live mites.[24] Other clinical manifestations of *Demodex* blepharitis include tear film disruptions, meibomian gland dysfunction, lid margin erythema, lid edema,

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eyelash misalignment or loss, recurrent chalazia and, more rarely, primary and recurrent pterygia, peripheral corneal vascularization, phlyctenule-like lesions, and corneal opacity.[25] *Demodex* blepharitis is also implicated as a comorbid ocular disease with other inflammatory diseases, such as rosacea, blepharokeratitis, and blepharoconjunctivitis.[4]

Currently, there are no FDA-approved treatments for *Demodex* blepharitis. Management may include the use of lid scrubs and warm compresses as well as mechanical removal of the eyelash collarettes, typically as an in-office procedure.[4] Over-the-counter *Demodex* shampoos and lid hygiene products containing tea tree oil (TTO) have shown varying and questionable efficacy in treating *Demodex* blepharitis.[24,26–28] Known side effects of topical tea tree oil, including contact dermatitis, ocular irritation, and allergic reactions, have limited its use.[12,29,30] In addition, terpinen-4-ol (T4O), one of the components of tea tree oil, has been reported to be toxic to human meibomian gland epithelial cells in vitro.[31]

Lotilaner is a well-characterized, highly lipophilic, antiparasitic agent that paralyzes and eradicates *Demodex* mites by selectively inhibiting parasite-specific γ-aminobutyric acid chloride channels.[32] The safety and efficacy of lotilaner ophthalmic solution, 0.25% (TP-03, Tarsus Pharmaceuticals Inc, Irvine CA), has been evaluated previously in humans in 2 single-arm[33,34] and 2 vehicle-controlled phase 2 studies with sample sizes ranging from 15 to 60 patients.[35,36] In these studies, lotilaner ophthalmic solution, 0.25%, was found to be well-tolerated, safe, and effective in reducing collarettes and mite density after 28-day or 42-day treatment regimens, with 42-day treatment yielding greater improvements in collarette grade and *Demodex* density.

Saturn-1 is the most recently completed clinical trial of the extensive program to evaluate lotilaner ophthalmic solution, 0.25%. The present Phase 2b/3 study was designed to compare the safety and efficacy of lotilaner ophthalmic solution, 0.25%, with vehicle control for the treatment of *Demodex* blepharitis in a large study population. This is the first of 2 planned pivotal studies; Saturn-2, the second pivotal study, has commenced enrollment.

MATERIALS AND METHODS

This randomized, double-masked, parallel, vehicle-controlled trial was conducted at 15 (Appendix 1) U.S. clinical sites (ClinicalTrials.gov Identifier: NCT04475432). This study adhered to the tenets of the Declaration of Helsinki and each site secured institutional review board (IRB) approval. All enrolled patients provided written informed consent using the IRB-approved informed consent forms.

Eligibility criteria for participating in this study included age 18 years or older, willingness to sign the informed consent and comply with the requirements of the study protocol, documented history of blepharitis due to *Demodex* infestation over the past year, and presence of all the following in at least one eye: 1) *Demodex* infestation with more than 10 lashes with collarettes present on the upper lid (collarette scale grade 2 or worse), 2) at least mild erythema of the upper eyelid margin, and 3) average mite density of ≥1.5 mites per lash (upper and lower eyelids combined). In addition, patients were required to have a corrected distance visual acuity (CDVA) better than or equal to 0.7 logMAR as assessed by the Early Treatment of Diabetic Retinopathy Study (ETDRS) scale in each eye at screening.

Patients were excluded if they had used any prescription antibacterial, antiparasitic, or anti-inflammatory steroid treatment or had used topical tea tree oil, hypochlorous acid, or any other lid hygiene products within the past 14 days or were unwilling to forego the use of lid hygiene products during this study. Patients were also excluded if they had used a topical prostaglandin analog (PGA) to promote eyelash growth within the past 30 days, had initiated PGA treatment for medical reasons within the past 30 days, or planned to change or discontinue PGA treatment during the study treatment phase. Patients were also excluded if they had used contact lenses, artificial eyelashes, or eyelash extensions within the past 7 days or were unwilling to forego the use of these products during this study. Patients with lid structural abnormalities; acute ocular infection; inflammation other than blepharitis; severe dry eye; hypersensitivity to lotilaner or any of the formulation components; unstable or uncontrolled cardiac, pulmonary, renal, oncological, neurological, metabolic, or other systemic conditions; and pregnancy/lactation were also excluded.

Patients who met the eligibility criteria were enrolled. Using a blocked randomization schedule, patients were randomly assigned in a 1:1 ratio to bilaterally receive either the TP-03 study medication (lotilaner ophthalmic solution, 0.25%) (study group) or the vehicle formulation without lotilaner (control group). At day 1 (baseline visit), the first dose of study medication or vehicle was administered in the clinic. Subsequent doses were applied by the patients at home, 1 drop in each eye twice daily (morning and evening). The dosing regimen continued for 43 days, and patients were evaluated at days 8, 15, 22, and 43. Both patient and site personnel performing study assessments were masked to the study medication throughout this study. Patients were not allowed to mechanically scrub or wipe their lids through the study duration until the final visit at day 43.

Collarettes were graded for each eyelid using the grading scale shown in Figure 1. Mite density (to determine mite eradication) was assessed by selecting and removing 2 or more lashes from each of the upper and lower eyelids, 1 lash from each half of each lid, using fine forceps. If present, lashes with collarettes were targeted for epilation. Targeted lashes were gently rotated on their axis and then extracted.[37,38] The lashes from each lid were placed in artificial tear drops on 4 separate glass slides. The number of *Demodex* mites observed and the number of lashes epilated were recorded, and mite density was calculated as the number of mites per lash. Mite eradication was defined as a mite density of 0 mites/lash. Erythema of the eyelid margin was graded on a scale from 0 to 3 (Fig. 2).

One eye of each patient was chosen as the analysis eye. If both eyes met the inclusion criteria, the eye with the higher mite density at the screening visit was considered the analysis eye; if both eyes had equal mite density, the right eye was the analysis eye.

The primary efficacy end point was complete collarette cure, based on a collarette grade of 0 (≤2 collarettes), of the

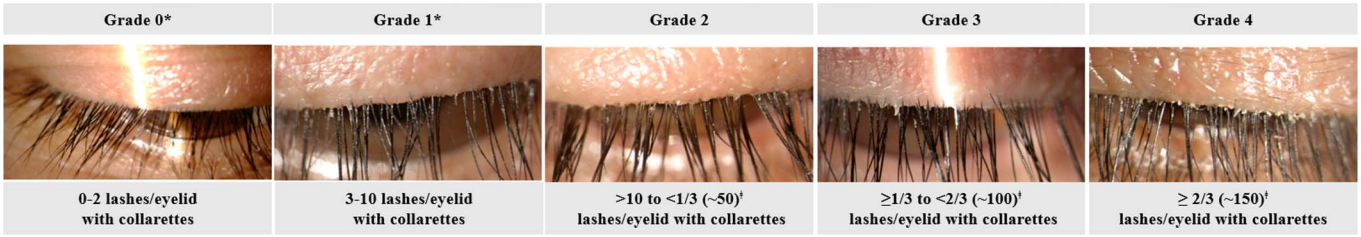

FIGURE 1. Grading scale (nonlinear) used for collarettes grading in each eyelid. *Grade 0–1: clinically meaningful; ǂfor an upper eyelid with 150 eyelashes, the number of eyelashes in upper eyelid may vary from 90 to 160.

upper eyelid of the analysis eye at day 43. The secondary efficacy end points (day 43) were mite eradication (0 mites/lash for the analysis eye) and composite cure, a combination of collarette and erythema grades (grade 0 for both collarettes and erythema for the upper eyelid of the analysis eye).

As shown previously by Gao et al,[22] a reduction in collarettes to ≤10 lashes is associated with reduced mite density and a clinically meaningful reduction in the severity of *Demodex* blepharitis. Therefore, in this study, clinically meaningful collarette cure (collarette grade of 0 or 1) was also evaluated as an additional parameter. Other parameters included mean collarette score for the upper eyelid of the analysis eye at baseline and each follow-up visit and mite density at baseline and at days 15, 22, and 43. Responder rates, defined as at least a 1-grade improvement in collarette grade and a mite density of 0.5 mites/lash or less, were also evaluated at each visit.

Safety parameters included assessment of adverse events and evaluation of any changes in CDVA, intraocular pressure, dilated fundus examination, endothelial cell assessments, corneal staining, and slitlamp biomicroscopy findings. CDVA was assessed at all visits using either the patient's own spectacles or a pinhole occluder, with an ETDRS visual acuity chart at a distance of 4 meters. The number of letters read correctly was used to compute the patient's logMAR CDVA. A change of more than 2 lines on the ETDRS chart (>0.2 logMAR) was considered clinically meaningful. Intraocular pressure was assessed at baseline and at day 43 using Goldmann or Perkins applanation tonometry. In a limited subset of patients (12 in the study group and 9 in the control group), central corneal endothelial cell density was determined at day 1 (before study drug instillation) and again at day 43 using noncontact specular microscopy. Fundus examination observations, performed at baseline and day 43, were graded as normal or abnormal for the vitreous, optic nerve, macula, retina, and choroid. Abnormal findings were categorized as clinically significant or not clinically significant.

Drop comfort was assessed at all visits. Patients rated the comfort of the study medications as very comfortable, slightly comfortable, neither comfortable nor uncomfortable, slightly uncomfortable, and very uncomfortable.

Sample size calculations were based on the response rates achieved in previous clinical studies of lotilaner ophthalmic solution, 0.25%, for the treatment of *Demodex* blepharitis. Assuming similar efficacy of lotilaner ophthalmic solution, 0.25%, and vehicle treatment as reported in the previous study[36] and 1-sided significance level of 0.025, a sample size of 300 patients (150 in each arm) would provide 99% power to establish the superiority of lotilaner ophthalmic solution, 0.25%, to vehicle in the patients meeting the primary efficacy end point. To account for a dropout rate of approximately 25% to 30% due to COVID-19, recruitment of 418 patients was planned.

All statistical analyses were performed using SAS (SAS Institute Inc, Cary NC). Continuous data were described using descriptive statistics (ie, n, mean and standard deviation), and categorical data were described using the patient count and percentage in each category. A two-sample *t* test or its nonparametric counterpart Wilcoxon rank-sum test was used as appropriate to assess the statistical significance of the

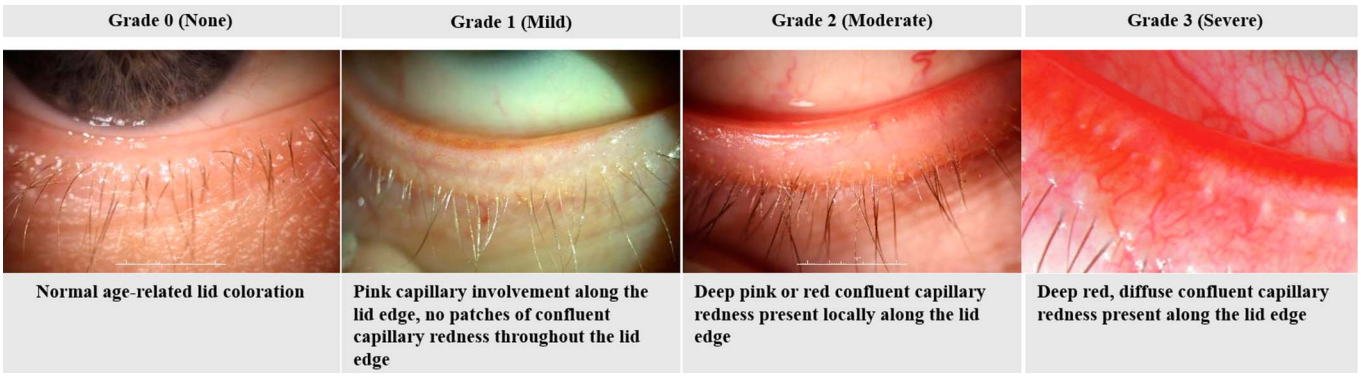

FIGURE 2. Lid margin erythema grading scale (nonlinear).

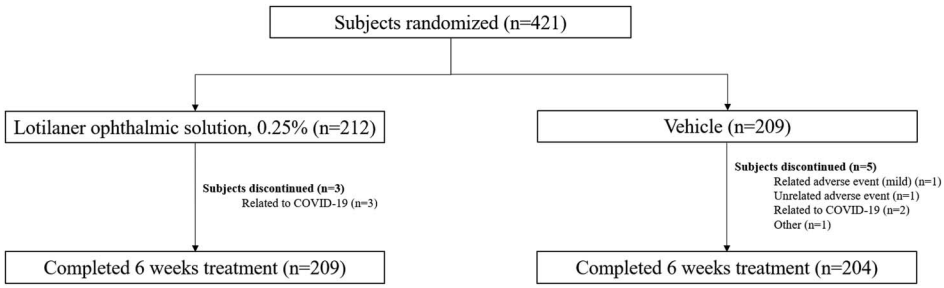

FIGURE 3. Patient disposition flowchart.

difference between treatment groups in the mean comparisons. The comparisons between the proportions were made using a difference in the proportions test. Comparisons were 1-sided using an α of 0.025.

RESULTS

A total of 421 patients were enrolled in this study, 212 in the study group and 209 in the control group. Eight patients (3 in the study group and 5 in the control group) were discontinued from this study before day 43 (Fig. 3). The mean age and demographic characteristics of all patients are presented in Table 1.

Collarette Cure and Collarette Grade

At day 43, 81.3% of patients in the study group achieved a clinically meaningful collarette cure (defined as a collarette grade of 0 or 1 in the upper eyelid of the analysis eye) compared with 23.0% in the control group ($P < 0.0001$) (Fig. 4). The proportion of patients in each group who achieved complete collarette cure (collarette grade of 0 in the upper eyelid of the analysis eye) at day 43 was 44.0% in the study group versus 7.4% in the control group ($P < 0.0001$) (Fig. 5).

Table 2 summarizes the mean collarette grades for the upper eyelid of the analysis eyes at each follow-up visit. The study group demonstrated a statistically significantly improved ($P < 0.0001$) collarette grade compared with the control group from day 8 onward. At day 43, 92.8% of patients in the study group versus 50.0% of patients in the control group demonstrated at least a 1-grade collarette improvement in the upper eyelid of the analysis eye ($P < 0.0001$) (Fig. 6).

Mite Eradication and Density

The proportion of patients in each group who achieved mite eradication (mite density of 0 mites/lash in the analysis eye) is shown in Figure 7. The proportion of study group patients achieving mite eradication was statistically significantly higher than in the control group at all visits at which mite density was measured from day 15 through day 43 ($P < 0.0001$).

Table 3 presents the mean mite density for the analysis eye at each follow-up visit. The study group demonstrated a statistically significantly lower ($P < 0.0001$) mite density compared with the control group at days 15, 22, and 43 (Table 3). At day 15, 91.7% of eyes in the study group had at least a 50.0% reduction in mite density, compared with 57.7% of the control group. At day 43, 94.7% of the eyes in the study group had mean mite density ≤0.5 mites/lash, compared with 35.8% in the control group (Fig. 8).

TABLE 1. Demographic and Pretreatment Characteristics of all Participants in the Study and Control Group

Characteristics	Lotilaner 0.25% (N = 212)	Vehicle (N = 209)
Age (yr) mean ± SD	66.1 ± 12.1	67.8 ± 12.6
Sex n (%)		
Male	89 (42.0%)	92 (44.0%)
Female	123 (58.0%)	117 (56.0%)
Ethnicity n (%)		
Hispanic or Latino	14 (6.6%)	11 (5.3%)
Not Hispanic or Latino	198 (93.4%)	198 (94.7%)
Race n (%)		
American Indian or Alaska Native	1 (0.5%)	1 (0.5%)
Asian	3 (1.4%)	2 (1.0%)
Black or African American	11 (5.2%)	16 (7.7%)
White	195 (92.0%)	187 (89.5%)
Multiple Race	2 (0.9%)	3 (1.4%)

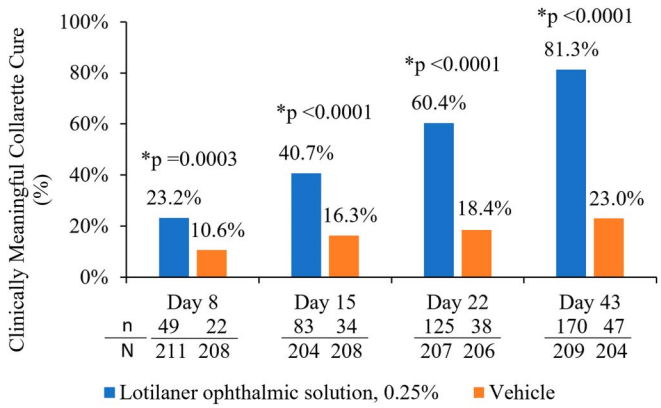

FIGURE 4. Proportion of patients with clinically meaningful collarette cure (grade 0–1, ≤10 collarettes) in the upper eyelid of the analysis eye in the study and control groups. (The full color version of this figure is available at www.corneajrnl.com.)

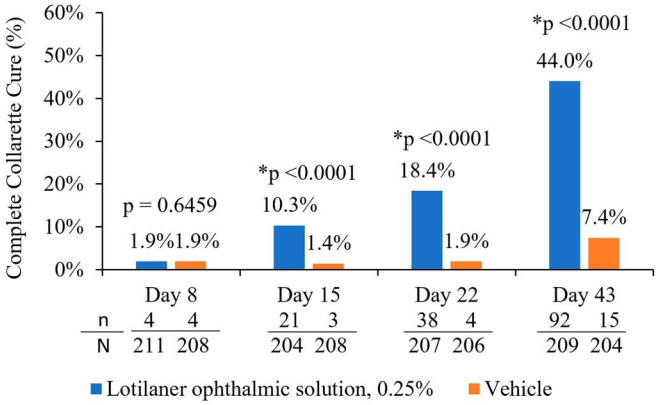

FIGURE 5. Proportion of patients with complete collarette cure (grade 0, ≤2 collarettes) in the upper eyelid of the analysis eye in the study and control groups. (The full color version of this figure is available at www.corneajrnl.com.)

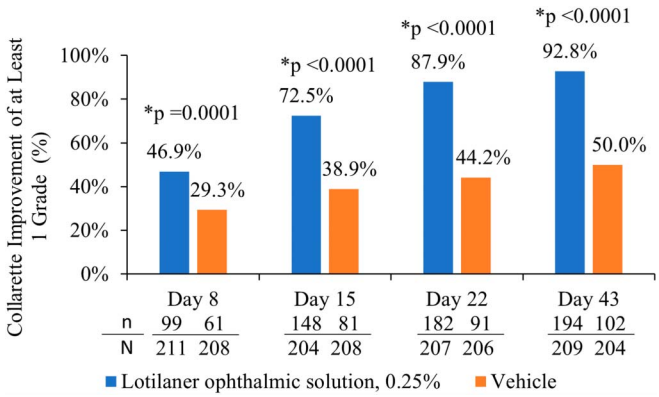

FIGURE 6. Proportion of patients with collarette improvement of at least 1 grade in the upper eyelid of the analysis eye in the study and control groups. (The full color version of this figure is available at www.corneajrnl.com.)

Erythema Cure

The mean erythema grade at baseline was 1.5 in both groups. The proportion of patients who achieved an erythema cure (grade 0 erythema) at day 43 was significantly higher in the study group compared with the control group (19.1% vs. 6.9%; $P = 0.0001$) (Fig. 9A). Similarly, the proportion of patients achieving at least a 1-grade improvement in erythema from baseline to day 43 was significantly higher (45.0%) in the study group compared with the control group (27.9%) ($P = 0.0002$) (Fig. 9B). The proportion of patients in each group who achieved a composite cure (grade 0 for collarettes and erythema) of the upper eyelid of the analysis eye at day 43 was 13.9%, which was significantly higher than the corresponding composite cure of 1.0% in the control group ($P < 0.0001$).

Drop Comfort

Figure 10 shows the proportion of patients in the study group who rated the drop as neutral to very comfortable at days 8, 15, 22, and 43. Most patients (91.9%) in the study group found the drops to be neutral to very comfortable at day 43. There was no significant difference in drop comfort between the study and vehicle control.

Adverse Events

The proportion of patients with at least 1 ocular treatment-emergent adverse event (TEAE) was 19.8% (42/212) in the study group and 21.5% (45/209) in the control group. All ocular TEAEs in the study group were mild, with the most common being instillation site pain (11.8%), compared with 7.7% in the control group. Other ocular TEAEs, with more than 1.0% incidence in either study or control group, included instillation site pruritis (1.4% vs. 3.3%), reduced visual acuity (2.8% vs. 2.9%), eye pain (1.4% vs. 1.4%), eye discharge (1.4% vs. 1.0%), and chalazion (0.5% vs. 1.4%), which were all mild.

One patient in the study group had mild swelling of the upper and lower eyelids for both eyes and was directed to discontinue treatment but remained in this study. Three patients (1.4%) in the study group and 1 patient (0.5%) in

TABLE 2. Mean Collarette Grade at Different Time Points for the Upper Eyelid of the Analysis Eye in the Study and Control Groups

Visit Day		Lotilaner 0.25%	Vehicle	*P* (Wilcoxon Rank-Sum Test)
Baseline	N	212	209	0.8104
	Mean ± SD	2.8 ± 0.77	2.8 ± 0.71	
8	N	211	208	0.0004
	Mean ± SD	2.2 ± 0.96	2.5 ± 0.92	
15	N	204	208	<0.0001
	Mean ± SD	1.7 ± 0.98	2.4 ± 0.93	
22	N	207	206	<0.0001
	Mean ± SD	1.3 ± 0.93	2.4 ± 0.96	
43	N	209	204	<0.0001
	Mean ± SD	0.8 ± 0.89	2.2 ± 1.08	

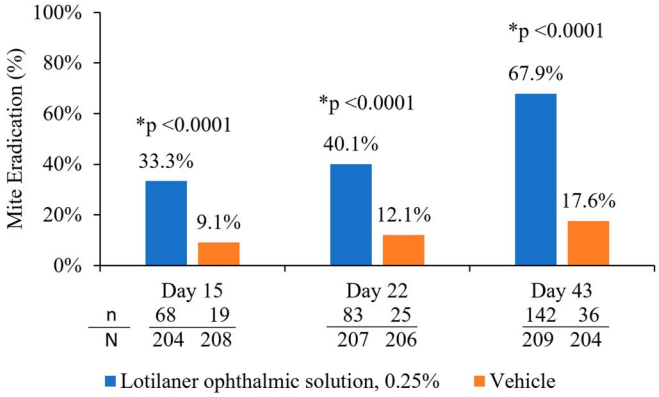

FIGURE 7. Proportion of patients with mite eradication (mite density of 0) in the study and control groups. (The full color version of this figure is available at www.corneajrnl.com.)

TABLE 3. Mean Mite Density at Different Time Points for the Analysis Eye in the Study and Control Groups

Visit Day		Lotilaner 0.25%	Vehicle	*P* (*t* test)
Baseline	N	212	209	0.8939
	Mean ± SD	3.19 ± 1.67	3.16 ± 1.59	
15	N	204	208	<0.0001
	Mean ± SD	0.57 ± 0.66	1.60 ± 1.32	
22	N	207	206	<0.0001
	Mean ± SD	0.35 ± 0.44	1.57 ± 1.40	
43	N	209	204	<0.0001
	Mean ± SD	0.14 ± 0.26	1.34 ± 1.27	

the control group had a non–treatment-related serious adverse event, including COVID-19, pneumonia, hematuria, and femoral vascular access site pseudoaneurysm.

Additional Safety Outcomes

Lotilaner ophthalmic solution, 0.25%, had no clinically significant adverse effects on multiple safety measures, including CDVA, corneal staining, intraocular pressure, slitlamp biomicroscopy, endothelial cell density, and dilated fundus examination.

DISCUSSION

This Phase 2b/3 clinical trial was designed to evaluate the safety and efficacy of lotilaner ophthalmic solution, 0.25%, for the treatment of *Demodex* blepharitis after 43 days of treatment. All prespecified primary and secondary end points were met at day 43 of treatment with lotilaner ophthalmic solution, 0.25%. The study drug demonstrated an early onset of action, with highly statistically significant changes seen in all outcome measures as early as day 15.

The collarette grading scale shown in Figure 1 was used in a previous phase 2a study[33] and was based on the groupings and/or scales used by Gao et al and Hosseini et al.[22,39] The collarette grading scale used is a nonlinear scale with grades 2 to 4 representing much higher levels of *Demodex* infestation.

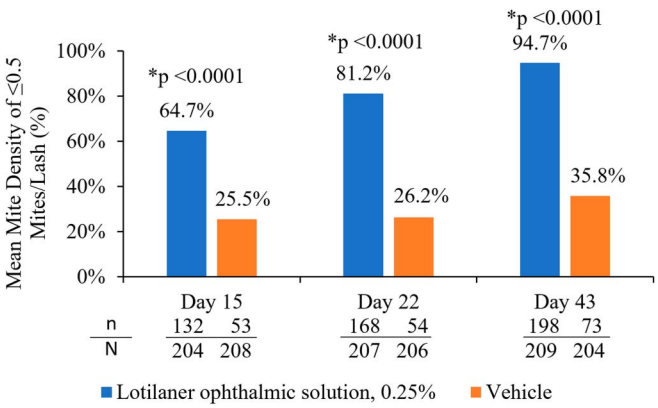

FIGURE 8. Proportion of patients achieving a mean mite density ≤0.5 mites/lash. (The full color version of this figure is available at www.corneajrnl.com.)

For example, an improvement in the collarette grade from grade 3 to grade 1 can reflect a 90% reduction in the number of collarettes per lid. In this study, a reduction in collarettes to Grade 0 or 1 (≤10 lashes per eyelid with collarettes) was considered a clinically meaningful collarette cure and grade zero (0–2 lashes per eyelid with collarettes) was considered a complete collarette cure. Given that the presence of collarettes is the pathognomonic sign of *Demodex* blepharitis,[20–22] this grading scale may be useful for diagnosing and monitoring *Demodex* blepharitis in clinical practice.

The proportion of eyes with a clinically meaningful collarette cure was 81.3% in the study group versus 23.0% in the control group at day 43 ($P < 0.0001$). The proportion of study group patients achieving a complete cure of collarettes (grade 0, Fig. 5) compared with patients in the control group was also highly significant (44.0% vs. 7.4%, $P < 0.0001$). The mean collarette grade improved from 2.8 to 0.8 in the study group. Because the collarette grading scale is nonlinear, the aforementioned mean collarette grade improvement represents an approximately 90% reduction in collarettes (from ~75–100 total collarettes on the lashes of the upper eyelid at baseline to <8 total collarettes after 6 weeks of treatment). Even patients who have Grade 1 collarettes after treatment are likely to see meaningful clinical improvements from this high degree of reduction in collarettes. Nearly all patients in the study group (92.8%) had a response to treatment of at least a 1-grade improvement in collarettes, compared with only half in the control group ($P < 0.0001$, Fig. 6).

In addition to the high rates of collarettes at baseline described above, the mean mite density at baseline was 3.2 mites/lash. Assuming that a typical upper eyelid has 90 to 160 eyelashes and extrapolating the baseline mites/lash to all lashes with collarettes, it is a reasonable assumption that these patients started this study with 160 to 256 mites per eyelid, on average.[11,40] Following lotilaner ophthalmic solution, 0.25% treatment, their *Demodex* load was reduced to a mean density of 0.6 mites/lash (equivalent to ~12–19 mites/eyelid) as early as day 15 and to 0.14 mites/lash (equivalent to <1 mite/eyelid) by day 43. The mite eradication rate was statistically significantly higher in the study group than the control group at all time points from day 15 onward. In addition, nearly all study patients (94.7%) responded to treatment as indicated by a reduction in mite density to ≤0.5 mites/lash at day 43, significantly more than the response rate in the control group (35.8%, $P < 0.0001$). This suggests that lotilaner, which is lipophilic, is successfully reaching and paralyzing the mites in the eyelash follicle.

Besides the presence of collarettes, eyelid erythema is a common clinical sign of *Demodex* blepharitis that signifies inflammation and also affects a person's physical appearance, potentially negatively influencing social and professional interactions.[41] A combined assessment of erythema and collarettes demonstrated that 67.5% of patients in the study group achieved a clinically meaningful composite cure (defined as a collarette grade and erythema grade of 0 or 1). Approximately 1 in 5 patients achieved a complete lid erythema cure (erythema grade 0), and nearly half had a 1-grade reduction in erythema with the 43-day treatment. The 6-week treatment with lotilaner in patients with *Demodex* blepharitis resulted in a substantial reduction in mite density, thereby likely decreasing the inflammation and

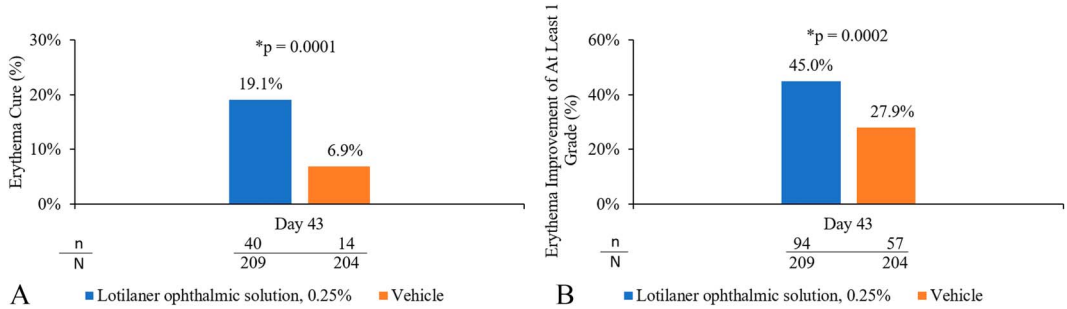

FIGURE 9. Proportion of patients with (A) erythema cure (grade 0) and (B) at least 1 grade erythema improvement at day 43 in the study and control groups. (The full color version of this figure is available at www.corneajrnl.com.)

resultant erythema. With the reduction in erythema levels achieved in this study, it can be hypothesized that lotilaner treatment in *Demodex* blepharitis improves lid margin health and may have an anti-inflammatory effect. It is possible that changes in erythema may lag behind reductions in mite density and that even greater erythema improvements could be seen with longer follow-up.

Lotilaner ophthalmic solution, 0.25%, used in this study was found to be safe and was well-tolerated. All ocular TEAEs in the study group were mild, with the most common being instillation site pain, and patients reported excellent subjective drop comfort throughout this study.

Management of *Demodex* blepharitis to date has no FDA-approved pharmaceutical option and typically involved lid hygiene products such as TTO and okra-based products.[5,12,22,29,42–47] The available evidence demonstrates questionable levels of efficacy.[3,4,12,27,28,30,44,48] At-home use of lid scrubs and wipes containing 3% to 10% TTO or one of its derivatives, T4O, has been recommended by some groups,[5,42] but there have been very few studies published in which these agents are compared with a control group.[42,45,47] Mite eradication rates with these products have been reported to be low, and side effects such as ocular irritation, burning sensation, contact dermatitis, and allergy have been reported.[12,29,30,49,50]

Before this phase 2b/3 study, the study drug, topical lotilaner ophthalmic solution, 0.25%, has been extensively evaluated in several phase 2 clinical trials.[33–36] In the first 2 clinical trials, Mars (single-arm pilot study, n = 15) and Jupiter (vehicle-controlled study, n = 60), patients with *Demodex* blepharitis were treated with lotilaner ophthalmic solution, 0.25%, for 4 weeks and followed for an additional 2 months after treatment cessation.[34,35] Statistically significant reductions in collarette grade and mite density were reported, and the improvement observed during the treatment period was maintained for at least 2 months after treatment cessation. In the next 2 clinical trials, Io (n = 18) and Europa (n = 54), a longer treatment duration of 6 weeks was evaluated[33,36] where the additional treatment improved the outcomes. This study with 6 weeks of treatment in 421 patients confirms the findings of the previous Phase 2 studies. This is the first of 2 pivotal studies for lotilaner ophthalmic solution, 0.25%, and it is expected that the results from the second pivotal study, if positive, will further validate the efficacy and safety of lotilaner ophthalmic solution, 0.25%.

Demodex blepharitis has significant clinical, functional, and psychosocial effects on patients, with 80% of patients in the Atlas study indicating that the disease had negatively affected their daily lives.[41] Lotilaner ophthalmic solution, 0.25%, is the first drug designed to treat and target the underlying cause of *Demodex* blepharitis. The results of this pivotal study demonstrate that twice-daily use of lotilaner ophthalmic solution, 0.25%, for 43 days is safe and effective for the treatment of *Demodex* blepharitis compared with the vehicle control. The resolution of *Demodex* blepharitis, a disease that currently has no FDA-approved treatments, is very promising.

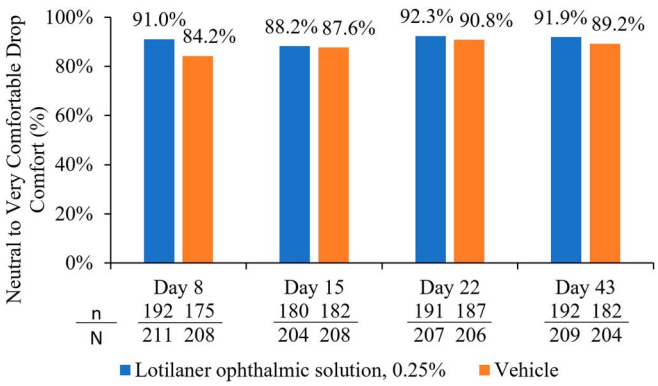

FIGURE 10. Proportion of patients in the study and control groups who rated the drop as neutral to very comfortable. (The full color version of this figure is available at www.corneajrnl.com.)

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