ADVANCING MANAGEMENT OF THE *DEMODEX* BLEPHARITIS PATIENT

5 luminaries discuss the evolving landscape of Demodex blepharitis

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Untangling the Causes and Effects of *DEMODEX* BLEPHARITIS

By Milton M. Hom, OD, FAAO; Paul M. Karpecki, OD, FAAO; and Ben Gaddie, OD

First, there was dry eye, then it was meibomian gland dysfunction (MGD); now, more and more we are talking about blepharitis in the clinical realm.

Blepharitis affects up to 47% of patients seen in the clinical setting, making it one of the most common ocular pathologies that optometrists encounter.[1,2,3] This chronic inflammatory condition affects individuals of all ages and causes ocular irritation and redness[4] that, in most patients, tends to ebb and flow in an ongoing cycle of exacerbation and remission.[1] Severity varies on a scale that ranges from mild to severe, with some cases resulting in permanent eyelid deformity and vision loss due to keratopathy.[1]

The classification of blepharitis generally is based on location and/or etiology. For example, blepharitis can cause anterior or posterior inflammation. In some cases, both anterior or posterior disease occurs simultaneously. This is termed marginal blepharitis. Blepharitis can be further subclassified as *Staphylococcal*, seborrheic, or meibomian gland dysfunction (MGD), any of which can occur alongside *Demodex* infestation.

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PRIMARY CLASSIFICATION

From an anatomical perspective, blepharitis is typically categorized as anterior or posterior,[10] but in reality, it is often marginal, meaning both anterior and

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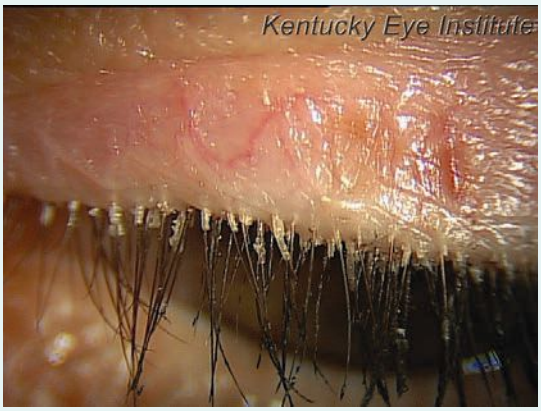
DEMODEX BLEPHARITIS

Demodex is the most common ectoparasite in human beings, and there is a close connection between infestation and blepharitis.[5] In fact, *Demodex folliculorum* and *Demodex brevis* have been implicated in both anterior and posterior blepharitis.[6]



***Demodex* blepharitis**

D. folliculorum cluster at the root of the eyelashes, infesting both the lashes and the follicles.[7] These mites consume epithelial cells, which leads to follicular distention and the formation of loose or misdirected lashes.[7] Meanwhile, the mite's claws cause microabrasions, inducing epithelial hyperplasia and reactive hyperkeratinization. Cylindrical dandruff is a tell-tale sign.[7,8,9] *D. brevis* infest the meibomian glands and mechanically block them,[7] leading to a cascade of MGD-related consequences.

Demodex mites also cause blepharitis because they are bacterial vectors for *Streptococci* and *Staphylococci*.[7] Finally, *Demodex* causes hypersensitivity reactions due to proteins inside of the mite as well as to their waste.[7,9]

posterior blepharitis coexist.[1,2,11]

Anterior blepharitis. Anterior blepharitis affects the skin of the eyelids, the base of the lashes and the lash follicles.[4,1] *Staphylococcus* infection and seborrheic dermatitis are commonly associated with anterior blepharitis.[1] Squamous debris or collarettes are also often present.[1,2,11]

Posterior blepharitis. Blepharitis can be classified as posterior when the meibomian glands are affected.[4] As such, meibomian gland dysfunction (MGD) can be conceptualized as a complication of posterior blepharitis wherein hyperkeratinization occurs, triggering inflammation and an alteration in glandular secretions that leads to tear film instability and dry eye.[10,12] Viewed in this way, MGD is a *result* of blepharitis; however, MGD can also *cause* blepharitis.[1,2,11] The important thing to remember is that MGD and blepharitis are not interchangeable terms, since both conditions have alternative causes.[1,13]

Marginal blepharitis. As most clinicians have witnessed, anterior and posterior blepharitis commonly coexist because the etiologies of blepharitis cause insult both anteriorly and posteriorly.[1] For example, *Demodex* mites[14] and, less commonly, Phthirus pubis (crab lice)[15] are both parasitic causes of marginal blepharitis.[1]

SUBCLASSIFICATION

Staphylococcal, seborrheic, and MGD are the three most common subcategories of blepharitis, but as with primary categories any of these can coexist.[4,16]

Staphylococcal blepharitis. Relative to other forms of blepharitis, *Staphylococcal* blepharitis is most common in younger female patients.[4,16,17] Clinically, it presents with lid margin scaling, crusting, and erythema alongside collarette formation.[4] Severe presentations include ulcerative blepharitis and corneal involvement.[4] Eyelid cultures have shown both

coagulase-negative *Staphylococcus* and *Staphylococcus aureus*,[4,16] but less than half of patients diagnosed with *Staph*. blepharitis have positive cultures.[1,18]

Seborrheic blepharitis. In patients with seborrheic blepharitis, there is significant crossover between anterior blepharitis and MGD.[1] These patients commonly present with greasy scaling anterior lids and seborrheic dermatitis of the brows and scalp.[4] In fact, 95% of seborrheic blepharitis patients have seborrheic dermatitis.[1,16]

Understanding the intersections between MGD and dry eye, and blepharitis and *Demodex,* are fundamental to successfully managing patients. When one condition is present, always look for the others.

Meibomian gland dysfunction. As discussed above, MGD can be both a cause or an effect of blepharitis. MGD also can be particularly insidious because of its close association with evaporative dry eye disease[4,3] and *Demodex brevis*, which mechanically blocks meibomian gland orifices, giving rise to lipid tear deficiency.[7,8] *D. brevis* also burrows deep into the glands, leaving behind a chitinous exoskeleton that can cause a granulomatous reaction.[7]

Demodex folliculorum is likewise implicated in MGD, and can be clinically discerned by the presence of collarettes or cylindrical dandruff at the base of the lashes.[4,8]

Understanding the intersections between MGD and dry eye, and blepharitis and *Demodex,* are fundamental to successfully managing patients. When one condition is present, always look for the others. ♦

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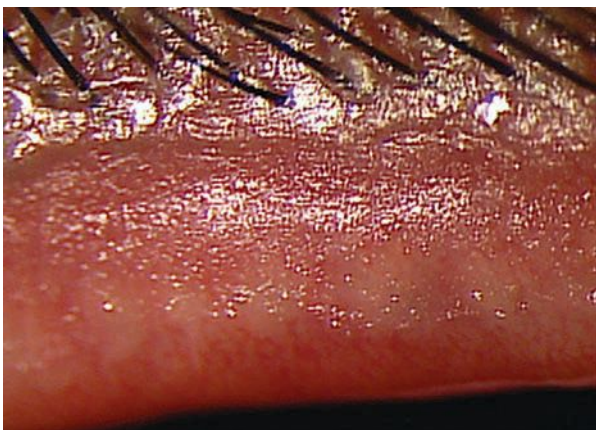
A Stepwise Approach to Diagnosing *DEMODEX* BLEPHARITIS in Its Many Forms

By Katherine M., Mastrota, MS, OD, FAAO, Dipl. ABO; Paul M. Karpecki, OD, FAAO; and Ben Gaddie, OD

Blepharitis is a common eye disorder and cause of ocular discomfort and irritation that can affect any age group across all demographics.[1] It is related to other ocular conditions like dry eye, chalazion, conjunctivitis, and keratitis.[1] Common symptoms associated with blepharitis are burning sensation, irritation, itching, tearing, photophobia, blurred vision, and ocular injection.[1] Clinical examination may reveal the presence of collarettes, discharge, scales, debris, telangiectatic vascular changes of the eyelid margin, inspissated meibomian glands, conjunctival hyperemia, punctate keratopathy, cornea vascularization, lid margin thickening, ulceration, eyelash loss and scars.[1]

The etiopathogenesis of blepharitis can be multifactorial, including chronic low-grade bacterial infections of the ocular surface, infestations with certain parasites such as *Demodex*, and inflammatory skin conditions such as atopy, rosacea, and seborrhea.[2] In any case, blepharitis can become a chronic inflammatory process of the eyelid margin.[1] Additionally, patients with longstanding chronic blepharitis may present with alterations in eyelid morphology that include meibomian gland dropout, an irregular or scalloped lid margin, vascular engorgement, plugging, anterior placement of the mucocutaneous junction, and exposed meibomian gland terminal ducts.[3] In short, the clinical signs of blepharitis are diverse and vary in severity.



Lid margin keratinization from chronic blepharitis.
Images: Katherine M. Mastrota, MS, OD, FAAO, Dipl. ABO

Importantly, blepharitis plays a big part in ocular surface disease—whether it's blepharitis affecting the eyelashes and eyelids, or meibomian gland dysfunction (MGD). This is just one of many reasons why an accurate diagnosis is so important. Furthermore, to select the most efficacious treatments, it's important to diagnose not simply "blepharitis" but also the *type* of blepharitis.

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PATIENT PRESENTATION

Evaluation of a blepharitis patient can begin with the intake symptom form to include the ocular surface disease index and the standard patient evaluation of eye dryness. Although these questionnaires are designed for the patient suffering from DES, the substantial overlap of symptoms and etiologies with blepharitis makes the intake form an important tool in diagnosis and management. Along with self-reported patient symptoms, a thorough review of systems, including systemic disease and current medications, will provide the optometrist with a more complete clinical picture.

The three most common forms of blepharitis can be easily differentiated. For example, the classic appearance of *Staphylococcal* blepharitis includes yellowish debris, matter or discharge, and erythema and hyperemia of the eyelid margins.[4] Patients typically present with debris on the lashes, mattering/crusting, irritated or swollen eyelids and eyelash margins, potential conjunctival involvement, hordeola development and, in severe cases, eyelid ulceration.

Patients with dermatologic seborrheic blepharitis present differently, with greasy flakes or scales.[5] They complain about how their eyelids feel and sometimes experience itch. They also often have mild conjunctival injection and inferior punctate epithelial erosions.

A third, very common presentation is *Demodex* blepharitis. On average, a healthy person's body hosts over 2,000 *Demodex* mites.[6] Those who have *Demodex* blepharitis have many more, which present as 'sleeves' known as collarettes, with debris at the base of the lashes. These patients commonly complain of itching of the lid margins, and we often note madarosis or misdirected lashes. *Demodex* blepharitis used to be a last-resort diagnosis that was tacked on when other treatments failed. This is not the preferred approach. Instead of viewing it as a diagnosis of exclusion, we should heighten our awareness of this prevalent condition in all at-risk patients. In fact, very often, patients have mixed blepharitis of any of the above three types of involvement.

MANAGING CLINICAL MANIFESTATIONS OF *DEMODEX* BLEPHARITIS:
NEW FINDINGS SHOW ROOM TO IMPROVE

A paper published in the June 2021 issue of *IOVS* concluded that "the symptom burden of blepharitis is considerable and leads patients to seek treatment and medical care, mostly unsuccessfully."[1]

The researchers clinically examined adult patients (age ≥18) with *Demodex* blepharitis and asked questions about their ocular symptoms, diagnoses, and history. These 311 patients had objective signs of *Demodex* blepharitis, including the presence of *Demodex* mites, collarettes on the lashes, and lid margin erythema. Questionnaire responses from the patients with confirmed *Demodex* blepharitis were analyzed.

Among the participants, 38% were male and 62% female. The mean age was 67 (range, 23 to 92). More than half (51%) had been experiencing signs and symptoms of blepharitis for at least four years, but most (58%) had never been diagnosed with blepharitis. A high degree of overlap with other ocular surface conditions was present, including individuals previously diagnosed with dry eye (81%), rosacea (3%), or both (16%). The most bothersome symptoms for patients were itchy, dry, and tearing eyes and foreign body sensation. The majority of patients experienced symptoms of dryness, itching, and ocular irritation frequently or all of the time in the past month.

Although most had seen an eye doctor only once, 33% had made at least two, and sometimes more than six, visits to a doctor for this condition. Eighty-one percent of patients sought some type of treatment for the condition. Of those who discontinued treatment, 43% discontinued due to ineffectiveness, tolerability issues, or other reasons. Women were more likely than men to have tried medication to treat their symptoms (90% vs. 66%)

These new findings show we have some room to improve when it comes to diagnosing and managing care of the *Demodex* blepharitis patient.

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INSPECTION OF THE FACIAL SKIN

When patients present with signs of blepharitis, further evaluation is needed. This often begins with the skin. Rosacea is a chronic facial skin condition, and two of the four subtypes have been associated with *Demodex* activity. It is characterized by marked involvement of the central face with transient or persistent erythema, telangiectasia, inflammatory papules and pustules, or hyperplasia of the connective tissue. Transient erythema,

or flushing, is often accompanied by a feeling of warmth. It usually lasts for less than five minutes and may spread to the neck and chest. Less common findings include erythematous plaques, scaling, edema, phymatous changes (thickening of the skin due to hyperplasia of sebaceous glands), and ocular symptoms. The National Rosacea Society Expert Committee defines four subtypes of rosacea (erythematotelangiectatic, papulopustular, phymatous, and ocular), and one variant (granulomatous).[7]

The most common signs of ocular rosacea include telangiectasia and irregularity of lid margins, and meibomian gland dysfunction.[8] Rosacea also was found to be a statistically significant risk factor for *Demodex* infestation in eyelashes, irrespective of age and sex, with a higher prevalence in the papulopustular variety.[9]

INSPECTION OF THE EYELASHES AND LASH LINE

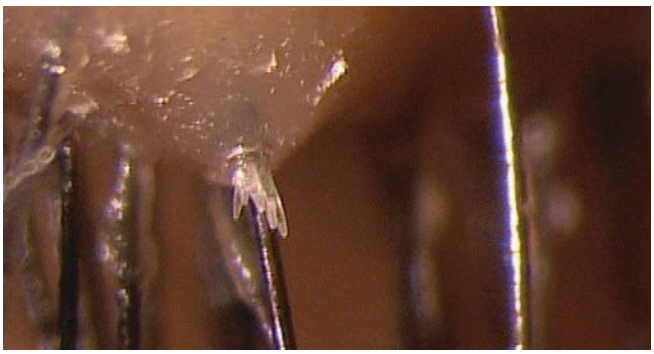
Changes in eyelashes secondary to blepharitis include madarosis, trichiasis, lash misdirection, distention of eyelash orifice, and poliosis. The patient should be instructed to look down during the slit lamp examination while the clinician uses low, then higher magnification to look for collarettes at the base of the lashes.

Eyelashes grow in imperfect rows of five to six in the upper lid, and three to four in the lower lid. Their mean number is 90 to 160 in the upper lid, and 75 to 80 in the lower lid; their length is 8 to 12mm in the upper lid, and 6 to 8mm in the lower lid. Eyelash follicles are free of arrector pili muscle and are served by the glands of Zeis and Moll.[10] They produce different substances released through channels that flow into the follicle. The glands, if Zeis, use a holocrine mechanism of action, thus liberating their complete cell content, which is sebum. It has antimicrobial and lubrication properties, just as it allows the transport of antioxidants, although the exact function of the sebum is unknown.[11] The glands of Moll, only found in the lids, are apocrine glands that produce secretions by fragmentation from one side of their cells. Their secretions, which contain a variety of sugar components, might play a critical role in the defense against microorganisms.[12]

The eyelash fiber has a structure very close to hair with three compartments from the outside to the inside: the cuticle, the cortex, and the medulla. Both hair and eyelash follicles go through a cycle of growth (anagen), transition (catagen), and resting (telogen). The eyelash has a shorter cycle than the hair, which is why eyelashes are short, with a growth rate of .12mm/day. The anagen phase is about 34 days, and the telogen is about 90 days. Lashes last five to six months before falling out.

PATHOLOGY OF *DEMODEX* BLEPHARITIS AND IDENTIFICATION STRATEGIES

Currently, it is accepted that a collarette along the shaft base of the eyelash is created by a response to *Demodex* mites that are harbored within the eyelash follicle and its associated sebaceous gland. These collarettes surrounding the base of eyelashes, thought to be an accumulation of *Demodex* excreta and other debris (keratins and lipids), are pathognomonic for ocular *Demodex* infestation.[13] Eyelash loss, however, also heralds the presence of chronic *Demodex,* among other pathologies.[14]

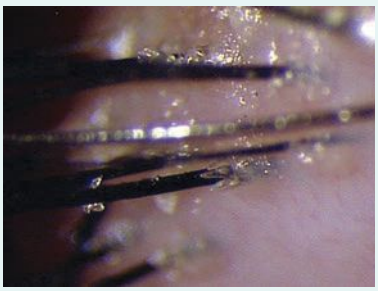


Traction on eyelashes exposes *Demodex*.

Demodex overpopulation is associated with trichiasis and eyelash disorganization, madarosis,[15] meibomian gland dysfunction, gland atrophy, conjunctival inflammation, and corneal pathology.[16] Furthermore, infestation of *Demodex* mites induces a change of tear cytokine levels, especially interleukin,[17] which can cause inflammation of the lid margin and ocular surface.[17] The presence of mites in meibomian glands can induce a granulomatous re-

AN EXCESS OF *DEMODEX*

Demodex folliculorum and *Demodex brevis* are two mites that infest the human eye and that may, in excess, lead to a wide range of anterior segment findings.



***Demodex* tails at base of eyelash.**

Demodex mites have been implicated in blepharitis, meibomian gland dysfunction, blepharoconjunctivitis, and blepharokeratitis.[1] *D. folliculorum* is most commonly identified and typically buries itself head-first within a hair follicle, with its tail protruding from the follicle. During infestation, several mites may be found clustered around one follicle.[2] *D. brevis*, the smaller of the two species, prefers to reside in areas of skin abundant in sebaceous glands. *D. brevis* has been implicated in several chronic facial dermatological conditions, such as acne rosacea, pityriasis folliculorum, and perioral dermatitis.[3] It has been proposed that these mites feed on follicular and glandular epithelial cells, as well as the meibum, leading to direct damage of the lid margin.[4] A comprehensive narrative synthesis has provided consistent evidence to support an association between ocular *Demodex* and chronic blepharitis.[5]

Overpopulation of *Demodex* mites is referred to as demodicidosis. Currently, it is thought that pathological changes secondary to demodicidosis of the eyelids/eyelashes are consequences of blockage of follicles and tubules of sebaceous glands by the mites and by reactive hyperkeratinization; epithelial hyperplasia from microabrasions caused by the mite's claws; the mites acting as bacterial vectors; the host's inflammatory reaction to the presence of parasite's chitin as a foreign body; and stimulation of the host's humoral responses and cell-mediated immunological reactions in response to the mites and their waste products.[6]

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sponse, as seen in the histopathology of a chalazion. When migrating through adipose tissue, its sharp claws rupture small vessels with resultant bleeding," and it produces intense localized inflammation in sebaceous glands.

Methods to identify *Demodex* within the eyelash follicle include having the patient look down during the slit lamp examination to closely examine the base of the lashes for collarettes, rotation of the lash to coax the organism out of the follicle, eyelash traction to reveal the mite deep within the follicle, lash epilation followed by light microscope inspection for the mite, and *in vivo* confocal microscopy.[18] Younger patients (under 35) with ocular demodicosis tend to have more *D. brevis* infestation, meibomian gland loss, and corneal involvement than patients over 45 years of age.[19]

It is clear that *Demodex* blepharitis, like so many other ocular conditions, is multifactorial. As such, swift identification and careful diagnosis is essential to selecting the right targeted treatment, as we look toward managing the disease. ♦

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The Promise of a New Era in *DEMODEX* BLEPHARITIS Treatment

By Selina McGee, OD, FAAO, Dipl. ABO; Paul M. Karpecki, OD, FAAO; and Ben Gaddie, OD

Demodex blepharitis is a significant public health challenge that rests largely on the shoulders of optometry. This condition is extremely prevalent and highly consequential in terms of patients' quality of life. In fact, the prevalence of *Demodex* blepharitis in the United States may be as high as 25 million.[1,2] Furthermore, beyond the physical symptoms, eight out of 10 patients who have *Demodex* blepharitis say the condition has a negative impact on their daily lives.[3] Specifically, they report difficulty wearing makeup, constantly worrying about their eyes, difficulty driving at night, and a negative appearance of the eyes or eyelids (see Figure 1).[3]

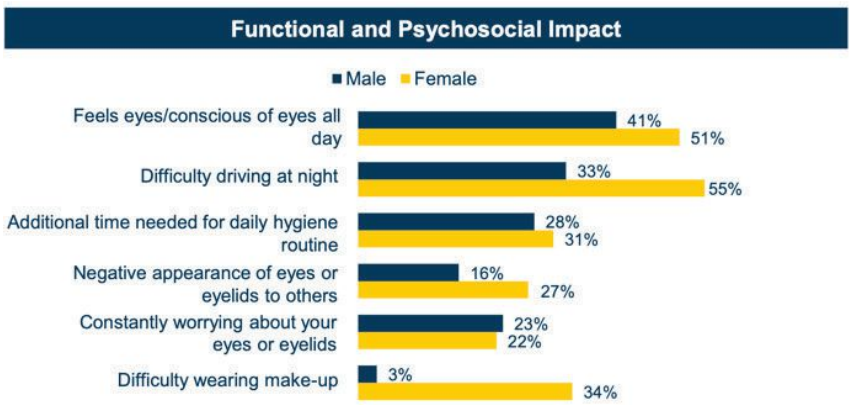

Figure 1.[3]

Historically, our ability to manage *Demodex* blepharitis has been limited to OTC products, but this may soon change, with the investigational treatment TP-03 (lotilaner 0.25% ophthalmic solution; Tarsus

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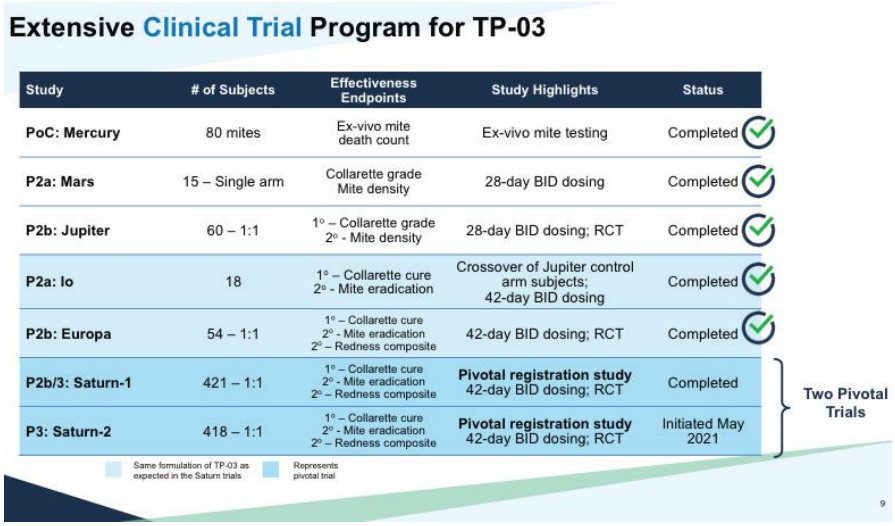

Figure 2 Source: Tarsus Pharmaceuticals data on file.

IMPACTS OF *DEMODEX* MITES

Here are some of the ways *Demodex* mites negatively impact patients:[5-8]

1. The mites' claws cause mechanical insult.
2. Mites lay eggs in lash follicles, causing irritation, follicular distension, misdirected lashes, and madarosis.
3. Bacteria live on the surface of the mite and within the mite's gut, causing an inflammatory response.
4. The mites excrete digestive enzymes as they feed. When they die, they leave behind digestive waste and collarettes, causing irritation, hyperemia, inflammation, and hyperplasia

Pharmaceuticals). As the data reveal in study after study, TP-03 has demonstrated positive results both in terms of safety and efficacy (see Figure 2).

THE IMPORTANCE OF TREATMENT

Demodex mites are particularly insidious because they lead to disease in several different ways and they are the most common ectoparasite in the human body.[4]

The mites' cycle of insult illuminates why we so often witness the tell-tale pathognomonic sign of collarettes in patients who have *Demodex* blepharitis. Importantly, 58% of patients presenting at eyecare offices have collarettes,[1,2,6] and in some studies, 100% of patients presenting with collarettes had *Demodex* blepharitis.[6] The collarettes emerge when the mites feed on patients' skin—and partially digested cells combine with keratin, mite waste, and eggs.[5,8] The resulting collarettes appear at the base of the lash and migrate upwards as the hair grows.

TREATMENT HISTORY

As the leading cause of blepharitis in the United States,[9,10] the need for treatment is great, yet no FDA-approved drugs currently exist for *Demodex* blepharitis.[11] Many of the drugs that have been proposed (such as sulfur or mercury oxide ointments,[12] iodized solutions,[6] and pilocarpine gel[6]) have not been proven effective, while the efficacy of several other approaches, (e.g., oral antiparasitics such as ivermectin, metronidazole, and tea tree oil solutions) show only variable success.[11]

Fortunately for patients, a new treatment has been proposed. Lotilaner is approved

for use in oral form for the treatment of fleas and ticks in pets, and is now under investigation as a topical formula for humans.[11] Known as TP-03, this topical formulation of preserved lotilaner is dispensed from a multidose eyedrop solution bottle for the treatment of *Demodex* blepharitis (see Figure 3). In terms of mechanism of action, the drug causes paralysis and death of the mites. Suggested dosing is b.i.d. for six weeks.

POSITIVE FINDINGS FOR A NEW APPROACH

The first four Phase 2 clinical trials looking at TP-03 all showed the drug to be well-tolerated, safe, and effective (see Figure 2). Both Mars and Jupiter demonstrated that it reduced collarettes and *Demodex* density after 28 days of treatment, beginning as early as day 14 of treatment, with effects lasting at least 90 days.[13,14] In both of these investigations, patients reported the drop to be comfortable with no treatment-related adverse effects (AEs).

The Phase 2a Io and the Phase 2b Europa studies likewise found positive results.[15] In Io, collarette cure was achieved in 72% of participants, and mite eradication was achieved in 78% of participants at day 42. In the Europa trial, collarette cure was reached in 80% of participants on TP-03 compared with 16% on vehicle ($p<.001$) at day 42, and mite eradication was reached

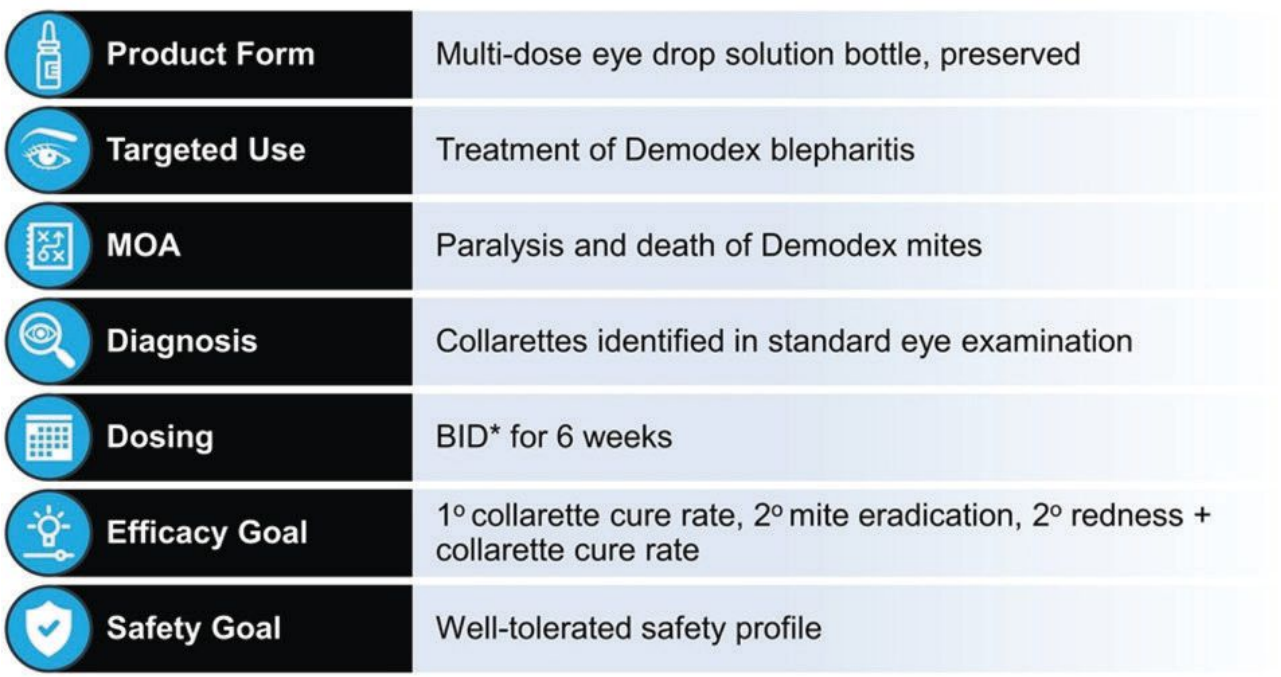

Figure 3. TP-03 At a Glance

Source: Tarsus Pharmaceuticals data on file.

in 73% of participants on TP-03 compared with 21% on vehicle (p=.003) at day 42. Again, in these two studies, the drug was well-tolerated, with no serious AEs or treatment discontinuations due to AEs.

ONE STEP CLOSER

More positive news arrived in June when the Phase 2b/3 Saturn-1 trial results were announced, again revealing statistically significant complete collarette cure at day 43 in patients treated with TP-03 compared to vehicle ($p<0.0001$).[16] Furthermore, the study showed mite eradication at day 43 ($p<0.0001$), and composite cure based on complete collarette and erythema cures at day 43 ($p<0.0001$). In addition, significant, clinically meaningful improvements were observed within two weeks across multiple endpoints. As in earlier trials, TP-03 was well-tolerated with a safety profile similar to vehicle, and no treatment-related discontinuations were reported.

Saturn-1 is the first of two pivotal trials. Topline results for the second pivotal trial, Saturn-2, are expected early in 2022. Combined, the two trials are expected to be used as the basis to support submission of a New Drug Application to the FDA, providing clinically-proven treatment for millions of patients who suffer with *Demodex* blepharitis.

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