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Running Head: Lotilaner and Demodex Blepharitis

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ABSTRACT:**Purpose:**

This review aims to assess the safety and efficacy of Lotilaner in the treatment of Demodex Blepharitis.

Design:

Systematic Review and Meta-Analysis

Background:

Demodex blepharitis is a common eye condition that arises from Demodex mites infestation within the hair follicles of eyelashes, resulting in detrimental effects. The disease affects a significant part of the general population, including general eye care patients and individuals diagnosed with blepharitis. Several treatments have been in use before the discovery of lotilaner, like tea tree oil, and antibiotics; however, they either have irritable effects or systemic adverse effects, respectively. Lotilaner, a novel ectoparasiticide, has been proposed as a treatment for patients grappling with Demodex blepharitis. We primarily aimed to assess the efficacy and safety of Lotilaner for the treatment of Demodex blepharitis.

Methods:

An extensive search was conducted on PubMed, Cochrane Library, Scopus, and Google Scholar to find relevant literature till 31 July 2023 following the PRISMA guidelines. A total of 143 articles were retrieved by database searching, out of which 6 studies met the inclusion criteria and were included in the review. Four RCTs were included in the meta-analysis of mite eradication incidence. The review is registered with PROSPERO: CRD42023459997.

Results:

Lotilaner is effective in eradicating Demodex mites in individuals suffering from Demodex blepharitis according to RR for the intervention versus the control group of 3.55 (95% CI: 2.87 – 4.40, $P < 0.00001$, $I^2 = 0\%$). The meta-analysis of clinically meaningful collarette score revealed

the summary RR for the intervention versus the control group was 3.15 (95% CI: 2.56 – 3.89, $P < 0.00001$, $I^2 = 27\%$). In conclusion, the results of the included studies were comparable and consistent.

Conclusions:

Our results indicated that Lotilaner is an effective, well-tolerated, and promising drug in treating patients with Demodex blepharitis. Lotilaner administration and cost-effectiveness should now be contemplated for the study population as these constituents have a vital impact on its treatment success.

Keywords: Blepharitis; Demodex; Mite infestations; Lotilaner; Collarettes

1. INTRODUCTION:

Demodex blepharitis, a common eye condition, arises from an infestation of Demodex mites within the hair follicles of eyelashes, resulting in detrimental effects through mechanical, chemical, and bacterial means [1]. These mites, *Demodex folliculorum* and *Demodex brevis*, are recognized as the primary culprits in the onset and progression of blepharitis [2]. The prevalence of Demodex blepharitis is significant, as evident by recent studies indicating that a considerable portion of both general eye care patients (55% to 58%) and individuals diagnosed with blepharitis (62% to 69%) are affected by this condition. Around 25 million adults in the United States alone are estimated to grapple with Demodex blepharitis [3-4].

The pathognomonic sign indicative of Demodex blepharitis is the presence of collarettes, characteristic formations similar to cylindrical dandruff. These collarettes comprise of undigested material, eggs, keratinized cells, deceased mites, and occasionally live mites, indicating the infestation clearly [5-7]. This condition presents a spectrum of clinical manifestations, including

disruptions in the tear film, dysfunction of meibomian glands, redness of the eyelid margins, swollen eyelids, and misalignment or loss of eyelashes. Additionally, affected individuals may experience recurring chalazion and, in rare instances, more severe complications like the development of pterygia, corneal vascularization, lesions resembling phlyctenules, and corneal opacity [8]. The impact of Demodex blepharitis on patients' daily lives is substantial, with a significant 80% reporting a detrimental effect due to this condition [9]. Furthermore, the infestation rate exhibits a notable age-dependent trend, with prevalence increasing to up to 84% in the population by the age of 60 and reaching 100% in individuals over 70 years old [10-11].

No treatments for Demodex blepharitis have received approval from the Food and Drug Administration (FDA) before lotilaner. Commonly employed management strategies before approval of lotilaner included topical tea tree oil along with its active component, terpinen-4-ol, both of them demonstrated favorable clinical findings. Additionally, options for second-line treatment, such as metronidazole, ivermectin, microblepharoexfoliation, and lid hygiene, have been investigated [12]. A meta-analysis has validated the effectiveness of these treatment modalities in managing Demodex blepharitis [13]. However, this meta-analysis does not discuss the efficacy of Lotilaner for the treatment of Demodex blepharitis. Additionally, these treatment options might contribute to symptom improvement but they did not show a very efficient mite eradication rate in the patients of Demodex blepharitis [13].

Targeted, novel therapies such as Lotilaner (TP-03) have been investigated for their use in Demodex Blepharitis in various studies [14-15] and trials [16-19], showcasing extremely positive results with minimal side effects. Lotilaner, an antiparasitic compound belonging to the isoxazoline class, acts by blocking the parasite's γ -aminobutyric acid chloride channels, resulting in paralysis and subsequent demise of Demodex mites [20]. Endorsed for the treatment of pet flea and tick infestations [21], Lotilaner has emerged as a promising therapeutic

medication for the management of Demodex blepharitis and has received FDA approval for demodex blepharitis as well.

Given the need for a novel therapy for this condition, a detailed understanding of Lotilaner's safety and efficacy is important. Despite the availability of ample data from the mentioned clinical trials and studies, there has been no synthesis done to assess the two criteria of the drug. We, therefore, carried out a systematic review and meta-analysis of randomized controlled trials (RCTs) along with observational studies, assessing the efficacy and safety of Lotilaner tested in patients with Demodex Blepharitis.

2. METHODS:

2.1 Registration and Protocol:

The Cochrane Handbook for Systematic Reviews of Interventions and PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) guidelines were followed in the conduct and reporting of this systematic review and meta-analysis [22].

The protocol for this review is registered with PROSPERO (International Prospective Register of Systematic Reviews; ID: CRD42023459997) and the PRISMA principles were implemented in the methodology of this review. There was no need for ethical approval for our study.

2.2 Information Sources and Search Strategy:

Without regard to language limitations, the following databases and international registers were searched from the time of their creation until August 2023: MEDLINE (via PubMed), Cochrane Central Register of Controlled Trials (via The Cochrane Library), Scopus, and Google Scholar. To find more potentially eligible studies, we screened the reference lists of the included articles and pertinent systematic reviews. A search strategy with keywords and Medical Subject

Headings (MeSH) terms pertaining to lotilaner and demodex blepharitis was used. The detailed search strategy utilized for each database is available in **Supplementary Table S1**.

2.3 Study Selection and Eligibility Criteria:

If the studies satisfied the following criteria, they were considered eligible for inclusion in our systematic review and meta-analysis: (a) observational studies (prospective or retrospective cohort or case-control studies), single-arm experimental studies or randomized controlled trials (RCTs); (b) they comprised all age groups of patients diagnosed with Demodex Blepharitis; (c) the intervention consisted of topical Lotilaner Ophthalmic Solution (0.25%) given to patients in at least one arm of the study/trial; (d) they reported the number of patients who achieved mite eradication or clinically meaningful collarette score. Excluded studies included letters and editorials, case reports, case series, reviews, non-human trials, studies with insufficient data, and studies with data unrelated to our predetermined objectives. Duplicates were removed from the articles retrieved from the systematic search of databases. The search strategy was independently developed by two authors (MT and MHA) in compliance with the specifications. In addition, after evaluating the titles and abstracts of the remaining papers, the full texts were examined to determine their relevance. Any disagreements or misunderstandings were resolved through consensus-building with an additional investigator.

2.4 Outcome Measures:

The treatment goals of Demodex blepharitis include decreasing the mite density by mite eradication. The mean collarette scores, mite eradication, clinically meaningful collarette score, and mean mite density were the main outcomes observed to determine the efficacy of the lotilaner. Safety by determining adverse events, and, drop comfort were secondary outcomes. However, they were not reported in all the studies.

2.5 Data Extraction:

To ensure consistency in data extraction, two reviewers (MT and MHA) extracted data from the chosen studies after they had been selected and screened. The data was then entered into an Excel spreadsheet. The data that follows was taken from each study that qualified: Name of the lead author; publication year; length of study; kind of study; nation or nations where study was conducted; the number of patients with Demodex Blepharitis; the number of patients who received intervention; average age; demographics; treatment protocols (treatment regimens and duration of treatment); outcomes and adverse effects. The outcomes we analyzed were mite eradication and clinically meaningful collarette score.

2.6 Risk of Bias Assessment:

Two distinct assessment instruments (checklists) were used to evaluate the risk of bias in the included studies: one for observational studies and another for experimental studies. For observational studies, the NHLBI [23] checklist was utilized. The Revised Cochrane Risk of Bias tool (Rob2) [24] was employed for experimental studies. It assesses bias in five domains: (i) randomization procedure; (ii) deviations from planned interventions; (iii) incomplete outcome data; (iv) outcome measurement; and (v) choice of reported result. Independently, two authors assigned a low, high, or some concern rating to each included study's risk of bias. A third reviewer arbitrated any disputes between them.

2.7. Data Analysis:

The software used for analysis is Review Manager (Version 5.4.1). The random-effects model was used to perform meta-analysis. Because of the estimated heterogeneity of the true effect sizes, the random-effects model was applied. Using Higgins I², heterogeneity between studies was assessed, with a value of 50% or higher taken into account. The results were presented as 95% Confidence Intervals corresponding to the Risk Ratios (RR). Using statistical tests to

assess funnel plot asymmetry was not practical due to the limited number of included studies in this review.

2.8. Certainty of Evidence Assessment:

For evaluation of the certainty of the evidence, the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach was used, and the quality of evidence of the pooled estimates was judged as high, moderate, low, or very low according to the GRADE Working Group [25-26].

3. RESULTS:

3.1. Study Selection & Characteristics of Included Studies:

An initial search of databases such as PubMed/Medline, Google Scholar, Scopus, and Cochrane CENTRAL Library provided a total of 143 articles. After exclusion based on the title, abstract, and full text, a total of 6 studies were deemed eligible for inclusion in our systematic review [14-19] and 4 in our meta-analysis [16-19]. The PRISMA flowchart that summarizes the study selection procedure is displayed in **Figure 1**. These trials, which included 2 single-arm observational studies and 4 trials with a total of 979 patients, were published between 2021 and 2023. The studies had slight variations in sample size, characteristics of patients, follow-up duration, and study design. The mean age of patients in studies ranged from 58 to 70 years. The total number of patients who received Lotilaner was 507. The remaining patients were included in the placebo group. **Table 1(A)** summarizes the baseline characteristics of patients enrolled in individual studies.

3.2. Risk of Bias in Included Studies:

The checklist for observational studies showed that the observational studies included had a fair quality rating, which means a moderate risk of bias (**Table 2**) [23]. However, based on the

experimental study checklist [24], there was little chance of bias in the included experimental studies (**Figure 2**). The small number of studies that met the criteria for the meta-analysis meant that statistical tests could not be used to assess the asymmetry of the funnel plot.

3.3 Results of Synthesis:

Four RCTs were included in the meta-analysis of mite eradication incidence. The summary (Risk Ratio) RR for the intervention versus the control group was 3.55 (95% CI: 2.87 – 4.40, $P < 0.00001$). There was no heterogeneity reported ($I^2 = 0\%$). The forest plot is depicted in **Figure 3**. The single-arm studies also reported 77.80% [14] and 57.1% [15] mite eradication in the intervention group. Four RCTs were included in the meta-analysis of clinically meaningful collarette score. The summary RR for the intervention versus the control group was 3.15 (95% CI: 2.56 – 3.89, $P < 0.00001$). Mild heterogeneity was reported ($I^2 = 27\%$) (**Figure 4**). Additionally, a significant decrease in mean collarette scores and mean mite density was observed in the lotilaner group. Mean mite density and collarette scores before and after therapy in the placebo versus lotilaner group in the included studies are represented in **Table 1(b)**. The GRADE evaluation yielded a moderate quality of evidence for the pooled results of both outcomes in **Table 3**.

3.4 Qualitative Review of Adverse Effects:

Although side effects of Lotilaner ophthalmic solution were rare, a few studies did report some treatment-related effects like mild burning, redness, or blurriness, mild eye pain, eye discharge, or mild skin irritation. Only 2 studies reported the rare incidence of chalazion [18-19]. Instillation side pain was the most commonly occurring event reported in 2 studies (11.8% and 7.9% in Lotilaner groups as compared to 7.7% and 6.7% in placebo groups) [18-19]. Other less commonly occurring events included dry eye, instillation site pruritus, mildly reduced visual acuity, conjunctival hyperemia, vital dye staining of the cornea, and photophobia.

4. DISCUSSION:

This systematic review and meta-analysis is the first of its kind to assess the safety and efficacy of Lotilaner as a treatment option for Demodex Blepharitis. We included data from 4 randomized controlled trials and 2 single-arm studies. Our findings illuminate a nuanced landscape.

In terms of efficacy, our study demonstrated statistically significant and better outcomes in patients treated with Lotilaner compared to those who received a placebo. Lotilaner showed a significantly greater likelihood of success in comparison to the control group in both primary endpoints, the number of patients with mite eradication, and clinically meaningful collarette scores. However, some mild variation was reported in the collarette score outcome in the included studies. Additional outcomes, such as the number of patients with erythema cure and composite cure, were also reported in some of the included studies [18, 19]. However, there wasn't enough evidence in the included studies to establish a meta-analysis. Nevertheless, the Lotilaner group showed a higher number of patients achieving these outcomes compared to the placebo group. Additionally, no or very little heterogeneity was observed in our studies.

Patients have demonstrated an encouraging response to Lotilaner, but like any medication, Lotilaner can also exhibit some undesired effects. Only minor side effects, such as mild burning, mild instillation site pain, mild reduction in visual acuity, and mild chalazion, were observed in some of the included studies. However, it's crucial to note that these side effects affected only a minority of the study participants. The majority of participants experienced no side effects, reaffirming the favorable safety profile of the treatment.

As far as we are aware, this is the first systematic review and meta-analysis that demonstrated the efficacy and safety of Lotilaner for the treatment of demodex blepharitis compared to the current existing literature. Prior to this, there was no FDA-approved treatment for this unpleasant ailment. However, several studies have been done on the management of this

disease that are reported in the literature [27]. Alternative interventions in these studies before the discovery of Lotilaner included tea tree oil (TTO), ivermectin, permethrin, metronidazole, crotamiton, light therapies, combined therapies etc [28-30]. This therapy is considered very complex owing to a hectic and prolonged process that could last for many months. The selection of drugs was a personal matter, including antibiotics like ivermectin and metronidazole and medicinal oils such as TTO, etc. Nonetheless, without a reliable method for getting rid of Demodex mites from affected areas of the eyelid margins, microorganisms could continue to reproduce, causing the respective symptoms [29]. Even though ivermectin and metronidazole have shown positive results in various trials and studies, [32-34, 28] treatment with oral ivermectin can lead to moderate-to-severe adverse reactions; however, the majority of these reactions are temporary and mild [35-36]. Conversely, the side effects associated with topical ivermectin are generally mild, encompassing irritation, allergic dermatitis, and redness [37-38]. These agents may only temporarily provide relief to patients suffering from Demodex infestation rather than completely cure it [13]. Hence, Lotilaner seems to have revolutionized the therapeutic landscape for this condition.

In a review conducted by Markoulli M et al., determining the relation between dry eyes and contact lens discomfort (CLD), demodex blepharitis was found to be a major factor. Using a light microscope to examine the lashes of contact lens wearers who are tolerant and intolerant has allowed researchers to investigate the link between CLD and Demodex. Interestingly, it was found that 94% of intolerant individuals had demodex blepharitis as compared to only 6% of tolerant individuals [31]. Hence, the breakthrough of lotilaner could also prove useful in other conditions, such as CLD, due to Demodex.

Limitations:

It is important to acknowledge possible limitations that were seen in our study. The meta-analysis we conducted only included experimental research and observational research was not

included due to possible heterogeneity that could arise due to different study designs.

Additionally, observational studies were single-arm studies. Another substantial issue was the variability in the characteristics of some studies, such as different follow-up durations or duration of intervention. The majority of the studies included relatively small sample sizes. Moreover, doi plots suggested major asymmetry, which indicated a publication bias in our studies. In addition, several studies had a higher percentage of women participation which may indicate it affects women more compared to men. Therefore, further research is needed to have a better understanding of the efficacy of Lotilaner in Demodex blepharitis. Future studies should include a larger sample population with longer follow-up periods. Additionally, more variables should be measured in future studies, like composite cure, erythema cure, both upper and lower eyelids collarette score, etc., as these were reported in only a few studies.

In conclusion, our study showcased the remarkably positive attributes of Lotilaner in patients with Demodex Blepharitis. The drug demonstrated significantly better outcomes compared to the placebo, with minimal side effects and high drop comfort. Additionally, the GRADE evaluation yielded a moderate quality of evidence which supports the robustness of our findings. These encouraging results further strengthen the case for adding Lotilaner as a great alternative option in comparison to the current management strategies. The availability of specific, novel therapy for this condition, rather than non-specific options that are currently being implemented, makes it easier for ophthalmologists and physicians to deal with these cases quickly and efficiently while improving the quality of life of patients.

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CRedit Author Contribution Statement:

Muhammad Talha: Writing - Original Draft, Conceptualization, Methodology, Data Curation;

Mohammad Haris Ali: Writing - Original Draft, Methodology, Data Curation; **Eeshal Fatima:** Writing - Original Draft, Data Curation, Software; **Arsalan Nadeem:** Writing - Review & Editing, Supervision; **Abdullah Ahmed:** Writing - Review & Editing, Supervision; **Abdulqadir Nashwan:** Writing - Review & Editing, Supervision.

Legends:

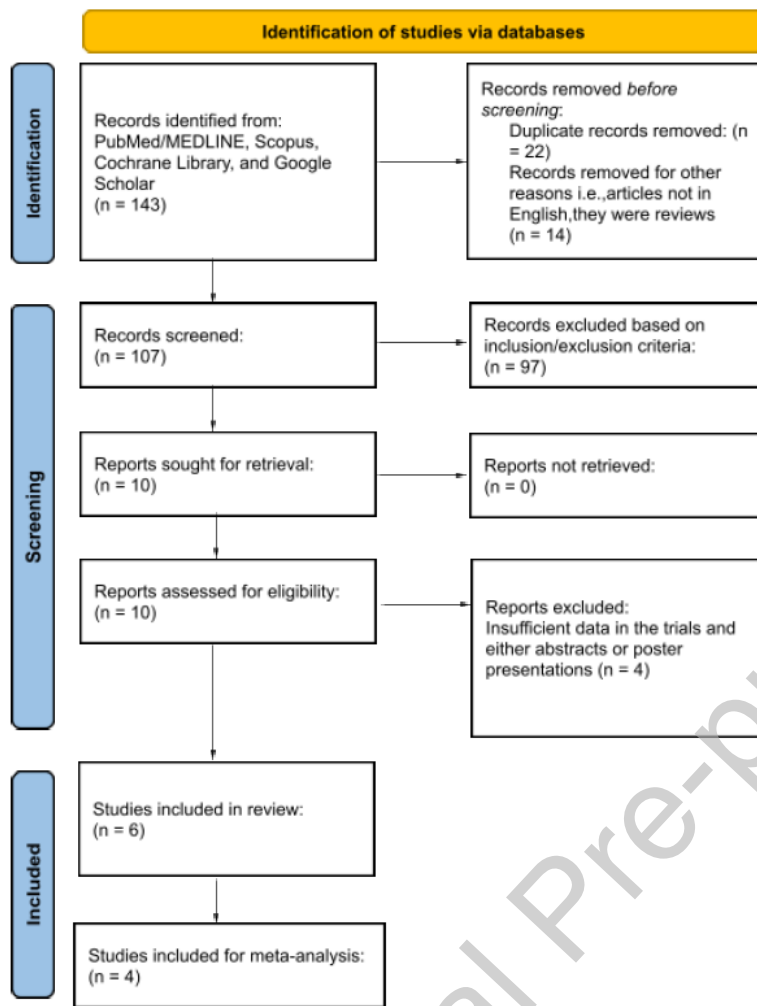


Figure 1: PRISMA Flow Diagram

Intention-to-treat	Study ID	D1	D2	D3	D4	D5	Overall	
	Roberto Gonzalez-Salinas et al. (2021)(3)	+	+	+	+	!	+	<div>+</div> Low risk
	Elizabeth Yeu et al. (2023)	+	+	+	+	!	+	<div>!</div> Some concerns
	Ian Benjamin Gaddie et al. (2023)	+	+	+	+	!	+	<div>-</div> High risk
	Elizabeth Yeu et al. (2022)	+	+	+	+	!	+	
								D1 Randomisation process D2 Deviations from the intended interventions D3 Missing outcome data D4 Measurement of the outcome D5 Selection of the reported result

Figure 2: Quality Assessment of RCTs Included in the Meta-Analysis

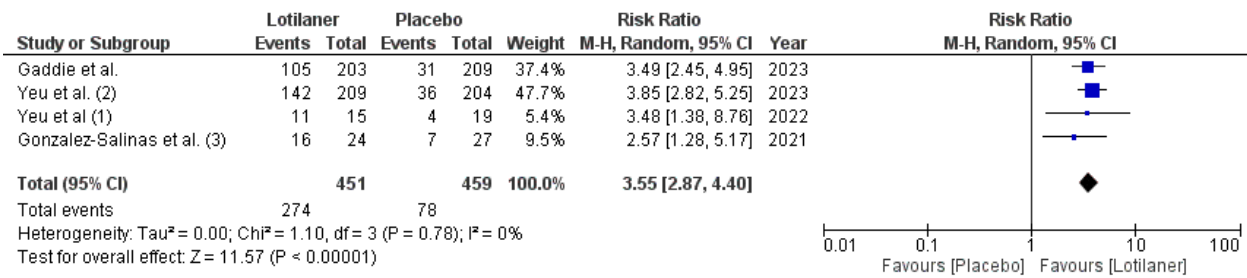


Figure 3: Pooled Incidence of the Mite Eradication

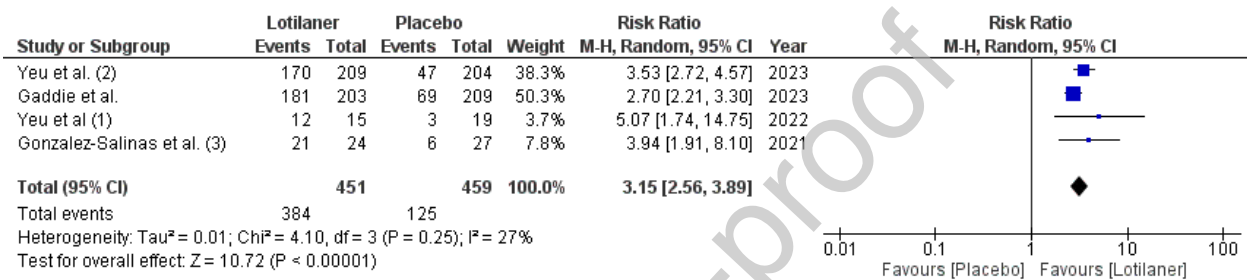


Figure 4: Pooled Incidence of Clinically Meaningful Collarette Score

Table 1 (A): Baseline Characteristics of the Included Studies

Table 1 (B): Baseline Characteristics of the Included Studies

Table 2: Quality Assessment of the Observational Studies Included in the Meta-Analysis

Table 3: Grading of Recommendations, Assessment, Development and Evaluation (GRADE)

Summary of Findings

Table 1 (A): Baseline Characteristics of Included Studies

Author	Year	Study design	Participants		Mean Age		Duration of intervention
			Vehicle	Lotilaner	Vehicle	Lotilaner	
Roberto Gonzalez-Salinas et al. (1)	2021	Single-arm, Open-label, Phase 2a Study	NA	18	NA	62.7 ± 2.3	42 days
Roberto Gonzalez-Salinas et al. (2)	2021	Single-arm, Open-label, Phase 2a Study	NA	14	NA	69.5 ± 13.2	28 days
Roberto Gonzalez-Salinas et al. (3)	2021	Phase II Clinical Trial	30	30	61.7 ± 1.9	59.6 ± 2.1	28 days
Elizabeth Yeu et al.	2023	Prospective, Multicenter, Phase 2b/3 Clinical Trial	209	212	67.8 ± 12.6	66.1 ± 12.1	43 days
Elizabeth Yeu et al.	2022	Phase 2b Clinical Trial	27	27	62.1 ± 8.3	58.5 ± 14.1	42 days
Ian Benjamin Gaddie et al.	2023	Prospective, Multicenter, Phase 3 Trial	209	203	65.1 ± 13.35	63.9 ± 15.15	42 days

Table 1 (B): Baseline Characteristics of Included Studies

Author	Year	Mean Collarette Score/grade before therapy		Mean mite density* before therapy		Mean Collarette Score/grade at the end of therapy		Mean mite density* at the end of therapy	
		Vehicle	Lotilaner	Vehicle	Lotilaner	Vehicle	Lotilaner	Vehicle	Lotilaner
Roberto Gonzalez-Salinas et al. (1)	2021	NA	3.56 ± 0.17 (UE) 3.00 ± 0.18 (LE)	NA	2.63 ± 0.39	NA	0.28 ± 0.11 (UE) 0.28 ± 0.11 (LE)	NA	0.12 ± 0.08
Roberto Gonzalez-Salinas et al. (2)	2021	NA	3.07 ± 0.21 (UE) 2.73 (LE)	NA	2.28 ± 0.16	NA	0.79 ± 0.19 (UE) 0.5 (LE)	NA	0.14 ± 0.05
Roberto Gonzalez-Salinas et al. (3)	2021	3.6 (UE), 3.3 (LE)	3.6 (UE), 3.2 (LE)	2.9	2.7	2.5 (UE), 2.1 (LE)	0.8 (UE), 0.9 (LE)	1.6	0.2
Elizabeth Yeu et al.	2023	2.8 ± 0.71 (UE)	2.8 ± 0.77 (UE)	3.16 ± 1.59	3.19 ± 1.67	2.2 ± 1.08 (UE)	0.8 ± 0.89 (UE)	1.39 ± 1.27	0.14 ± 0.26
Elizabeth Yeu et al.	2022	3.33 ± 0.16 (UE) 3.13 ± 0.18 (LE)	3.16 ± 0.19 (UE) 3.04 ± 0.20 (LE)	2.95 ± 0.25	3.27 ± 0.35	2.16 ± 0.31 (UE) 1.89 ± 0.27 (LE)	0.27 ± 0.15 (UE) 0.33 ± 0.16 (LE)	1.39 ± 0.52	0.18 ± 0.09
Ian Benjamin Gaddie et al.	2023	3.0 ± 0.80 (UE)	2.9 ± 0.77 (UE)	3.33 ± 1.71	3.16 ± 1.42	2.0 (UE)	0.6 (UE)	1.39	0.27

*mites per lash; UE = Upper Eyelid; LE = Lower Eyelid;

Table 2: Quality assessment of the observational studies included in the meta-analysis

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Rater #1 Initials: MT	Rater #2 Initials: MHA
Roberto Gonzalez-Salinas et al. (1) (2021)	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	N/A	Fair	Fair
Roberto Gonzalez-Salinas et al. (2) (2021)	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	N/A		

Questions:

1. Was the research question or objective in this paper clearly stated?
2. Was the study population clearly specified and defined?
3. Was the participation rate of eligible persons at least 50%?
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?
5. Was a sample size justification, power description, or variance and effect estimates provided?
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
10. Was the exposure(s) assessed more than once over time?
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
12. Were the outcome assessors blinded to the exposure status of participants?
13. Was loss to follow-up after baseline 20% or less?

14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

Table 3: Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Summary of Findings

Certainty assessment						No of patients		Effect		Certainty
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Lotilaner	Control	Relative (95% CI)	Absolute (95% CI)	
Mite Eradication Incidence										
4	RCT	not serious	not serious	not serious	serious ¹	274/451	78/459	RR 3.55 (2.87 - 4.40)	434 more per 1000 (from 318 more to 578 more)	⊕⊕⊕⊖ Moderate
Clinically Meaningful Collarette Score										
4	RCT	not serious	not serious	not serious	serious ²	384/451	125/459	RR 3.15 (2.56 - 3.89)	586 more per 1000 (from 425 more to 787 more)	⊕⊕⊕⊖ Moderate

CI: confidence interval; RR: risk ratio; RCT: Randomised Control Trials;

1 = Optimal Information size (OIS) of 1928 was not met; 2 = Optimal Information size (OIS) of 1526 was not met

Table of Contents Statement:

Exploring Lotilaner's Efficacy in Mitigating Severe Demodex blepharitis: Insights from a Rigorous Meta-Analysis. This study comprehensively assesses the potential of lotilaner in treating demodex blepharitis. Valuable insights into its clinical implications for patients suffering from demodex blepharitis are highlighted, contributing to improved management strategies and enhanced quality of life for these individuals.

Declaration of Competing Interest:

None to Declare