The Ocular Surface 29 (2023) 537–546

Contents lists available at ScienceDirect

The Ocular Surface

journal homepage: www.elsevier.com/locate/jtos

Efficacy and safety of AZR-MD-001 selenium sulfide ophthalmic ointment in adults with meibomian gland dysfunction: A vehicle-controlled, randomized clinical trial

Stephanie L. Watson [a,*], Lyndon W. Jones [b], Fiona Stapleton [c], Mark Hinds [d], Alison Ng [b], Jacqueline Tan [c], Yair Alster [e], Charles Bosworth [e], Omer Rafaeli [e], Venita DePuy [f], The CELESTIAL STUDY Group

[a] The University of Sydney, Faculty of Medicine and Health, Save Sight Institute, Sydney, NSW, 2000, Australia
[b] Centre for Ocular Research & Education (CORE), School of Optometry & Vision Science, University of Waterloo, Waterloo, Ontario, N2L 3G1, Canada
[c] School of Optometry and Vision Science, UNSW Sydney, Australia
[d] Ophthalmic Trials Australia, Brisbane, Australia
[e] Azura Ophthalmics, Tel Aviv, Israel
[f] Bowden Analytics, Pittsboro, NC, United States

A B S T R A C T

Purpose: Meibomian gland dysfunction (MGD) is a chronic progressive disease with downstream effects on ocular signs and symptoms. AZR-MD-001 is a selenium sulfide ophthalmic ointment that was investigated as a potential treatment option for patients with MGD.
Methods: A Phase 2, multi-center, double-masked, parallel group study was conducted across 29 sites, with 245 patients randomized 1:1:1 to AZR-MD-001 0.5%, AZR-MD-001 1.0% or vehicle applied to the lower eyelid, twice weekly. Patients were eligible for the trial if they presented with signs and symptoms of MGD. Co-primary efficacy endpoints were the changes from baseline in number of open glands (Meibomian Glands Yielding Liquid Secretion [MGYLS] score) and patient-reported ocular surface symptoms (Ocular Surface Disease Index [OSDI] total score) at Month 3. Efficacy outcomes were captured at Day 14, Month 1.5 and Month 3. Safety and tolerability were assessed for treatment-emergent adverse events (TEAEs).
Results: AZR-MD-001 0.5% (n = 82 patients) treatment resulted in significant improvements in MGYLS score, with patients experiencing an average increase from baseline of 4.2 and 2.4 open glands secreting meibum for the drug and vehicle, respectively ($p < 0.001$) and from baseline a mean OSDI total score improvement of 7.3 and 3.8 for the drug and vehicle, respectively ($p < 0.05$). Most TEAEs were mild and transient, with 3 serious adverse events (SAEs) reported with AZR-MD-001 (none related to study drug).
Conclusions: Co-primary endpoints were met for AZR-MD-001 0.5% at Month 3, with a statistically significant improvement in the signs and symptoms of MGD. AZR-MD-001 was safe and well tolerated.
Trial registration: ClinicalTrials.gov Identifier: NCT03652051, ANZCTR Registration Number: AZ201801.

1. Introduction

Meibomian gland dysfunction (MGD) is a chronic and progressive condition associated with blockage of meibomian glands and alteration in meibum quality [1]. In 2011, expert consensus elaborated that MGD possesses 'intrinsic features including orifice plugging, duct obstruction and dilatation, gland atrophy and dropout, and qualitative changes in expressed secretions [2,3]. Abnormal keratin production and aggregation, which alters meibum quality and quantity, leads to blockage of meibomian glands [4]. Meibum, which is secreted by meibomian glands located within the tarsus, consists of hundreds of different wax and cholesteryl ester lipids and 90 different proteins, that include various forms of keratin [5–7]. Meibum provides tear film stability, ocular surface protection against microbial agents and organic matter, and reduces evaporation of aqueous components of the tear film, playing an integral role in maintaining eye health [8, 9].

MGD prevalence is estimated to be as high as 35%–70% in certain populations, with total prevalence estimated at over 100 million Americans [10–13]. Notably, there appears to be a higher prevalence of MGD in reports from Asian populations compared to populations with a majority of Caucasians. Studies conducted in Bangkok, Taiwan, Japan, and Beijing reported MGD prevalence rates of 46.2%, 60.8%, 61.9%,

* Corresponding author. Save Sight Institute, Faculty of Medicine and Health, The University of Sydney, 8 Macquarie Street, Sydney, NSW, 2000, Australia.
E-mail address: stephanie.watson@sydney.edu.au (S.L. Watson).

https://doi.org/10.1016/j.jtos.2023.07.002
Received 20 April 2023; Received in revised form 22 June 2023; Accepted 2 July 2023
Available online 20 July 2023

and 69.3%, respectively. In contrast, studies from Australian populations predominantly composed of Caucasians reported lower prevalence rates, such as 3.5% in the Salisbury Eye Evaluation study and 19.9% in the Melbourne Visual Impairment Project [14–19]. It is important to exercise caution when drawing broad conclusions due to variations in definition and diagnostic criteria used across countries, which can drive different rates of prevalence. Further, large population-based studies estimate that over 80% of people diagnosed with dry eye symptoms also have MGD [20,21]. The impact of MGD-associated abnormalities commonly includes alterations of the tear film and vision quality, ocular irritation, clinically apparent inflammation, anterior blepharitis and contact lens discomfort (CLD), though individuals with early-stage or mild MGD may be asymptomatic [2,22].

The primary treatment goal in MGD is ensuring a healthy lipid layer for the ocular surface by improving tear film stability, which is dependent on high-quality meibum secretion and normal flow [23]. Conventional treatments for obstructive MGD entail eyelid hygiene [24], omega-3 dietary supplementation [25], topical antibiotics [26], corticosteroids [27], cyclosporine [28], diquafosol [29], oral tetracycline antibiotics (e.g., doxycycline, minocycline, and tetracycline) [30,31], and oral omega-6 fatty acids as well as mechanical expression for the unclogging of glands that are blocked [32,33]. Specifically, the use of topical antibiotics and corticosteroids to suppress bacterial colonization and inflammation of the eyelid margin associated with MGD has been shown to be effective in the relief of symptoms and the signs of MGD, but the success of the treatment may have little to do with the changed meibum. Oral antibiotics (including doxycycline, tetracycline, and minocycline) are used to suppress bacterial colonization and reduce inflammation of the lid margin, as well as suppress some of the lipase breakdown of the meibum, leading to decreased free fatty acids and diglycerides. Drug intolerance and prolonged therapy have limited the clinical application of oral antibiotics [34]. Eyelid-warming devices have also been employed in the treatment of patients with obstructive MGD [35–39]. Warm compresses and thermal/mechanical devices such as LipiFlow®, a vectored thermal pulsation treatment, attempt to alleviate meibum blockages [40,41] by raising the internal temperature of the meibomian glands over the normal melting point for meibum (i.e., 32 °C–40 °C) [37].

There are currently no approved pharmacotherapies for MGD and current dry eye disease–approved medications do not target key MGD pathophysiology [42,43]. Selenium sulfide-containing products are poorly absorbed through intact skin, but as topical preparations they have been reported to induce sebum production and to possess keratolytic and keratostatic effects, making them a logical development candidate for the treatment of MGD. Due to its poor ability to cross competent epithelial boundaries, selenium sulfide should be applied directly to the site of action where a redox reaction causes it to break disulfide bonds, causing proteins to disaggregate, potentially unblocking the meibomian gland orifices and decreasing meibum viscosity [44,45].

AZR-MD-001 is a semi-solid ophthalmic ointment containing selenium sulfide. This Phase 2 clinical study was designed to evaluate the safety and efficacy of AZR-MD-001 (0.5% and 1.0%) over a 6-month dosing period in patients with signs and symptoms of MGD. Results from the primary endpoints, evaluated at 3 months, are discussed here.

2. Methods

2.1. Design

This Phase 2 study was a randomized, double-masked, vehicle-controlled, parallel-group, multicenter study investigating the safety and efficacy of AZR-MD-001 (0.5% and 1.0%) in patients with signs and symptoms of MGD (NCT03652051; ANZ201801). It was conducted from February 2021 to August 2022 across 29 sites in Australia, New Zealand and Canada. Patients were enrolled based on eligibility criteria at screening and baseline visits. If initially deemed eligible, patients were instructed to withdraw all treatments for MGD or dry eye disease, including artificial tears (washout period), and to return to the site for the baseline visit 14 days later. During the baseline visit, eligibility criteria were confirmed, and patients were required to demonstrate ability to follow dosing instructions by correctly dispensing ointment using a dispensing aid and applying the demonstration medication (petrolatum white) to their lower eyelid.

Patients were randomized in a 1:1:1 ratio to one of two concentrations of AZR-MD-001 (0.5%, 1.0%) or vehicle in both eyes and assessed at the 3-month endpoint of the treatment period (eFigure A). Patients were randomized to study treatment using an interactive web response system (IWRS). Randomization numbers were assigned sequentially in order of enrolment within the patient's stratum. The IWRS reported a medication kit number for each patient that corresponded to the randomization number. Study sites used the IWRS at subsequent study visits to obtain medication kit numbers for dispensing study drug to patients.

All patients were stratified by MGD diagnosis duration (<5 or ≥ 5 years) and Meibomian Gland Secretion (MGS) score (<6, or ≥ 6 and ≤ 12) at baseline.

2.2. Eligibility criteria

Full eligibility criteria are detailed in eAppendix A. Key inclusion criteria included being aged ≥ 18 years with evidence of meibomian gland obstruction in both eyes, a history of associated dry eye signs and symptoms within the past 3 months, and no significant glandular atrophy on meibography ($<75\%$). Key exclusion criteria included a history or presence of any other ocular condition in either eye that would likely interfere with data interpretation. Patients with glaucoma or ocular hypertension in either eye or the planned insertion/removal of glaucoma filtration shunts/devices during the study were excluded. No corneal abnormality or disorder that impacted the normal spreading of the tear film (keratoconus, pterygia, scarring) or corneal integrity was allowed. The use of contact lenses, artificial tears, saline drops or ocular lubricants was not permitted.

2.3. Treatments

All treatments consisted of AZR-MD-001 0.5%, AZR-MD-001 1.0% or vehicle and were provided in identical 5 g multi-use opaque white tubes with a screw cap to maintain masking. All patients and site staff were masked to treatment assignment. The randomized study drug was applied twice weekly immediately before sleep, on the lower eyelids, by the patient using their washed index finger. Subsequent blinking transferred drug to the upper eyelid. To ensure consistent dosing between patients and between applications, patients were trained on appropriate dispensing at the baseline visit.

Patients were instructed to have at least a one-day gap between doses. For example, if they dose on Tuesday their next dose should be on a Thursday night at the earliest and Sunday night at the latest if they intend to dose on Tuesday night again the following week. The twice-weekly regimen was initially based on the recommended use of selenium sulfide medicated shampoo and was further tested in a Phase 2a program where daily and twice-weekly regimens were tested. In the Phase 2a program, the twice-weekly regimen was found to produce good efficacy and safety and was advanced into the current study as it represented the least amount of drug exposure required to achieve desired efficacy in this patient population.

2.4. Assessments

Visits occurred at screening (Visit 1, Day −14), baseline (Visit 2, Day 0), Day 14 (Visit 3), Month 1.5 (Visit 4) and Month 3 (Visit 5, primary endpoint). Best-corrected visual acuity, slit-lamp biomicroscopy (including eyelid margin erythema/telangiectasia), sodium fluorescein

corneal staining (Oxford scale), lissamine green conjunctival staining (Oxford scale) and meibomian glands [46–48] were assessed at all study visits. Meibomian gland evaluations were performed by the same investigator for all visits for a patient. Unanesthetized Schirmer tests were performed at screening, baseline and Month 3, with intraocular pressure, ophthalmoscopy exam, and meibography assessed at screening and Month 3. Signs of MGD were measured by the number of Meibomian Glands Yielding Liquid Secretion (MGYLS) and MGS scores. AZR-MD-001's mechanism of action includes increased lipogenesis, the breaking down of protein aggregates, and slowing down the future deposition of keratin, which should help open obstructed meibomian glands and restore normal meibum viscosity. Therefore, MGYLS and MGS, both of which are closely linked to the mechanism of action for AZR-MD-001, were evaluated. Similarly, the symptoms of MGD were assessed using the Ocular Surface Disease Index (OSDI) Version 1 (©1995 Allergan, all rights reserved), the only validated symptom endpoint, in addition to other patient-reported outcomes such as Standard Patient Evaluation of Eye Dryness (SPEED). A Phase 2a program confirmed that MGYLS had better signal to noise ratio compared to MGS. Phase 2a also evaluated OSDI, SPEED and VAS scales and determined that total OSDI had the best signal to noise ratio for a symptom endpoint. Thus, total OSDI and MGYLS were selected as the co-primary endpoints for this confirmatory efficacy study. Tear break-up time (TBUT) was used to assess downstream effects of MGS and MGYLS.

The number of MGYLS was based on a standardized technique for meibomian gland expression, where secretion in the lower eyelid of each eye was measured for 5 consecutive glands per region (temporal, central and nasal). Expression was performed using a standardized expression device, the Meibomian Gland Evaluator (Johnson & Johnson [49]) on 15 glands individually, with 0 (none observed) or 1 (liquid observed) recorded following expression. The MGYLS was scored from 0 to 15, where lower scores indicated more severe disease. To be a 'MGYLS responder,' a patient needed a clinically meaningful increase in open glands associated with symptom resolution, demonstrated by an increase of $\geq$5 MGYLS from baseline, which is between a score consistent with symptomatic disease ($\leq$4 responding glands) and non-symptomatic disease ($\geq$6 responding glands) [3].

The MGS was based on visual evidence of meibum quality. Using similar methodology as MGYLS, secretion in the lower eyelid of each eye was measured on a total score scale of 0–45 per eye, with lower scores indicating more severe disease. Each gland was scored using a four-point scale where; 0 = no secretion, 1 = inspissated/toothpaste consistency, 2 = cloudy liquid secretion and 3 = clear liquid secretion. A 'MGS responder' was defined as a patient with MGS score >12, indicating normal meibum quality [37].

The impacts of MGD were evaluated by symptoms (OSDI, SPEED) and TBUT. The OSDI questionnaire evaluated ocular symptoms, environmental triggers and vision-related functioning. OSDI total score ranges 0–100, with higher scores representing greater disability. An 'OSDI total score responder' was defined as a patient with OSDI total score <13, which was considered normal or asymptomatic for dry eye disease [50].

The SPEED total score was based on the occurrence, frequency and severity of four symptoms of eye dryness, with the patient recording the time/occurrence of symptoms (at this visit, within past 72 h or within past 3 months) [51]. SPEED total score ranged from 0 to 28, with higher scores indicating increasing severity. Scores from 0 to 4 were classified as 'mild' disease, 5–7 as 'moderate' and $\geq$8 as 'severe' based on previous guidelines [52].

TBUT [53] was the time (seconds) taken for the first dry spot to appear on the cornea after a complete blink and was evaluated using a micropipette (5 μL of 2%) to deliver non-preserved sodium fluorescein and the cobalt blue light on a slit lamp with measurements in triplicate per eye. Increased values in TBUT indicated improvement, with 'TBUT responders' defined as patients with normal response, i.e., TBUT $\geq$10 s [53].

2.5. Statistical analyses

The co-primary efficacy endpoints were the change from baseline in signs of MGD (measured by MGYLS) and symptoms of MGD (measured by OSDI). The co-primary endpoints were evaluated using a hierarchical approach. For each endpoint, the subsequent endpoint was not evaluated unless the prior endpoint was significant at $\alpha = 0.05$. Therefore, the hierarchical approach controlled for the family-wise Type I error and did not require adjustment for multiplicity [54]. The hierarchical approach was change from baseline to Month 3 in MGYLS, comparing AZR-MD-001 0.5% to placebo, followed by OSDI total score, comparing AZR-MD-001 0.5% to placebo, MGYLS, comparing AZR-MD-001 1.0% to placebo and finally OSDI total score, comparing AZR-MD-001 1.0% to placebo. Analysis was performed using an ANCOVA model with (continuous) baseline MGYLS score or OSDI total score as a covariate and treatment (0.5% or 1.0% AZR-MD-001 or placebo), duration of disease category (<5 or $\geq$5 years), and baseline MGS score category (<6 or $\geq$6 and $\leq$ 12) as factors in the model. The ANCOVA model was also performed for each AZR-MD-001 dosing level versus placebo. The least square mean differences between treatments (0.5% versus placebo and 1.0% versus placebo) were presented along with two-sided (95%) confidence intervals. For further information on the hierarchical approach and sample size determination, please see eAppendix B.

Efficacy analyses were performed on available data from the intent-to-treat (ITT) population, which included all randomized patients. The safety population included all randomized patients who received $\geq$1 dose of study treatment. Co-primary endpoints were analyzed separately using an ANCOVA model including terms for baseline value and analysis. Additional secondary and exploratory efficacy endpoints were similarly analyzed. Categorical variables were summarized by sample size (N), frequency count and percent, and analyzed using Cochran-Mantel-Haenszel to evaluate differences between treatments, controlling for disease duration category and baseline MGS score category. SAS® software for Windows Version 9.4 or higher was used (SAS® Institute Inc., Cary, NC, USA).

2.6. Ethics

The study was conducted in accordance with US Code of Federal Regulations Title 21, the International Conference on Harmonisation Consolidated Good Clinical Practices Guideline (E6), the standard operating procedures of the sponsor and vendors participating in the conduct of the study, and the ethical principles of the Declaration of Helsinki. The study protocol and associated documents were reviewed and approved in writing by a properly constituted Institutional Review Board or Independent Ethics Committee at each site, with approval obtained prior to study initiation. Written informed consent and related materials were obtained in accordance with applicable regulations; informed consent was required before any study-specific procedures were initiated.

3. Results

3.1. Baseline characteristics

A total of 245 patients with signs and symptoms of MGD were randomized and included in the ITT and safety populations (Fig. 1); 35 (14.3%) patients discontinued the study before the Month 3 visit, with 3-month completion rates being 79.3% (n = 65/82) for AZR-MD-001 0.5%, 80.7% (n = 67/83) for AZR-MD-001 1.0% and 95.0% (n = 76/80) for vehicle. Over 3 months of exposure, patients were expected to administer 24 doses of study drug; a total of 196 (94.2%) patients were compliant (80–125% of doses taken) with drug administration, with similar overall compliance across treatment groups.

The primary reason for discontinuation overall was study withdrawal (11 [13.4%] patients in the 0.5% group, 9 [10.8%] patients in

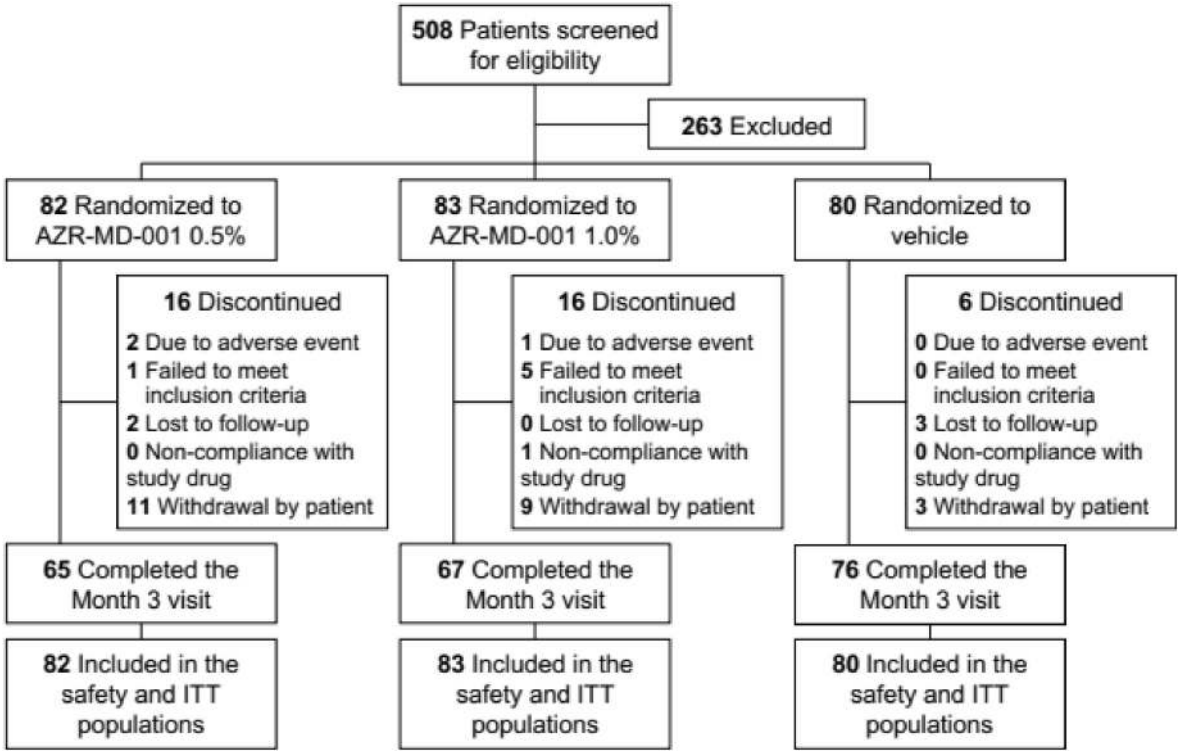

Fig. 1. Recruitment, randomization, and patient flow
Two patients did not attend the Month 3 visit but continued with the study.

the 1.0% group, and 3 [3.8%] patients in the placebo group). The increased withdrawal by patients observed across the treatment groups was associated with mild to moderate application site discomfort/irritation recorded around the time of withdrawal. The 1.0% group had the most patients (5 [6.0%]) fail to meet inclusion criteria after randomization.

Baseline demographics and clinical characteristics were similar across treatment arms, with signs and symptoms consistent with that for an MGD patient population (Table 1). Patients were largely white (72.2%), female (66.5%), and had a mean age (SD) of 53.2 (17.5) years. MGD duration, self-reported at baseline, was ≥5 years in 64.5% of patients, with 57.1% of patients presenting with a baseline MGS score between 6 and 12, inclusive.

3.2. Co-primary endpoints

AZR-MD-001 0.5% met both co-primary endpoints (Table 2). There was significantly greater improvement in MGYLS scores from baseline to Month 3 with 0.5% compared to vehicle, indicating that AZR-MD-001 treatment resulted in more open meibomian glands (Fig. 2A). There was significantly greater improvement from baseline to Month 3 in mean OSDI total score with 0.5% compared to vehicle, indicating that AZR-MD-001 0.5% resulted in greater symptom relief than vehicle (Fig. 2B). For both co-primary endpoints, there was numerical improvement with AZR-MD-001 1.0% over vehicle that did not reach statistical significance.

Table 1
Baseline demographics and patient clinical characteristics of the safety population.

		AZR-MD-001 0.5% (N = 82)	AZR-MD-001 1.0% (N = 83)	Vehicle (N = 80)
Age (years)	Mean (SD)	52.1 (16.9)	55.6 (17.2)	51.9 (18.5)
	Range	18–80	20–93	20–97
Gender, n (%)	Male	31 (37.8)	27 (32.5)	24 (30.0)
	Female	51 (62.2)	56 (67.5)	56 (70.0)
Race, n (%)	White	57 (69.5)	64 (77.1)	56 (70.0)
	Asian	16 (19.5)	10 (12.0)	21 (26.3)
	Black	3 (3.7)	3 (3.6)	1 (1.3)
	Pacific Islander	0	1 (1.2)	0
	Other	6 (7.3)	5 (6.0)	2 (2.5)
Duration of MGD, n (%)	<5 years	29 (35.4)	30 (36.1)	28 (35.0)
	≥5 years	53 (64.6)	53 (63.9)	52 (65.0)
MGYLS score	Mean (SD)	1.7 (1.4)	1.9 (1.4)	1.8 (1.3)
MGS score, n (%)	<6	38 (46.3)	33 (39.8)	34 (42.5)
	≥6 and ≤ 12	44 (53.7)	50 (60.2)	46 (57.5)
OSDI total score	Mean (SD)	25.2 (7.5)	24.2 (6.0)	25.0 (6.7)

MGD: meibomian gland dysfunction; MGS: Meibomian Gland Secretion; MGYLS: Meibomian Glands Yielding Liquid Secretion; OSDI: Ocular Surface Disease Index; SD: standard deviation.

Table 2
Summary of co-primary and secondary efficacy endpoints (ITT population).

	AZR-MD-001 0.5% (N = 82)	AZR-MD-001 1.0% (N = 83)	Vehicle (N = 80)
Co-primary Endpoints			
Change from baseline in MGYLS score at Month 3, LS mean (SE)	4.2 (0.36)	3.2 (0.37)	2.4 (0.34)
P value vs baseline	<0.0001	<0.0001	<0.0001
P value vs vehicle	0.0004	0.14	
Change from baseline in OSDI total score at Month 3, LS mean (SE)	−7.3 (1.26)	−6.1 (1.30)	−3.8 (1.22)
P value vs baseline	<0.0001	<0.0001	0.0028
P value vs vehicle	0.04	0.18	
Secondary Endpoints			
Change from baseline in MGYLS score			
Day 14, LS mean (SE)	1.6 (0.22)	1.6 (0.22)	0.8 (0.21)
P value vs baseline	<0.0001	<0.0001	0.0002
P value vs vehicle	0.0080	0.0071	
Month 1.5, LS mean (SE)	2.9 (0.29)	2.8 (0.28)	1.8 (0.28)
P value vs baseline	<0.0001	<0.0001	<0.0001
P value vs vehicle	0.0046	0.0078	
Change from baseline in OSDI total score			
Day 14, LS mean (SE)	−2.4 (1.28)	−1.7 (1.30)	−2.3 (1.27)
P value vs baseline	0.0635	0.19	0.0684
P value vs vehicle	0.97	0.73	
Month 1.5, LS mean (SE)	−5.0 (1.26)	−3.3 (1.27)	−3.3 (1.23)
P value vs baseline	0.0002	0.013	0.0084
P value vs vehicle	0.33	0.97	
MGYLS responder rate			
Day 14 (mean %)	7.8	9.8	1.3
P value vs vehicle	0.10	0.033	
Month 1.5 (mean %)	27.2	28.4	5.4
P value vs vehicle	0.0012	0.0006	
Month 3 (mean %)	45.7	28.8	14.7
P value vs vehicle	0.0005	0.096	
OSDI total score responder rate			
Day 14 (mean %)	17.7	23.5	16.3
P value vs vehicle	0.53	0.52	
Month 1.5 (mean %)	31.5	27.1	23.8
P value vs vehicle	0.53	0.70	
Month 3 (mean %)	46.9	38.4	28.3
P value vs vehicle	0.020	0.39	
Change from baseline in SPEED score			
Day 14, LS mean (SE)	−2.3 (0.46)	−1.4 (0.46)	−2.2 (0.46)
P value vs baseline	<0.0001	0.0028	<0.0001
P value vs vehicle	0.88	0.21	
Month 1.5, LS mean (SE)	−2.7 (0.50)	−2.1 (0.52)	−2.3 (0.49)
P value vs baseline	<0.0001	0.0002	<0.0001
P value vs vehicle	0.61	0.74	
Month 3, LS mean (SE)	−4.3 (0.46)	−4.1 (0.45)	−2.8 (0.44)
P value vs baseline	<0.0001	<0.0001	<0.0001
P value vs vehicle	0.018	0.031	
Change from baseline in MGS score			
Day 14, LS mean (SE)	4.0 (0.51)	4.1 (0.51)	2.1 (0.50)
P value vs baseline	<0.0001	<0.0001	<0.0001
P value vs vehicle	0.0081	0.0035	
Month 1.5, LS mean (SE)	7.1 (0.75)	7.0 (0.71)	4.2 (0.72)
P value vs baseline	<0.0001	<0.0001	<0.0001
P value vs vehicle	0.0048	0.0056	
Month 3, LS mean (SE)	10.5 (0.91)	8.1 (0.88)	6.0 (0.84)
P value vs baseline	<0.0001	<0.0001	<0.0001
P value vs vehicle	0.0003	0.075	
MGS responder rates			
Day 14 (mean %)	19.9	18.5	7.6
P value vs vehicle	0.038	0.095	
Month 1.5 (mean %)	49.7	46.1	27.8
P value vs vehicle	0.0073	0.038	
Month 3 (mean %)	68.7	50.7	44.4
P value vs vehicle	0.0069	0.98	
Change from baseline in TBUT			
Month 3, LS mean (SE) seconds	2.21 (0.29)	1.53 (0.33)	0.52 (0.29)
P value vs baseline	<0.0001	<0.0001	0.079
P value vs vehicle	<0.0001	0.019	

ITT: intent-to-treat; LS: least squares; MGS: Meibomian Gland Secretion; MGYLS: Meibomian Glands Yielding Liquid Secretion; OSDI: Ocular Surface Disease Index; SE: standard error; SPEED: Standard Patient Evaluation of Eye Dryness; TBUT: tear break-up time.

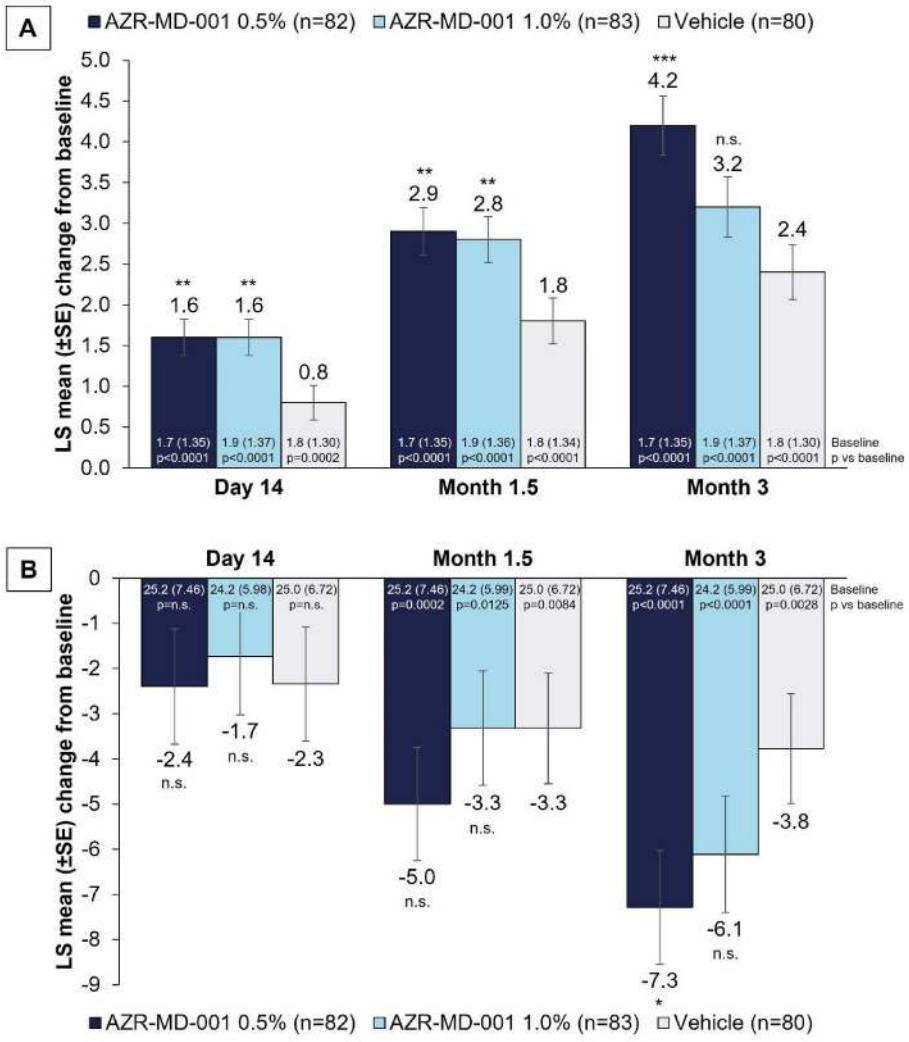

Fig. 2. Co-primary endpoints: change from baseline at Month 3 in (A) number of MGYLS and (B) OSDI total score (ITT population)

*p < 0.05, **p < 0.01, ***p < 0.001 vs vehicle; n.s., not significant.

LS means, differences, and p-values based on analysis of covariance (ANCOVA) model with baseline score as a covariate and treatment group, disease duration category (<5 vs ≥ 5 years), and baseline Meibomian Gland Secretion score category (<6 vs 6–12) as factors. ANCOVA models are created separately for each visit. Multiple imputation was performed within the ITT population.

Baseline: baseline mean (standard deviation) score; ITT: intent-to-treat; LS: least squares; MGYLS: Meibomian Glands Yielding Liquid Secretion (higher scores are better); OSDI: Ocular Surface Disease Index (lower scores are better); SE: standard error.

3.3. Key secondary analyses

There was significantly greater improvement in MGYLS scores from baseline to Day 14 and to Month 1.5 in both AZR-MD-001 treatment groups and at Month 3 for the 0.5% treatment group compared to vehicle (Table 2; Fig. 2A). At Months 1.5 and 3, a significantly greater percentage of patients treated with AZR-MD-001 0.5% than vehicle were MGYLS responders (i.e., ≥5-gland increase from baseline), and at Day 14 and Month 1.5, significantly more patients treated with AZR-MD-001 1.0% than with vehicle were MGYLS responders (Table 2; eFigure B). At all timepoints, the percentage of responders with AZR-MD-001 was numerically higher than with vehicle without reaching statistical significance.

At baseline, no patients were classified as 'normal' or asymptomatic per OSDI (score <13) as all patients were diagnosed with symptomatic MGD. OSDI total score responder rates analysis at Month 3 found significantly more patients were asymptomatic in the 0.5% group compared to vehicle; at all three timepoints, the responder rates in both treatment groups were numerically higher than in the vehicle group but without statistical significance (Table 2; eFigure C).

At Month 3, SPEED scores significantly decreased for both the 0.5% and 1.0% treatment groups relative to vehicle (Table 2; eFigure D).

There was greater improvement from baseline in MGS score at all three timepoints in the 0.5% and 1.0% treatment groups (Table 2). The 0.5% treatment group showed significantly greater improvement in MGS scores compared to vehicle at all timepoints. The 1.0% group demonstrated significantly greater improvement in MGS scores at Day 14 and Month 1.5 and numerically greater improvement at Month 3 compared to vehicle. At all three timepoints in the clinical trial, the percentage of MGS responders (i.e., patients with a 'normal' value of MGS >12) in both treatment groups was higher than for vehicle (Table 2; eFigure E). Significantly more patients in the 0.5% treatment group had 'normal' quality meibum at all timepoints, with numerically greater MGS responders in the 1.0% group at each timepoint compared to vehicle.

Downstream effects of MGS and MGYLS improvements were assessed by changes in TBUT, which reached significant improvements from baseline at all timepoints for the 0.5% and 1.0% groups and significant difference compared to vehicle at Month 1.5 for 0.5% and Month 3 for both treatment groups (Table 2; eFigure F). Significantly higher percentage of patients treated with AZR-MD-001 achieved normal TBUT of ≥10 s (i.e., TBUT responders) at Month 3 compared with vehicle (eFigure F).

3.4. Safety and tolerability

One hundred thirty-seven of 245 (55.9%) patients across all groups reported a treatment-emergent adverse event (TEAE; 47 with non-ophthalmic events, 118 with ophthalmic events) (Table 3). TEAEs reported in ≥5% of any treatment group were application-site pain (0.5%, n = 14 [17.1%]; 1.0%, n = 13 [15.7%]; and vehicle, n = 0, respectively), increased lacrimation (11.0%, 1.2%, 0%), superficial punctate keratitis

Table 3
Summary of treatment-emergent adverse events (TEAEs; safety population).

	AZR-MD-001 0.5% (N = 82)	AZR-MD-001 1.0% (N = 83)	Vehicle (N = 80)
Any TEAEs, n (%)	54 (65.9)	61 (73.5)	22 (27.5)
Any ophthalmic TEAEs (in either eye), n (%)	47 (57.3)	57 (68.7)	14 (17.5)
Any non-ophthalmic TEAEs (in either eye), n (%)	16 (19.5)	18 (21.7)	13 (16.3)
Any possibly, probably, or certainly related TEAEs, n (%)	42 (51.2)	50 (60.2)	10 (12.5)
TEAEs reported in ≥5% of patients, n (%)			
Application-site pain	14 (17.1)	13 (15.7)	0
Lacrimation increased	9 (11.0)	1 (1.2)	0
Superficial punctate keratitis[a]	5 (6.1)	6 (7.2)	1 (1.3)
Eye pain	5 (6.1)	6 (7.2)	1 (1.3)
Vital dye staining cornea present[a b]	4 (4.9)	7 (8.4)	1 (1.3)
Eye irritation	4 (4.9)	5 (6.0)	2 (2.5)
Application-site irritation	2 (2.4)	5 (6.0)	0
Any serious TEAEs, n (%)[c]	1 (1.2)	1 (1.2)	2 (2.5)
Study drug withdrawal due to TEAEs, n (%)[d]	11 (13.4)	9 (10.8)	1 (1.3)

[a] Defined as associated with an increase in corneal staining of ≥2 grades.
[b] 62% baseline incidence of corneal staining (Oxford Score 1 or 2 units) signifying early moderate inflammation.
[c] No serious TEAEs were considered related to study drug.
[d] Patients may have restarted study drug after resolution of the event. Only 3 patients were discontinued from the study due to an adverse event (2 in the AZR-MD-001 0.5% group and 1 in the AZR-MD-001 1.0% group).

(9.8%, 8.4%, 1.3%), corneal staining (6.1%, 8.4%, 1.3%), eye pain (6.1%, 7.2%, 1.3%), eye irritation (4.9%, 6.0%, 2.5%), application-site irritation (2.4%, 6.0%, 0%) and eye inflammation (3.7%, 9.6%, 1.3%). The majority (93.6%) of ophthalmic adverse events in AZR-MD-001 patients were rated as mild to moderate.

Two (2.4%) patients in the 0.5% group discontinued the study due to superficial punctate keratitis (SPK) and one patient (1.2%) in the 1.0% group discontinued due to stinging and irritated eyes. All cases of SPK resolved following cessation of treatment with no sequela. Five serious TEAEs were reported by four patients: pericarditis, thyroid mass, pneumonia, post procedural hemorrhage and nephrolithiasis. All SAEs were non-ophthalmic and not considered study drug–related by the investigator. No deaths were reported during the study.

4. Discussion

We report the first double masked, controlled study that demonstrates that AZR-MD-001, a keratolytic and lipogenic agent, improves outcome measures representing the key drivers for resolving MGD: open glands (MGYLS) and meibum quality (MGS), and in turn, downstream effects on tear film stability (as measured by TBUT) and patient symptoms (OSDI, SPEED), which were statistically significant and clinically meaningful relative to control at 0.5% concentration by Month 3. Patients in our study had pathophysiological signs of MGD (blocked glands, poor meibum quality) and histories of related ocular surface symptoms, with two-thirds of patients having MGD for >5 years.

This is the first report on using selenium sulfide for the treatment of MGD. While clinical studies from the 1950s have evaluated topical selenium sulfide for treating seborrheic blepharitis, some evaluations were not statistically significant [55–58], and none evaluated selenium sulfide for treatment of MGD. Across these early investigations, topical application of 0.5% selenium sulfide up to twice daily to the eyelid margin was safe and well tolerated over three months of treatment and demonstrated good efficacy in reducing signs of seborrheic blepharitis. Variables measured included urinary selenium excretion [57], corneal damage [58], skin oiliness [56], and meibum quality [55], compared to the main variables (number of open glands and meibum quality) measured in this study. The most severe TEAE reported was epithelial keratitis [56]. Evidence based upon rechallenge after dosing application retraining in several patients suggests that improper application contributed to this finding. This has been both observed in studies undertaken in the 1950s, where a few cases of improper application resulted in similar AEs [56–58], as well as by the observation of complete eradication of this AE for months 4–6 of therapy following further clarification to study patients on proper dose application (data on file).

Notably, AZR-MD-001 was administered just twice weekly compared to the twice-daily regimen of the seborrheic blepharitis studies, which likely contributed to the 94.2% compliance rate of patients with MGD. While in the current study, the 1.0% concentration showed significance at early timepoints, it did not perform as consistently as the 0.5% concentration of AZR-MD-001. Evidence from pre-clinical studies for selenium sulfide (data on file) suggested that the effect of the selenium sulfide on lipid production in sebaceous cells (similar embryonic origin and mode of lipid release as meibocytes) may be non-linear, resulting in a lower lipogenic effect at higher concentrations. Since MGYLS counts the number of open glands secreting meibum, AZR-MD-001 0.5% was prioritized in the statistical hierarchy as the optimal concentration.

While both concentrations used in this study positively benefit lipid production, and the percentage of TEAEs reported were similar between the 0.5% and 1.0% groups, the results of the current study are consistent with an earlier Phase 2a clinical study which confirmed that AZR-MD-001 0.5% was much more likely than AZR-MD-001 1.0% to achieve improvements in both sign and symptom response (data on file). This information justified the hierarchical testing approach which was used to control Type 1 error with multiple measures and treatment arms (i.e., AZR-MD-001 0.5% changes in MGYLS followed by OSDI total score were prioritized over those endpoints with AZR-MD-001 1.0%) to preserve statistical rigor and to maintain pivotal regulatory standards.

In patients treated with vehicle, while showing reduced effect compared to drug, improvement from baseline was noted. This observation is typical for many other ocular surface treatment studies. Modern clinical studies in ocular surface disease are designed with the intent of comparing drug effects on signs and symptoms in a treatment arm to a placebo/vehicle arm, which ideally will portray the natural course of the disease. The perceived efficacy of a control in clinical trials may be skewed by several factors unrelated to pharmacology and which included the natural course of the disease: placebo effect (e.g., cytokine or allergen washout from frequent application or irritating controls [Xiidra™]) [59], Hawthorne effect (subjects' knowledge of being observed leads to changes in behavior), regression towards the mean (subjects are most likely to seek treatment when their symptoms are at their worst), environmental challenges (e.g., time of year), and manipulation of the lids (impacts glandular secretion, necessitating non-therapeutic expression techniques and could include vehicle application in the current study).

Vehicle response rates from 14.7% (MGYLS responders) to 44.2% (MGS responders) indicate that the study design features (e.g., repeat baseline measures, population characteristics, and use of the MGE)

worked to control the perceived efficacy of control, leaving ample room to observe the therapeutic effects of AZR-MD-001. The observed placebo/vehicle arm response rates in the current study compare well with historical rates in ocular surface disease trials, which can be as high as 80% [60,61].

Overall, AZR-MD-001 0.5% potentially provides several positive advantages over current widely used mechanical and thermal treatments for MGD such as iLux®, LipiFlow® and warm compresses. Across the studies evaluating these devices, the program used to support approval for LipiFlow® is the most comparable to the current study design. Lane and colleagues [37] randomized a total of 69 subjects (138 eyes) to LipiFlow® – a one-time, 12-min in-office treatment. Subjects meeting inclusion criteria were ≥18 years of age; were willing to comply with the study procedures and follow-up schedule; reported dry eye symptoms within 3 months of the baseline examination, with a Standard Patient Evaluation for Eye Dryness (SPEED) score ≥6 at the baseline visit; had evidence of meibomian gland obstruction (based on a total meibomian gland secretion score of ≤12 for 15 glands of the lower lid); and completed the informed consent process. Prior to the baseline visit, subjects were required to discontinue use of systemic antihistamines or isotretinoin (Accutane) for ≥1 month, cyclosporine-A (Restasis) for ≥2 months, and other dry eye or MGD related medication (e.g., antibiotics, non-steroidal and anti-inflammatory drugs, and corticosteroids) for at least ≥2 weeks and to maintain abstinence throughout the duration of study. Ocular lubricants and nutritional supplements were not restricted.

A systematic review and meta-analysis of randomized controlled trials found that LipiFlow® treatments were superior to warm compresses for total OSDI but not gland score at 3 months, showing a −6.92-point improvement (total OSDI) and a 2.87-point improvement (gland score) over warm compresses [62]. The most common safety findings in that study for LipiFlow® were traced to mild conjunctival vascular injection, hyperemia, or redness.

In comparison, AZR-MD-001 0.5% was superior to vehicle for both total OSDI and MGYLS at 3 months, with an average 7.3-point improvement for total OSDI and a 4.2-point improvement for MGYLS at 3 months. Although limited to low level cross trial data comparisons at this time, the change from baseline with AZR-MD-001 0.5% for signs and symptoms was greater than that for warm compress, and AZR-MD-001 0.5% was able to significantly improve both MGYLS and total OSDI relative to vehicle, while LipiFlow® could not achieve this outcome relative to their control [62].

Importantly, device trials can be limited by bias toward a novelty effect in favor of LipiFlow®; three trials had potential selection bias and thus were given a rank of some concern, and two trials were open label and did not involve masking patients and assessors [37,62–65]. AZR-MD-001 0.5% appears to provide a positive advantage over both LipiFlow® and warm compresses. Compression procedures can also be time-consuming, energy intensive, and comprised of multiple steps, leading to patient non-compliance [38,42]. Other pharmaceutical approaches to managing MGD amongst patients that are not responsive to mechanical and heat treatment includes the use of topical and/or oral antibiotics. While these therapies can be effective for some patients, evidence for sustained benefits after a completion of a course of antibiotic therapy is lacking, and concerns relating to the risk of antibiotic microbial resistance outweigh their perceived benefits in long-term MGD management [66].

4.1. Limitations

Generalizability is limited by the study population (primarily Caucasian with meibomian gland loss not exceeding 75%). Future evaluation of AZR-MD-001 will be conducted in a larger population with a longer follow-up period to confirm the long-term, sustained maintenance of improvements in signs and symptoms of MGD after cessation of treatment, as well as long-term clinical efficacy. This study demonstrated that a concentration of 0.5% AZR-MD-001 selenium sulfide applied twice weekly at bedtime yields clinically meaningful improvements in MGD, with no further benefits in using concentrations beyond this, under the same dosing conditions. Given the novel nature of AZR-MD-001, the results presented here will assist future clinical trial design of AZR-MD-001.

5. Conclusions

MGD is a chronic, debilitating, and progressive abnormality of the meibomian glands, which has significant downstream consequences if not managed effectively. There are limited approved pharmacological treatments for MGD. This study has shown clinically meaningful and statistically significant improvements across multiple signs and symptoms of MGD as early as Day 14 with a 0.5% selenium sulfide ointment used twice weekly, compared to vehicle, with increased efficacy through Month 3. The trial endpoints were designed to reflect signs of MGD and are closely linked to the number of open meibomian glands and improvement in meibum quality. Combined with the favorable safety and tolerability profile, the results from this Phase 2 study suggest that this novel therapy represents a major advance in the treatment of this common and debilitation condition.

Financial support

The research and preparation of the manuscript were funded by Azura Ophthalmics, Tel Aviv, Israel.

Role of the funding source

Azura Ophthalmics (Tel Aviv, Israel), in collaboration with the authors, participated in study design; in the collection, analysis and interpretation of the data; in the writing of the report; and in the decision to submit the article for publication.

Declaration of competing interest

Stephanie Watson (ORCID ID: 0000-0001-6699-1765): Within the past 3 years, **SW** has received grant support, allocated to her research group, from Seqirus; has participated on an advisory board for Alcon Global; and has received honoraria for lectures or speakers bureaus from Novartis and Seqirus. **SW** also serves as a Chair of Australian Vision Research and is an inventor on US Patent US20200281924.

Lyndon W. Jones (ORCID ID: 0000-0002-7409-7349): Within the past 3 years, **LWJ** has received research support or lectureship honoraria from the following companies, allocated to the Centre for Ocular Research and Education (CORE): Alcon, Azura Ophthalmics, Bausch Health, CooperVision, Essilor, Hoya, i-Med Pharma, J&J Vision, Menicon, Novartis, Ophtecs, Oté Pharma, Santen, SightGlass, SightSage, Topcon and Visioneering. **LWJ** is also a consultant and/or serves on an advisory board for Alcon, CooperVision, J&J Vision, Novartis and Ophtecs.

Fiona Stapleton: Within the past 3 years, **FS** has received research support from the following companies: Alcon, Azura Ophthalmics, Exonate, Kedalion Therapeutics, Menicon, Novartis and Nthalmics. **FS** has also been a consultant for CooperVision and has participated on advisory boards for Alcon, Seqirus, and Novartis. **FS** is the immediate past-president of the International Society for Contact Lens Research and is a steering committee member and subcommittee chair of Tear Film and Ocular Surface Society, Lifestyle Epidemic Workshop.

Mark Hinds: MH has received research funding and/or honoraria from Vyluma, Kiora Pharmaceuticals, SynergEyes, CORE Research Group (Eli Lilly and Company), Novo Nordisk, Alcon and the Queensland University of Technology (School of Optometry and Vision Science). He has provided expert testimony for Remedy Medicolegal, Avant Insurance and Murphey's Law. **MH** is also a consultant for and/or serves

on an advisory board for Kiora Pharmaceuticals and the Dry Eye Society.

Alison Ng (ORCID ID: 0000-0002-6277-8470): AN is an employee of the Centre for Ocular Research and Education (CORE). Within the past 3 years, her institution has received research funding and/or honoraria from the 17 companies and 7 funding agencies listed: Alcon, Azura Ophthalmics, Bausch + Lomb Corp, CooperVision, Essilor, Hoya, I-MED Pharma, Johnson & Johnson Vision, Menicon, Novartis, Ophtecs, Oté Pharma, Santen, SightGlass, SightSage, Topcon, Visioneering Tech Inc, NSERC, CIHR, Mitacs, Canadian Association of Optometrists, European Commission Horizon 2020, Canada Foundation for Innovation, Innovation and Technology Commission (Government of the Hong Kong Special Administrative Region of the People's Republic of China).

Jacqueline Tan (ORCID ID: 0000-0003-4986-4945): JT has received research funding (paid to institution) from Alcon, Azura Ophthalmics, Exonate, Kedalion Therapeutics, Novartis, nthalmic and Rodenstock; has received support for attending International Society for Contact Lens Research and Tear Film and Ocular Society; has participated on an advisory board for Azura Ophthalmics; and has received non-monetary support (e.g., equipment, materials, other services) from Melcare and OptiMed.

Yair Alster: YA is an inventor on patents related to AZR-MD-001 and is an employee of and has stock and options in Azura Ophthalmics.

Charles Bosworth: CB is an employee of Azura Ophthalmics.

Omer Rafaeli: OR is an employee of Azura Ophthalmics.

Venita DePuy: VD is a statistical consultant to Azura Ophthalmics.

Acknowledgments

The authors thank Philip J. Sjostedt, PharmD, Jessica A. Weaver, PhD, and Nicole Coolbaugh, CMPP, of The Medicine Group, LLC (New Hope, Pennsylvania, United States) for providing medical writing support, which was funded by Azura Ophthalmics and in accordance with Good Publication Practice guidelines. We thank the members of the CELESTIAL STUDY Group. The CELESTIAL STUDY Group comprised: Jacqueline Tan, Fiona Stapleton, Katherine Wong, and Tianni Jia (School of Optometry and Vision Science, UNSW Sydney); Laura Downie and Eve Makrai (Department of Optometry and Vision Sciences); Stephanie Watson, Constantinos Petsoglou, Nino Hirnschall, and Blanca Benito Pascual (Save Sight Institute, University of Sydney); Dean Corbett and Dr. Chi-Ying Chou (AucklandEye); Scott Read, Stephen Vincent, and Lindsay McGrath (Queensland University of Technology); Jennifer Craig, Eva Pheng, Dian Zhuang, Simon Dean (University of Auckland); James Armitage, Alissa Maillet, and Heather Connor (Deakin University); Vivek Phakey and Janice Thean (Waverley Eye Clinic); Brendan Cronin and David Gunn (Queensland Eye Institute); Michael Jamieson and Dujon Fuzzard (Bendigo Eye Clinic); Anton Van Heerden (Eye Laser Specialists); Mark Hinds, Brendan Cronin, and Luisa Holguin-Colorado (Mark Hinds Optometrists). The authors also thank the group members of the Centre for Ocular Research and Education (CORE) at the University of Waterloo: Hugh Jellie, Jill Woods, Amir Moezzi, and Jaya Dantam. Finally, the authors thank the investigators of the Cliantha sites (eAppendix C).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtos.2023.07.002.

References

[1] Knop E, Knop N, Millar T, Obata H, Sullivan D. The international Workshop on meibomian gland dysfunction: report of the subcommittee on anatomy, physiology, and pathophysiology of the meibomian gland. Invest Ophthalmol Vis Sci 2011;52:1938–78.

[2] Nelson JD, Shimazaki J, Benitez-del-Castillo JM, Craig JP, McCulley JP, Den S, et al. The international Workshop on meibomian gland dysfunction: report of the definition and classification subcommittee. Invest Ophthalmol Vis Sci 2011;52:1930–7.

[3] Tomlinson A, Bron AJ, Korb DR, Amano S, Paugh JR, Pearce EI, et al. The international Workshop on meibomian gland dysfunction: report of the diagnosis subcommittee. Invest Ophthalmol Vis Sci 2011;52:2006–49.

[4] Nichols J, Jones L, Nelson J, Stapleton F, Sullivan D, Willcox M, et al. The TFOS international Workshop on contact lens discomfort: introduction. Investig Ophthalmol Vis Sci 2013;54:TFOS1–6.

[5] Green-Church K, Butovich I, Willcox M, Borchman D, Paulsen F, Barabino S, et al. The international Workshop on meibomian gland dysfunction: report of the subcommittee on tear film lipids and lipid–protein interactions in health and disease. Invest Ophthalmol Vis Sci 2011;52:1979–93.

[6] Tsai P, Evans J, Green K, Sullivan R, Schaumberg D, Richards S, et al. Proteomic analysis of human meibomian gland secretions. Br J Ophthalmol 2006;90:372–7.

[7] Butovich IA. The meibomian puzzle: combining pieces together. Prog Retin Eye Res 2009;28:483–98.

[8] Craig JP, Tomlinson A. Importance of the LIpid layer in human team film stability and evaporation. Optom Vis Sci 1997;74:8–13.

[9] Borchman D, Ramakrishnan V, Henry C, Ramasubramanian A. Differences in meibum and tear lipid composition and conformation. Cornea 2020;39:122–8.

[10] Molinari JF. Meibomian gland status comparison between active duty personnel and U.S. Veterans. Mil Med 2000;165:591–3.

[11] Hom MM, Martinson JR, Knapp LL, Paugh JR. Prevalence of meibomian gland dysfunction. Optom Vis Sci 1990;67:710–2.

[12] Blackie CA, Folly E, Ruppenkamp J, Holy C. Prevalence of Meibomian Gland dysfunction - a systematic review and analysis of published evidence. In: ARVO annual meeting. Vancover, Canada: Investigative Ophthalmology & Visual Science; 2019. p. 2736.

[13] Hassanzadeh S, Varmaghani M, Zarei-Ghanavati S, Heravian Shandiz J, Azimi Khorasani A. Global prevalence of meibomian gland dysfunction: a systematic review and meta-analysis. Ocul Immunol Inflamm 2021;29:66–75.

[14] Lekhanont K, Rojanaporn D, Chuck RS, Vongthongsri A. Prevalence of dry eye in Bangkok, Thailand. Cornea 2006;25:1162–7.

[15] Lin PY, Tsai SY, Cheng CY, Liu JH, Chou P, Hsu WM. Prevalence of dry eye among an elderly Chinese population in Taiwan: the Shihpai Eye Study. Ophthalmology 2003;110:1096–101.

[16] Uchino M, Dogru M, Yagi Y, Goto E, Tomita M, Kon T, et al. The features of dry eye disease in a Japanese elderly population. Optom Vis Sci 2006;83:792–802.

[17] Jie Y, Xu L, Wu YY, Jonas JB. Prevalence of dry eye among adult Chinese in the Beijing Eye Study. Eye 2009;23:688–93.

[18] McCarty CA, Bansal AK, Livingston PM, Stanislavsky YL, Taylor HR. The epidemiology of dry eye in Melbourne, Australia. Ophthalmology 1998;105:1114–9.

[19] Schein OD, Hochberg MC, Muñoz B, Tielsch JM, Bandeen-Roche K, Provost T, et al. Dry eye and dry mouth in the elderly: a population-based assessment. Arch Intern Med 1999;159:1359–63.

[20] Lemp MA, Crews LA, Bron AJ, Foulks GN, Sullivan BD. Distribution of aqueous-deficient and evaporative dry eye in a clinic-based patient cohort: a retrospective study. Cornea 2012;31:472–8.

[21] Schaumberg DA, Nichols JJ, Papas EB, Tong L, Uchino M, Nichols KK. The international Workshop on meibomian gland dysfunction: report of the subcommittee on the epidemiology of, and associated rish factors for, MGD. Invest Ophthalmol Vis Sci 2011;52:1994–2005.

[22] Viso E, Rodríguez-Ares MT, Abelenda D, Oubiña B, Gude F. Prevalence of asymptomatic and symptomatic meibomian gland dysfunction in the general population of Spain. Invest Ophthalmol Vis Sci 2012;53:2601–6.

[23] Shine WE, McCulley JP. Meibomianitis: polar lipid abnormalities. Cornea 2004;23:781–3.

[24] Romero JM, Biser SA, Perry HD, Levinson DH, Doshi SJ, Terraciano A, et al. Conservative treatment of meibomian gland dysfunction. Eye Contact Lens 2004;30:14–9.

[25] Al-Namaeh M. A systematic review of the effect of omega-3 supplements on meibomian gland dysfunction. Ther Adv Ophthalmol 2020;12:1–9.

[26] Akyol-Salman I, Azizi S, Murncu UY, Ates O, Baykal O. Comparison of the efficacy of topical N-acetylcysteine and a topical steroid-antibiotic combination therapy in the treatment of Meibomian gland dysfunction. J Ocul Pharmacol Therapeut 2012;28:49–52.

[27] Thode AR, Latkany RA. Current and emerging therapeutic strategies for the treatment of meibomian gland dysfunction (MGD). Drugs 2015;75:1177–85.

[28] Perry HD, Doshi-Carnevale S, Donnenfeld ED, Solomon R, Biser SA, Bloom AH. Efficacy of commercially available topical cyclosporine A 0.05% in the treatment of meibomian gland dysfunction. Cornea 2006;25:171–5.

[29] Fukuoka S, Arita R. Tear film lipid layer increase after diquafosol instillation in dry eye patients with meibomian gland dysfunction: a randomized clinical study. Sci Rep 2019;9:9091.

[30] Souchier MJC, Gregoire S, et al. Changes in Meibomian fatty acids and clinical signs in patients with meibomian gland dysfunction after minocycline treatment. Br J Ophthalmol 2008;92:819–22.

[31] Yoo S-E, Lee D-C, Change M-H. The effect of low-dose doxycycline therapy in chronic meibomian gland dysfunction. Korean J Ophthalmol 2005;19:258–63.

[32] Pinna A, Piccinini P, F C. Effect of oral linoleic and gammalinolenic acid on meibomian gland dysfunction. Cornea 2007;26:260–4.

[33] Olson MC, Korb DR, Greiner JV. Increase in tear film lipid layer thickness following treatment with warm compresses in patients with meibomian gland dysfunction. Eye Contact Lens 2003;29:96–9.

[34] Qiao J, Yan X. Emerging treatment options for meibomian gland dysfunction. Clin Ophthalmol 2013;7:1797–803.
[35] Goto E, Monden Y, Takano Y. Treatment of non-inflamed obstructive meibomian gland dysfunction by an infrared warm compression device. Br J Ophthalmol 2002; 86:1403–7.
[36] Mitra M, Menon GJ, Casini A. Tear film lipid layer thickness and ocular comfort after meibomian therapy via latent heat with a novel device in normal subjects. Eye 2005;19:657–60.
[37] Lane S, DuBiner H, Epstein R, Ernest P, Greiner J, Hardten D, et al. A new system, the LipiFlow, for the treatment of meibomian gland dysfunction. Cornea 2012;31: 396–404.
[38] Geerling G, Baudouin C, Aragona P, Rolando M, Boboridis K, Benítez-Del-Castillo J, et al. Emerging strategies for the diagnosis and treatment of meibomian gland dysfunction: proceedings of the OCEAN group meeting. Ocul Surf 2017;15:179–92.
[39] Matsumoto Y, Dogru M, Goto E. Efficacy of a new warm moist air device on tear functions of patients with simple meibomian gland dysfunction. Cornea 2006;25: 644–50.
[40] Tauber J, Owen J, Bloomenstein M, Hovanesian J, Bullimore M. Comparison of the iLUX and the LipiFlow for the treatment of meibomian gland dysfunction and symptoms: a randomized clinical trial. Clin Ophthalmol 2020;14:405–18.
[41] Wesley G, Bickle K, Downing J, Fisher B, Greene B, Heinrich C, et al. Systane iLux thermal pulsation system in the treatment of meibomian gland dysfunction: a post-hoc analysis of a 12-month, randomized, multicenter study. Clin Ophthalmol 2022; 16:3631–40.
[42] Sheppard JD, Nichols KK. Dry eye disease associated with meibomian gland dysfunction: focus on tear film characteristics and the therapeutic landscape. Ophthalmol Ther 2023;12:1397–418.
[43] Khoo P, Ooi K-J, Watson S. Effectiveness of pharmaceutical interventions for meibomian gland dysfunction: an evidence-based review of clinical trials. Clin Exp Ophthalmol 2019;47:658–68.
[44] Goldschmidt H, Kligman AM. Increased sebum secretion following selenium sulfide shampoos. Acta Derm Venereol 1968;48:489–91.
[45] Piérard-franchimont C, Arrese J, Piérard G. Sebum flow dynamics and antidandruff shampoos. J Soc Cosmet Chem 1997;48:117–21.
[46] Korb D, Blackie C. Meibomian gland diagnostic expressibility: correlation with dry eye symptoms and gland location. Cornea 2008;27:1142–7.
[47] Blackie C, Korb D. Recovery time of an optimally secreting meibomian gland. Cornea 2009;28:293–7.
[48] Blackie C, Korb D. The diurnal secretory characteristics in individual meibomian glands. Cornea 2010;29:34–8.
[49] Claypool C, Farid M, Karpecki PM, Matossian C, Raviv T. Modern management of MGD: practical strategies to elevate care. 2019. p. 1–12.
[50] Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the ocular surface index. Arch Ophthalmol 2000;118:615–21.
[51] Ngo W, Situ P, Keir N, Korb D, Blackie C, Simpson T. Psychometric properties and validation of the standard patient evaluation of eye dryness questionnaire. Cornea 2013;32:1204–10.
[52] Blackie C, Solomon J, Scaffidi R, Greiner J, Lemp M, Korb D. The relationship between dry eye symptoms and lipid layer thickness. Cornea 2009;28:789–94.
[53] Lemp M, Hamill Jr J. Factors affecting tear film breakup in normal eyes. Arch Ophthalmol 1973;89:103–5.
[54] Dmitrienko A, D'Agostino Rb Sr, Huque MF. Key multiplicity issues in clinical drug development. Stat Med 2013;32:1079–111.
[55] Bahn G. The treatment of seborrheic blepharitis. South Med J 1954;47:749–53.
[56] Thygeson P, Vaughan DE. Seborrheic Blepharitis. Transactions of the American Ophthalmological Society. 1954;52:173–88.
[57] Wong A, Fasanella R, Haley L, Marshall C, Krehl W. Selenium (selsun) in the treatment of marginal blepharitis. Ama Arch Opthalmol 1956;55:246–53.
[58] Cohen LB. Use of selsun in blepharitis marginalis. Am J Ophthalmol 1954;38: 560–2.
[59] Keating GM. Lifitegrast ophthalmic solution 5%: a review in dry eye disease. Drugs 2017;77:201–8.
[60] Montecchi-Palmer M, Wu M, Rolando M, et al. Possible strategies to mitigate placebo or vehicle response in dry eye disease trials: a narrative review. Ophthalmol Ther 2023:1–23.
[61] Abelson MB. The placebo effect and other confounders. Review of Ophthalmology; 2010.
[62] Pang S, Chen Y, Tam K, Lin I, Loh E. Efficacy of vectored thermal pulsation and warm compress treatments in meibomian gland dysfunction: a meta-analysis of randomized controlled trials. Cornea 2019;38:690–7.
[63] Blackie C, Coleman C, Holland E. The sustained effect (12 months) of a single-dose vectored thermal pulsation procedure for meibomian gland dysfunction and evaporative dry eye. Clin Ophthalmol 2016;10:1385–96.
[64] Finis D, Hayajneh J, König C, Borrelli M, Schrader S, Geerling G. Evaluation of an automated thermodynamic treatment (LipiFlow®) system for meibomian gland dysfunction: a prospective, randomized, observer-masked trial. Ocul Surf 2014;12: 146–54.
[65] Hagen K, Dedi R, Blackie C, Christenson K. Comparison of a single-dose vectored thermal pulsation procedure with a 3-month course of daily oral doxycycline for moderate-to-severe meibomian gland dysfunction. Clin Ophthalmol 2018;12: 161–8.
[66] Vernhardsdottir R, Magno M, Hynnekleiv L, Lagali N, Dartt D, Vehof J, et al. Antibiotic treatment for dry eye disease related to meibomian gland dysfunction and blepharitis – a review. Ocul Surf 2022;26:211–21.