Efficacy and safety of AZR-MD-001 selenium sulfide ophthalmic ointment in adults with meibomian gland dysfunction over six months of treatment: A Phase 2, vehicle-controlled, randomized extension trial

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ARTICLE INFO

ABSTRACT

Purpose: To determine the efficacy and safety of AZR-MD-001 (0.5 % and 1.0 %) ophthalmic ointment, relative to vehicle, over 3–6 months of treatment, in participants with meibomian gland dysfunction (MGD).

Methods: This was a Phase 2, randomized, vehicle-controlled, multicenter extension clinical trial. Eligible participants were adults with MGD (meibomian gland secretion score (MGS) ≤12 out of 15 glands) who discontinued all other dry eye or MGD treatments. Participants were randomized 1:1:1 to apply AZR-MD-001 1.0 %, 0.5 %, or vehicle to the lower eyelids, twice weekly. Key exploratory endpoints included the least-squared mean difference between groups in the change from baseline in clinical signs (meibomian gland yielding score; MGYLS) and symptoms (Ocular Surface Disease Index; OSDI), at clinic visits at Month 4.5 and 6, and safety measures from 36 months.

Results: Participants (66.5 % female) were randomized, at baseline, to AZR-MD-001 0.5 % (n = 82), 1.0 % (n = 83), or vehicle (n = 80). Statistically significant improvements, compared to vehicle, were observed at Month 6 in MGYLS for both AZR-MD-001 groups (0.5 % group: 1.9, 95 % CI 0.9 to 2.8, $P = 0.002$; 1.0 % group: 1.1, 95 % CI 0.2 to 2.1, $P = 0.026$), and in OSDI score for the 0.5 % group (−4.5, 95 % CI -8.0 to −0.9, $P = 0.0135$). The most common adverse events for AZR-MD-001 were application site pain, superficial punctate keratitis and eye pain; most were mild to moderate in severity, and decreased in incidence over time.

Conclusions: AZR-MD-001 (0.5 %) was efficacious in treating signs and symptoms of MGD over six months, with a lower observed incidence of new adverse events over time.

1. Introduction

Meibomian gland dysfunction (MGD) is a chronic, progressive condition associated with the blockage of meibomian glands and alterations to meibum [1]. Abnormal keratin production and aggregation alter meibum quantity and quality, leading to blockage of the meibomian glands in MGD [2,3]. Keratinization of the terminal ducts and concomitant squamous debris leads to obstructive MGD, with downstream effects resulting in meibum thickening [1]. Meibomian gland dysfunction is associated with alterations to the tear film, vision quality and ocular comfort, although early stages of MGD or mild presentations may be largely asymptomatic [4–6]. Over 80 % of people diagnosed with dry eye disease show signs of MGD [7,8]. Early MGD, when signs are observed in patients prior to symptom onset, affords the opportunity for a proactive treatment approach, before progression to symptomatic disease [1].

Selenium sulfide-containing products possess keratolytic, keratostatic, and lipogenic effects and have been used in dermatologic conditions as keratolytic agents. A redox reaction allows selenium sulfide to break disulfide bonds, causing proteins to disaggregate [9,10]. As a

Table 1
Efficacy variables, scoring criteria, and clinically meaningful change criteria.

Variable	Description	Scoring Criteria	Clinical Relevance	Clinically Meaningful Change Criteria
Meibomian Glands Yielding Liquid Secretion (MGYLS)	Number of meibomian glands that yield liquid secretion upon applying pressure with a diagnostic expression device[a] to the lower eyelid to five consecutive glands over three eyelid regions	Each gland scored with a 0 (no liquid) or 1 (liquid observed) over 15 glands; total score 0–15 across the lower eyelid for a given eye	Lower scores indicate a lower number of glands yielding meibum (i.e., more severe MGD)	An increase of ≥5 glands from baseline is indicative of a reduction in symptomatic disease [16]
Meibomian Gland Score (MGS)	Visual appearance of meibum quality upon gland expression, including the secretion and quality of meibum	Scoring of each gland over 15 glands; 0 = no secretion, 1 = inspissated/toothpaste consistency, 2 = cloudy/liquid secretion, 3 = clear liquid secretion; aggregate score of 0–45, for a given eye	Lower scores indicate more severe disease	An MGS score of >12 is indicative of normal meibum secretion [17]
Tear breakup time (TBUT)	Evaluated as the average of three repeat measures, following administration of 5 µL of 2 % sodium fluorescein into the eye	Time in seconds for the first dark spot to appear on the cornea after a blink, for a given eye	Lower values indicate a poorer quality tear film which is associated with a higher tear film evaporation rate	A finding of ≥10 s for the first appearance of a dark spot after a blink indicates normal tear film stability [18]
Ocular Surface Disease Index (OSDI)[b]	Participant-reported symptom index that evaluates ocular symptoms, environmental triggers, and vision-related functioning	Scored from 0100 for the participant	Higher scores represent more severe dry eye symptoms	An OSDI total score of <13 is considered asymptomatic for dry eye disease [14]
Standard Patient Evaluation of Eye Dryness (SPEED)	Participant-reported symptom index based on severity, occurrence, and frequency of four symptoms of eye dryness within the past 72 h of the visit	Scores range from 028; classified into mild (0–4), moderate (5–7), and severe disease (≥8) for the participant	Higher scores indicate more severe dry eye disease	A SPEED score of <6 indicates no noticeable symptoms of dry eye [19,20]
Ocular Discomfort Visual Analogue Scale (VAS)	Participant-reported index of the incidence and impact of ocular discomfort	Scored from 0100; a score of <5 indicates no discomfort; subscales for various types of eye discomfort and symptoms for the participant	Higher scores indicate more impact and incidence of ocular discomfort	Not applicable[c]

[a] Diagnostic expression device used was the TearScience™ Meibomian Gland Evaluator; Johnson & Johnson.
[b] 1995 Allergan®, all rights reserved.
[c] No validated measure of a clinically meaningful response is available for the VAS.
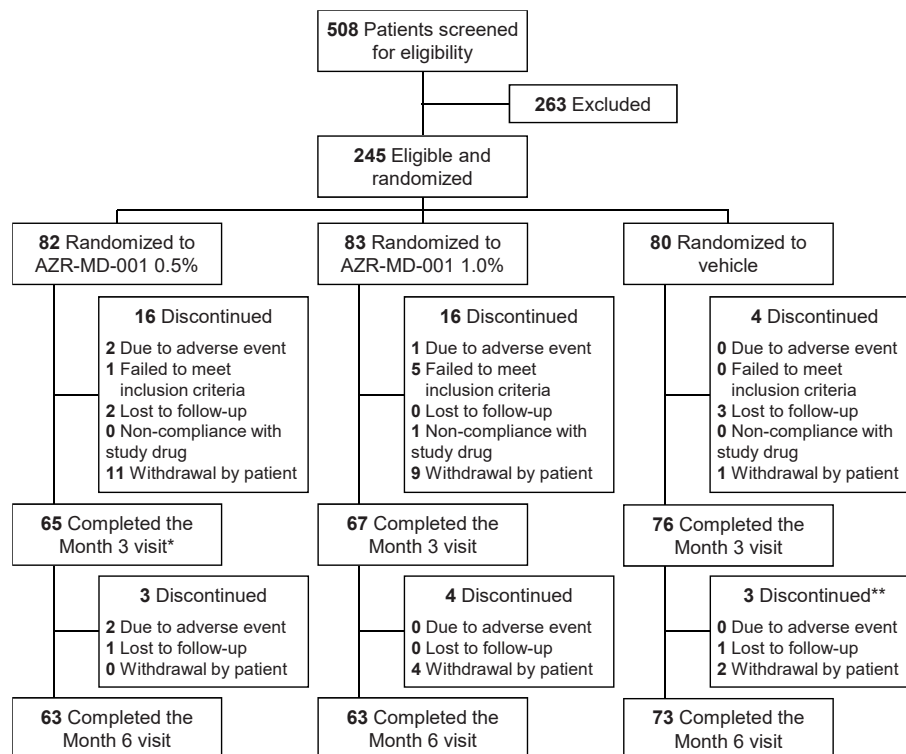
Fig. 1. Participant Flow
Caption: *One participant in the AZR-MD-001 0.5 % group did not complete the Month 3 visit but continued on in the study. **Two participants in the vehicle group withdrew from the study at the Month 3 visit, but completed the visit before exiting the study.

result of these actions, selenium sulfide has been identified as a key candidate for the treatment of MGD, with the potential to decrease meibum viscosity and unblock gland orifices [11]. AZR-MD-001 is an

investigational ophthalmic ointment containing selenium sulfide in 0.5 % and 1.0 % concentrations. The ointment is applied along the full length of the lower eyelid margin, immediately prior to sleep, twice

Table 2

Baseline participant demographics and clinical characteristics (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. Published in Watson et al., 2023 [11]; license: https://creativecommons.org/licenses/by/4.0/.
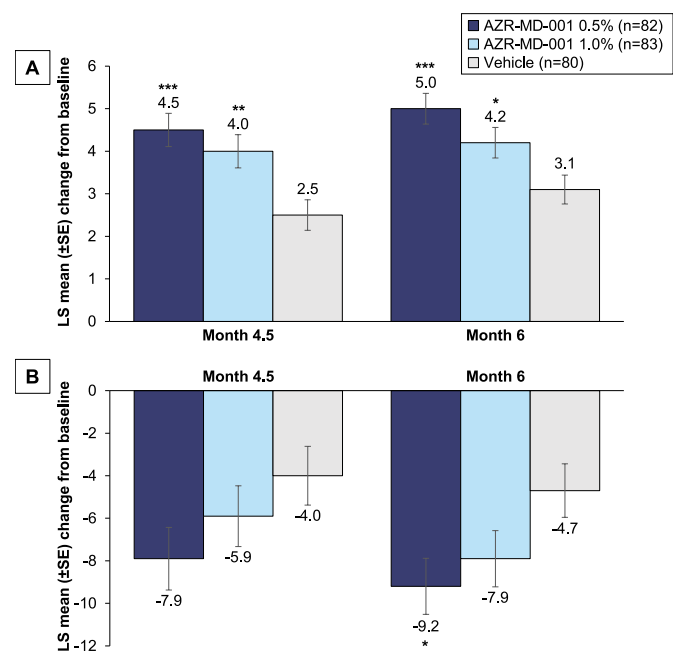
Fig. 2. Key Efficacy Endpoints (ITT Population) - Change from Baseline in A) Meibomian Gland Expression and Quality (MGYLS score), B) Dry Eye Symptoms and Impact (OSDI score) Over Time.
Caption: Values are shown as the mean change from baseline for each group. Asterisks indicate statistical significance in the change from baseline for each group, relative to vehicle. Increases in average scores for MGYLS (in A) indicate more glands yielding liquid secretions (i.e., an improvement in clinical signs). Decreases in the OSDI score (B) indicate reductions in dry eye symptom incidence and impact. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ indicate change from baseline vs. vehicle.

weekly.

Previously, statistically significant improvements in signs and symptoms of MGD in adult participants with the use of AZR-MD-001 (0.5 % and 1.0 %) over a period of three months have been reported in a Phase 2 trial [11]. In this three-month study MGD signs and

symptoms continued to improve at each clinical visit, over the duration of the trial. Utilization of keratolytics for hyperkeratotic skin conditions can show sustained efficacy and tolerability with months of use [12]. We hypothesized that treatment with AZR-MD-001 would show increasing efficacy and decreasing safety concerns over a longer time period, in participants with MGD. The present manuscript reports data from the extension of this study, to evaluate the efficacy of treatment and safety outcomes up to six months post-baseline, compared to vehicle, including the exploratory endpoints of safety and efficacy for the extension portion of the study, for AZR-MD-001 ophthalmic ointment 0.5 % or 1.0 %, compared to vehicle from three to six months post-baseline.

2. Methods

2.1. Ethics

The study was conducted in accordance with ethical principles of the Declaration of Helsinki, the US Code of Federal Regulations Title 21, and the International Conference on Harmonization of Consolidated Good Clinical Practices Guideline (E6). The protocol and associated documents were reviewed and approved by an Institutional Review Board or Independent Ethics Committee at each site. All participants in the study completed written informed consent before they entered the study.

2.2. Study design

This Phase 2 extension study was a randomized, double-masked, parallel-group, multicenter, vehicle-controlled trial investigating the efficacy of AZR-MD-001 (0.5 % or 1.0 %) vs. vehicle in participants with signs and symptoms of MGD (NCT03652051; ANZ201801; conducted from February 2021 to October 2022) at 28 sites in Canada, Australia and New Zealand. The study remained masked until after all visits were completed. Participants were ≥18 years old, with evidence of bilateral meibomian gland obstruction, a history of dry eye, and sufficient number of functioning meibomian glands (defined as ≤75 % gland atrophy quantified using infrared meibography or retroillumination of the eyelid with white light). Complete participant eligibility criteria have been previously reported [11]. Participants were randomized to a study group (1:1:1) at baseline to receive either one of two concentrations of AZR-MD-001 (0.5 % or 1.0 %) or vehicle, using an interactive web response system (IWRS). Randomization numbers were sequentially assigned in order of enrollment, and the IWRS allocated a medication kit number for each participant that corresponded to the randomization number for dispensing AZR-MD-001 0.5 %, 1.0 %, or vehicle. Use of contact lenses, artificial tears, saline eye drops, ocular lubricants, and any other MGD treatments were not permitted throughout the study, to reduce confounding variables. All study personnel and the participants were masked to the treatment assignment throughout the study.

All clinical efficacy and safety assessments for analysis are reported for the participant's study eye, which was defined as the eye with the worst meibomian gland secretion (MGS) score (see Table 1 for detail on scoring criteria). If both eyes had the same MGS score, the participant's right eye was used as the study eye. Participants were instructed to dispense approximately 5 g of the study drug using a snap-on visual guide, and apply the ointment along their lower eyelid using their washed index finger, immediately prior to sleep, twice weekly, with at least a 48-h gap between applications.

2.3. Assessments

Study visits included screening (Day −14, visit 1), baseline (Day 0, visit 2), Day 14 (visit 3), Month 1.5 (visit 4), and Month 3 (visit 5, primary endpoint) [11], with extension visits at Month 4.5 (visit 6) and Month 6 (visit 7). Signs of MGD were assessed according to the number of meibomian glands yielding liquid secretions (MGYLS [13]), MGS scores and fluorescein tear breakup time (TBUT). Symptoms and
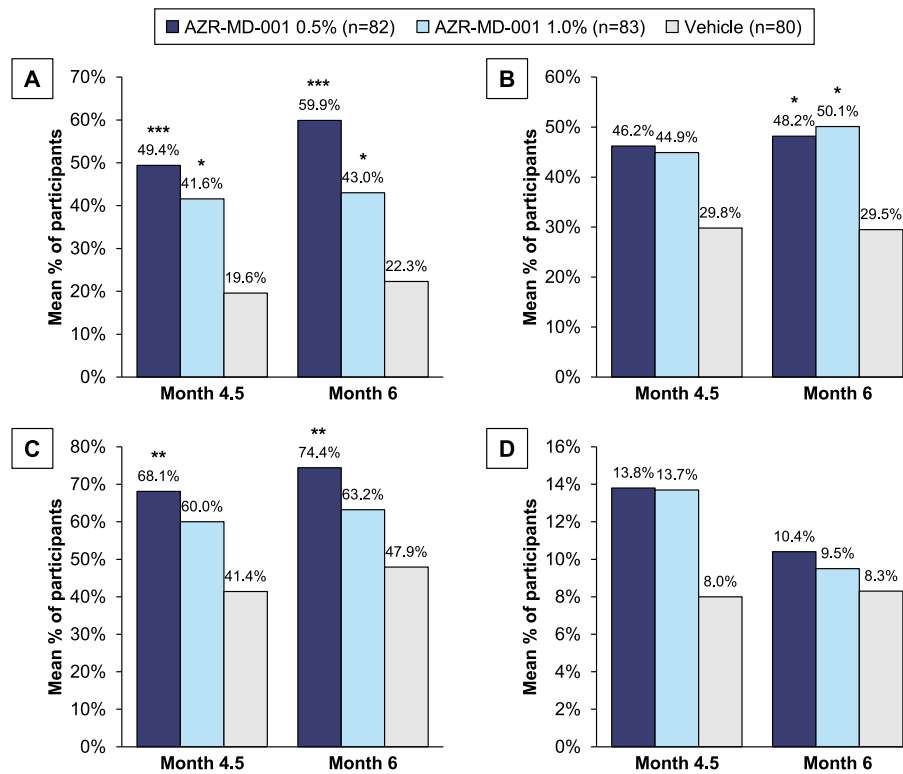
Fig. 3. Percentage of Participants with Clinically Meaningful Changes in MGD Signs and Symptoms: A) Participants with a Clinically Meaningful Change in Number of Glands Yielding Normal Meibum (MGYLS increase ≥5 from baseline), B) Participants who are Asymptomatic for Dry Eye (OSDI total score <13), C) Participants with Normal Meibomian Gland Secretion (MGS Score >12), D) Participants with Normal Tear Film Stability (Fluorescein TBUT ≥10 s).
Caption: The criteria to achieve a clinically meaningful change for each parameter is defined in Table 1. *$P < 0.05$, **$P < 0.01$, ***$P \leq 0.001$ indicate statistical differences in the change from baseline vs. vehicle.

participant-reported outcomes of MGD were assessed using the validated Ocular Surface Disease Index (OSDI) (Version 1, 1995 Allergan®) [14], Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire [15] and Ocular Discomfort Visual Analogue Scale (VAS). More detail on these measures and published criteria defining clinically meaningful changes are summarized in Table 1.

Safety was assessed by collecting reports of the new incidence, severity, and relationship to the study treatment of treatment-emergent adverse events (TEAEs), documenting participant discontinuations from the study, and collecting data on ocular-specific measurements (i.e., best-corrected visual acuity (BCVA), slit lamp biomicroscopic findings, ophthalmoscopy, intraocular pressure (IOP) and conjunctival bulbar hyperemia/redness) [13,15,18,20]. Investigators could elect to temporarily withhold treatment due to a TEAE and recommence treatment at a later date during the study, which was noted as a "drug withdrawal". Treatment tolerability was evaluated by calculating discontinuation rates due to TEAEs for each study group.

For the present report, the incidence of TEAEs was quantified based on reports of new TEAEs or worsening of severity of existing TEAEs, from when participants entered the extended study period (after the Month 3 visit) to the Month 6 visit. The TEAEs that were most commonly reported (≥5 %) during Baseline to Month 3 of the trial were also reported for this extension period. As the new incidence is reported in these analyses, any ongoing TEAEs that began during treatment from Baseline to Month 3 and continued through the extension portion of the trial were not included in the safety outcomes reported here for Month 3–6. Events per person-years were calculated to show the rates for the two time periods (i.e., Baseline to Month 3, and Month 3–6).

2.4. Endpoints

Pre-specified key exploratory efficacy endpoints included change from baseline in MGYLS score at Month 6, and change from baseline in OSDI total score at Month 6, for each AZR-MD-001 dose group (0.5 % and 1.0 %) compared to vehicle. Additional exploratory endpoints included comparisons for the change from baseline between groups for MGYLS score and OSDI total score at Month 4.5, as well as clinically meaningful changes (see Table 1) in MGYLS and OSDI total score, MGS total score, SPEED score, and TBUT, at Months 4.5 and 6, and ocular surface staining at each visit. Analyses of the new incidence of TEAEs, as well as per person-years calculations for the Baseline to Month 3 and Month 3–6 time periods were completed *post hoc*.

2.5. Statistical analyses

SAS® software was used for the statistical analyses (SAS® Institute Inc., Cary, NC, USA). Analyses were performed using an ANCOVA model with continuous baseline MGYLS or OSDI total score as a covariate, and baseline duration of disease category (<5 or at ≥ 5 years), and baseline MGS score category (<6, or ≥ 6 to ≤12) as factors in the model. The ANCOVA model was also performed for each AZR-MD-001 group versus vehicle. The least square mean differences (LSMD) between treatments (0.5 % versus vehicle and 1.0 % versus vehicle) are presented along with two-sided (95 %) confidence intervals (CIs).

Odds ratios (OR), along with 95 % CIs, were obtained by pairwise comparisons of the proportion of participants with a clinically meaningful response for each AZR-MD-001 group versus vehicle group using logistic regression, stratifying by baseline MGS score for the qualified eye (i.e., <6, or ≥ 6 to ≤ 12) and duration of disease (i.e., <5 years or ≥ 5 years). There were no alpha adjustments for the multiple tests for the

Table 3
Efficacy Endpoints by Measure and Timepoint (ITT population).

Endpoint	AZR-MD-001 0.5 % (n = 82)	AZR-MD-001 1.0 % (n = 83)	Vehicle (n = 80)
MGYLS score			
Change from baseline at Month 4.5, LS mean (SE)	4.5 (0.39)	4.0 (0.39)	2.5 (0.36)
P value vs baseline	<0.001	<0.001	<0.001
Difference from vehicle, LS mean (95 % CI)	2.0 (1.0, 3.0)	1.5 (0.5, 2.5)	NA
P value vs vehicle	**<0.001**	**0.004**	NA
Change from baseline at Month 6, LS mean (SE)	5.0 (0.36)	4.2 (0.36)	3.1 (0.34)
P value vs baseline	<0.001	<0.001	<0.001
Difference from vehicle, LS mean (95 % CI)	1.9 (0.9, 2.8)	1.1 (0.2, 2.1)	NA
P value vs vehicle	**<0.001**	**0.02**	NA
OSDI total score			
Change from baseline at Month 4.5, LS mean (SE)	−7.9 (1.47)	−5.9 (1.43)	−4.0 (1.38)
P value vs baseline	<0.001	<0.001	0.005
Difference from vehicle, LS mean (95 % CI)	−3.9 (−7.8, 0.0)	−1.9 (−5.7, 2.0)	NA
P value vs vehicle	0.05	0.34	NA
Change from baseline at Month 6, LS mean (SE)	−9.2 (1.32)	−7.9 (1.32)	−4.7 (1.26)
P value vs baseline	<0.001	<0.001	<0.001
Difference from vehicle, LS mean (95 % CI)	−4.5 (−8.0, −0.9)	−3.2 (−6.8, 0.3)	NA
P value vs vehicle	**0.01**	0.07	NA
SPEED score			
Change from baseline at Month 4.5, LS mean (SE)	−4.7 (0.55)	−3.8 (0.54)	−3.0 (0.52)
P value vs baseline	<0.001	<0.001	<0.001
Difference from vehicle, LS mean (95 % CI)	−1.7 (−3.2, −0.3)	−0.9 (−2.3, 0.6)	NA
P value vs vehicle	**0.02**	0.24	NA
Change from baseline at Month 6, LS mean (SE)	−4.8 (0.54)	−4.6 (0.54)	−2.5 (0.52)
P value vs baseline	<0.001	<0.001	<0.001
Difference from vehicle, LS mean (95 % CI)	−2.3 (−3.7, −0.8)	−2.1 (−3.5, −0.6)	NA
P value vs vehicle	**0.003**	**0.006**	
SPEED clinically meaningful change (score <6)			
Mean % of participants at Month 4.5	27.9	19.4	14.8
P value vs vehicle	0.10	0.94	NA
Mean % of participants at Month 6	24.3	27.6	16.0
P value vs vehicle	0.45	0.17	NA
MGS score			
Change from baseline at Month 4.5, LS mean (SE)	10.9 (0.99)	9.6 (0.94)	5.9 (0.90)
P value vs baseline	<0.001	<0.001	<0.001
Difference from vehicle, LS mean (95 % CI)	5.0 (2.4, 7.6)	3.7 (1.2, 6.2)	NA
P value vs vehicle	**<0.001**	**0.005**	NA
Change from baseline at Month 6, LS mean (SE)	12.3 (0.92)	10.1 (0.90)	7.6 (0.84)
P value vs baseline	<0.001	<0.001	<0.001
Difference from vehicle, LS mean (95 % CI)	4.7 (2.3, 7.0)	2.5 (0.1, 4.8)	NA
P value vs vehicle	**<0.001**	**0.04**	NA
TBUT (seconds)			
Change from baseline at Month 4.5, LS mean (SE)	2.02 (0.38)	1.65 (0.38)	1.013 (0.36)
P value vs baseline	<0.001	<0.001	0.007
Difference from vehicle, LS mean (95 % CI)	1.01 (−0.02, 2.03)	0.64 (−0.37, 1.64)	NA
P value vs vehicle	0.05	0.21	NA
Change from baseline at Month 6, LS mean (SE)	2.26 (0.40)	1.31 (0.40)	1.564 (0.38)
P value vs baseline	<0.001	0.002	<0.001
Difference from vehicle, LS mean (95 % CI)	0.69 (−0.37, 1.76)	−0.26 (−1.33, 0.82)	NA
P value vs vehicle	0.20	0.63	NA
Average VAS score[a]			

Table 3 (*continued*)

Endpoint	AZR-MD-001 0.5 % (n = 82)	AZR-MD-001 1.0 % (n = 83)	Vehicle (n = 80)
Change from baseline at Month 4.5, LS mean (SE)	−14.2 (1.81)	−10.2 (1.80)	−11.6 (1.80)
P value vs baseline	<0.001	<0.001	<0.001
Difference from vehicle, LS mean (95 % CI)	−2.6 (−7.5, 2.4)	1.4 (−3.6, 6.3)	NA
P value vs vehicle	0.31	0.58	NA
Change from baseline at Month 6, LS mean (SE)	−17.7 (1.56)	−15.9 (1.56)	−11.4 (1.57)
P value vs baseline	<0.001	<0.001	<0.001
Difference from vehicle, LS mean (95 % CI)	−6.3 (−10.6, −2.0)	−4.4 (−8.7, −0.1)	NA
P value vs vehicle	**0.004**	**0.04**	NA
Worst VAS score[b]			
Change from baseline at Month 4.5, LS mean (SE)	−33.8 (2.74)	−30.6 (2.72)	−28.3 (2.68)
P value vs baseline	<0.001	<0.001	<0.001
Difference from vehicle, LS mean (95 % CI)	−5.5 (−12.9, 2.0)	−2.2 (−9.6, 5.2)	NA
P value vs vehicle	0.15	0.55	NA
Change from baseline at Month 6, LS mean (SE)	−37.9 (2.60)	−35.0 (2.57)	−27.5 (2.54)
P value vs baseline	<0.001	<0.001	<0.001
Difference from vehicle, LS mean (95 % CI)	−10.4 (−17.4, −3.3)	−7.4 (−14.4, −0.5)	NA
P value vs vehicle	**0.004**	**0.04**	NA
Eye Dryness VAS score			
Change from baseline at Month 4.5, LS mean (SE)	−27.3 (2.66)	−25.7 (2.61)	−21.3 (2.56)
P value vs baseline	<0.001	<0.001	<0.001
Difference from vehicle, LS mean (95 % CI)	−5.9 (−13.1, 1.2)	−4.3 (−11.4, 2.7)	NA
P value vs vehicle	0.10	0.23	NA
Change from baseline at Month 6, LS mean (SE)	−32.3 (2.62)	−29.9 (2.60)	−21.8 (2.53)
P value vs baseline	<0.001	<0.001	<0.001
Difference from vehicle, LS mean (95 % CI)	−10.5 (−17.5, −3.5)	−8.1 (−15.1, −1.1)	NA
P value vs vehicle	**0.004**	**0.02**	NA
Eye Discomfort VAS score			
Change from baseline at Month 4.5, LS mean (SE)	−21.3 (2.58)	−15.0 (2.54)	−17.0 (2.46)
P value vs baseline	<0.001	<0.001	<0.001
Difference from vehicle, LS mean (95 % CI)	−4.3 (−11.2, 2.6)	2.0 (−4.9, 8.9)	NA
P value vs vehicle	0.22	0.56	NA
Change from baseline at Month 6, LS mean (SE)	−24.0 (2.35)	−22.1 (2.34)	−14.6 (2.25)
P value vs baseline	<0.001	<0.001	<0.001
Difference from vehicle, LS mean (95 % CI)	−9.4 (−15.7, −3.2)	−7.5 (−13.8, −1.2)	NA
P value vs vehicle	**0.003**	**0.02**	NA
Burning/Stinging VAS score			
Change from baseline at Month 4.5, LS mean (SE)	−8.2 (2.73)	−5.7 (2.64)	−9.8 (2.59)
P value vs baseline	0.004	0.04	0.0003
Difference from vehicle, LS mean (95 % CI)	1.6 (−5.7, 8.8)	4.1 (−3.0, 11.2)	NA
P value vs vehicle	0.67	0.26	NA
Change from baseline at Month 6, LS mean (SE)	−14.5 (2.09)	−13.9 (2.08)	−9.5 (2.02)
P value vs baseline	<0.001	<0.001	<0.001
Difference from vehicle, LS mean (95 % CI)	−5.0 (−10.6, 0.6)	−4.4 (−10.0, 1.2)	NA
P value vs vehicle	0.08	0.12	NA
Itching VAS score			
Change from baseline at Month 4.5, LS mean (SE)	−14.0 (2.52)	−11.0 (2.47)	−7.3 (2.41)
P value vs baseline	<0.001	<0.001	0.004
Difference from vehicle, LS mean (95 % CI)	−6.7 (−13.5, 0.0)	−3.7 (−10.4, 3.0)	NA
P value vs vehicle	0.05	0.28	NA
Change from baseline at Month 6, LS mean (SE)	−18.9 (2.20)	−14.0 (2.22)	−8.5 (2.14)
P value vs baseline	<0.001	<0.001	<0.001

Table 3 (*continued*)

Endpoint	AZR-MD-001 0.5 % (n = 82)	AZR-MD-001 1.0 % (n = 83)	Vehicle (n = 80)
Difference from vehicle, LS mean (95 % CI)	−10.5 (−16.4, −4.5)	−5.5 (−11.5, 0.5)	NA
P value vs vehicle	**<0.001**	0.07	NA
Foreign Body Sensation VAS score			
Change from baseline at Month 4.5, LS mean (SE)	−14.3 (2.36)	−7.8 (2.32)	−9.6 (2.29)
P value vs baseline	<0.001	0.001	<0.001
Difference from vehicle, LS mean (95 % CI)	−4.6 (−11.0, 1.7)	1.8 (−4.5, 8.1)	NA
P value vs vehicle	0.15	0.57	NA
Change from baseline at Month 6, LS mean (SE)	−15.7 (1.97)	−15.1 (1.97)	−8.8 (1.94)
P value vs baseline	<0.001	<0.001	<0.001
Difference from vehicle, LS mean (95 % CI)	−6.9 (−12.3, −1.6)	−6.3 (−11.6, −1.0)	NA
P value vs vehicle	**0.01**	**0.02**	NA
Photophobia VAS score			
Change from baseline at Month 4.5, LS mean (SE)	−9.7 (2.52)	−10.1 (2.42)	−10.5 (2.39)
P value vs baseline	<0.001	<0.001	<0.001
Difference from vehicle, LS mean (95 % CI)	0.8 (−5.9, 7.6)	0.4 (−6.2, 7.0)	NA
P value vs vehicle	0.81	0.91	NA
Change from baseline at Month 6, LS mean (SE)	−11.5 (2.24)	−12.5 (2.21)	−10.6 (2.16)
P value vs baseline	<0.001	<0.001	<0.001
Difference from vehicle, LS mean (95 % CI)	−0.9 (−6.9, 5.2)	−1.9 (−7.9, 4.1)	NA
P value vs vehicle	0.77	0.54	NA
Pain VAS score			
Change from baseline at Month 4.5, LS mean (SE)	−2.7 (2.35)	2.1 (2.26)	−4.4 (2.21)
P value vs baseline	0.25	0.36	0.05
Difference from vehicle, LS mean (95 % CI)	1.6 (−4.6, 7.9)	6.4 (0.3, 12.6)	NA
P value vs vehicle	0.61	**0.04**	NA
Change from baseline at Month 6, LS mean (SE)	−5.3 (1.63)	−5.1 (1.61)	−5.3 (1.57)
P value vs baseline	0.002	0.002	0.001
Difference from vehicle, LS mean (95 % CI)	0.0 (−4.4, 4.4)	0.2 (−4.1, 4.6)	NA
P value vs vehicle	>0.99	0.91	NA

Bolded values are *P* values < 0.05 versus vehicle.
Abbreviations: CI, confidence interval; ITT, intent to treat, LS, least squares; MGS, meibomian gland secretion score; MGYLS, meibomian glands yielding liquid secretion; NA, not applicable; OSDI, Ocular Surface Disease Index; SE, standard error; SPEED, Standard Patient Evaluation of Eye Dryness; TBUT, tear break-up time; VAS, Visual Analogue Scale.
[a] Average VAS is calculated as the average of all individual VAS scores.
[b] Worst VAS is the VAS item with the lowest score at baseline, or the average of the VAS items with lowest scores at baseline if there is a tie.

pairwise comparisons.

Categorical variables were summarized by sample size (n), frequency count and percent, and analyzed using Cochrane-Mantel-Haenszel tests to evaluate differences between treatments, controlling for disease duration category and baseline MGS score category. Descriptive statistics were completed for baseline demographics, including the mean, standard deviation (SD), range, and percentage, when appropriate. To address multiplicity considerations, the key exploratory endpoints (MGYLS and OSDI) were prioritized into a hierarchical structure, such that the MGYLS endpoint was required to be statistically significant to proceed with statistical analyses for the OSDI endpoint.

2.6. Analysis populations

Efficacy analyses were completed on available data from the intent-to-treat (ITT) population (all participants randomized at baseline). Safety analyses were completed using the safety population (all participants randomized at baseline who received at least one dose of study

treatment and continued to the extension portion of the trial at Month 3).

2.7. Power calculations

Power calculations were completed to ensure an appropriate number of participants for the key exploratory endpoints at Month 6. A sample size of 45 participants per group was targeted for 90 % power to detect a difference of 2.0 units between active treatment and vehicle groups for MGYLS, and 58 participants per group were required to detect a difference of 4.5 units for Total OSDI [21]. Both of these power calculations used a two-sample *t*-test at a significance level of 0.05. To allow for inter-site variability the sample size per group was increased to approximately 75 participants for Months 3–6.

3. Results

A total of 245 participants were enrolled into the study at baseline, and were randomized to treatment with AZR-MD-001 0.5 % (n = 82), AZR-MD-001 1.0 % (n = 83) or vehicle (n = 80) (Fig. 1). Baseline demographics and clinical characteristics were similar across treatment groups (Table 2). Clinical signs and symptoms were consistent with an MGD population. Participants entering the extension phase of the study, after the Month 3 visit, included n = 65 in the AZR-MD-001 0.5 % group, n = 67 in the AZR-MD-001 1.0 % group, and n = 74 in the vehicle group.

3.1. Key exploratory endpoints

Treatment with both concentrations of AZR-MD-001 resulted in a statistically significant increase from baseline in the number of meibomian glands yielding liquid meibum relative to vehicle, at both Month 4.5 (MGYLS LSMD (95 % CI); 0.5 % group: 2.0 (1.0, 3.0) *P* = 0.0002; 1.0 % group: 1.5 (0.5, 2.5), *P* = 0.0042) and Month 6 (0.5 % group: 1.9 (0.9, 2.8), *P* = 0.0002; 1.0 % group: 1.1 (0.2, 2.1) *P* = 0.0226) (Fig. 2). For participant-reported dry eye symptoms, the change from baseline in OSDI score reached statistical significance for the 0.5 % group vs. vehicle at Month 6 (OSDI score LSMD -4.5 (CI -8.0, −0.9) points, *P* = 0.0135) (Fig. 2), but was not statistically significant at Month 4.5 for the 0.5 % group (LSMD (95 % CI) 0.5 % dose: 3.9 (−7.8, 0.0) vs. vehicle: 1.9 (−5.7, 2.0) OSDI units), or for the 1.0 % group relative to vehicle at Months 4.5 or 6 (*P* > 0.05 for both comparisons).

The percentage of participants with normal meibomian gland expression (≥5 gland increase from baseline) was statistically significantly higher in the AZR-MD-001 0.5 % and 1.0 % treatment groups, compared to vehicle, at Month 4.5 (0.5 % group: 49.4 % vs. vehicle: 19.6 %, *P* = 0.001; 1.0 % group: 41.6 % vs. vehicle: 19.6 % *P* = 0.0102) and at Month 6 (0.5 % group: 59.9 % vs. vehicle: 22.3 % *P* < 0.0001; 1.0 % group: 43.0 %, vs vehicle: 22.3 %, *P* = 0.0218) (Fig. 3A).

The percentage of participants who no longer showed evidence dry eye symptoms (i.e., who achieved an OSDI score <13) was statistically significantly higher for both AZR-MD-001 treatment groups at Month 6 compared to vehicle (0.5 % group: 48.2 % vs. vehicle: 29.5 % *P* = 0.0333; 1.0 % group: 50.1 % vs. vehicle: 29.5 %, *P* = 0.0205; Fig. 3B).

The change from baseline, relative to vehicle, for MGS score was statistically significantly greater (i.e., showed a greater improvement) for both AZR-MD-001 treatment groups compared to vehicle at both Month 4.5 (LSMD (95 % CI) 0.5 % group: 5.0 (2.4, 7.6), *P* = 0.0002; 1.0 % group: 3.7 (1.2, 6.2), *P* = 0.004) and Month 6 (0.5 % group: 4.7 (2.3, 7.0), *P* = 0.0002; 1.0 % group: 2.5 (0.1, 4.8), *P* = 0.03) (Table 3). The percentage of participants with normal meibum secretion quality (i.e., an MGS score >12) was significantly higher in the AZR-MD-001 0.5 % treatment group, compared to vehicle, at Month 4.5 (0.5 % group: 68.1 % vs vehicle: 41.4 %, *P* = 0.0022) and Month 6 (0.5 % group: 74.4 % vs. vehicle: 47.9 %, *P* = 0.001). The 1.0 % group did not show a statistically significant difference relative to vehicle for MGS at either time point (*P* > 0.05; Fig. 3C).

Table 4
Safety summary (safety population).

	AZR-MD-001 0.5 %				AZR-MD-1.0 %				Vehicle			
	0–3 Months (n = 82)		3–6 Months (n = 65)		0–3 Months (n = 83)		3–6 Months (n = 67)		0–3 Months (n = 80)		3–6 Months (n = 74)	
	Incidence n (%)	Events per person-year	Incidence n (%)	Events per person-year	Incidence n (%)	Events per person-year	Incidence n (%)	Events per person-year	Incidence n (%)	Events per person-year	Incidence n (%)	Events per person-year
Any TEAEs	54 (65.9)	6.89	23 (28.0)	2.26	61 (73.5)	8.91	30 (36.1)	3.56	22 (27.5)	2.32	18 (22.5)	2.65
Any Ophthalmic TEAEs	47 (57.3)	5.49	15 (18.3)	1.46	57 (68.7)	7.7	23 (27.7)	2.26	14 (17.5)	1.24	10 (12.5)	0.73
Any serious TEAEs[a]	1 (1.2)	0.06	0 (0)	0	1 (1.2)	0.11	0 (0)	0	2 (2.5)	0.11	1 (1.3)	0.06
Study drug withdrawal due to TEAEs[b]	11 (13.4)	0.99	1 (1.2)	0.33	9 (10.8)	1.09	1 (1.2)	0.07	1 (1.3)	0.16	0 (0)	0
TEAEs (study eye) reported in ≥5 % of participants												
Application Site Pain	13 (15.9)	0.82	0 (0)	0	12 (14.5)	0.8	1 (1.2)	0.07	0 (0)	0	0 (0)	0
Superficial punctate keratitis	6 (7.3)	0.35	0 (0)	0	6 (7.2)	0.46	2 (2.4)	0.14	1 (1.3)	0.11	0 (0)	0
Eye pain	5 (6.1)	0.29	2 (2.4)	0.13	6 (7.2)	0.57	0 (0)	0	1 (1.3)	0.05	0 (0)	0
Vital dye staining of the cornea present	3 (3.7)	0.18	1 (1.2)	0.07	5 (6.0)	0.4	0 (0)	0	1 (1.3)	0.05	0 (0)	0

[a] No serious TEAEs were considered by the investigators to be treatment-related.
[b] Drug withdrawal indicates withholding of treatment for a period of time due to adverse events, with an option to restart treatment. Missing values are due to missed visits or discontinuations. A person-year is calculated by multiplying the number of people in a study by the time each person spent in the study to account for discontinuations. All terms used are based on the Medical Dictionary for Regulatory Activities (MeDRA) as coded by the investigators. TEAE, treatment emergent adverse event.

Change from baseline in tear film stability, based on fluorescein TBUT, was not statistically significantly different for either AZR-MD-001 treatment group, compared to vehicle (Table 3), nor were there differences in the percentage of participants who achieved 'healthy' tear film stability (i.e., TBUT ≥10 s) at Month 4.5 or Month 6 (Fig. 3D).

Participant-reported eye-dryness (SPEED) scores were significantly decreased from baseline (signifying improvement) for the AZR-MD-001 0.5 % treatment group, compared to vehicle, at Month 4.5 (LSMD (95 % CI) −1.7 (−3.2, 0.3), $P = 0.0198$). Both AZR-MD-001 treatment groups had SPEED scores that were statistically significantly decreased relative to baseline compared to vehicle at Month 6 (0.5 % group $P = 0.0025$; 1.0 % group $P = 0.0059$; Table 3). Participant-reported symptoms of ocular discomfort (quantified as the mean VAS) were significantly decreased at Month 6 for the overall measure, as well as for the worst score, eye dryness, and foreign body sensation subscales, for participants treated with either the 0.5 % or 1.0 % concentrations of AZR-MD-001, compared to those treated with vehicle (see Table 3 for detail).

3.2. Safety

The incidence of new TEAEs was 55.91 % (137/245) of all participants from Baseline to Month 3, and 8.25 % (71/206) between Months 3–6. TEAEs were mostly mild to moderate, with severe ophthalmic TEAEs reported in each group for Month 0–3 (0.5 % group: n = 4, 4.9 %; 1.0 % group: n = 5, 6.0 %; vehicle: n = 1, 1.3 %) that decreased in incidence between Month 3–6 (0.5 % group: n = 1, 1.2 %; 1.0 % group: n = 0, 0 %; vehicle: n = 0, 0 %). TEAEs leading to withdrawal of the study drug occurred in 13.4 % (n = 11), 10.8 % (n = 9), and 1.3 % (n = 1) of participants treated with AZR-MD-001 0.5 %, 1.0 %, and vehicle, respectively for Baseline to Month 3, and decreased between Month 3–6 to 1.2 % (n = 1) for each of the AZR-MD-001 groups and 0 % (n = 0) for vehicle (Table 4). Participant discontinuations from the study due to TEAEs occurred in 13.4 % (n = 11), 10.8 % (n = 9), and 1.3 % (n = 1) of the AZR-MD-001 0.5 %, 1.0 %, and vehicle groups respectively, during

Baseline to Month 3, and 1.2 % (n = 1), 1.2 % (n = 1), and 0 % (n = 0) from Months 3–6.

The TEAEs with an incidence of ≥5 % in any group during Months 0–3 that were judged by the investigator to be treatment-related included application site pain, superficial punctate keratitis, eye pain, and vital dye staining of the cornea, which decreased throughout the study to Month 6 (see Table 4 for further detail on the incidence of new TEAEs, and events per person-year). There were no serious TEAEs during the study that were considered by investigators to be related to treatment. Overall, ocular surface staining scores appeared to improve with AZR-MD-001 (see Table 5).

4. Discussion

Meibomian gland dysfunction is a progressive and chronic abnormality of the production and flow of meibum onto the ocular surface from the meibomian glands, resulting in a reduction in meibum quality and/or meibomian gland obstruction, and (in the longer term) typically progressing to ocular discomfort [1]. This extension of a Phase 2 clinical trial evaluating AZR-MD-001 ointment for the treatment of MGD demonstrated continued improvements over six months for clinical MGD signs and dry eye symptoms. These improvements included effects on meibum quality and meibomian gland expressibility, as well as downstream effects on dry eye symptoms.

In the present analyses of the extended study period, similar efficacy findings were observed compared to the original Phase 2 study period (Baseline to Month 3), but with findings for efficacy improvements for specific parameters (Months 3–6). These data also confirm the value of studies that are of longer duration (i.e., >3 months) for evaluating the potential benefits of sustained intervention periods for treating dry eye symptoms due to MGD. Results from the present analysis of the extension dataset also demonstrate improved safety outcomes over time with the use of the twice-weekly, topical selenium sulfide preparation, with a reduced incidence of new TEAEs in the latter time period of the study. A

Table 5
Ocular surface staining scores (ITT population).

	AZR-MD-001 0.5 % (n = 65)	AZR-MD-001 1.0 % (n = 67)	Vehicle (n = 74)
Conjunctival Lissamine Green Scores			
Nasal region score			
Oxford classification at Month 4.5, no. (%)			
0	38 (58.5)	37 (55.2)	39 (52.7)
I	14 (21.5)	19 (28.4)	20 (27.0)
II	4 (6.2)	9 (13.4)	10 (13.5)
III	1 (1.5)	0 (0)	0 (0)
IV	0 (0)	0 (0)	0 (0)
V	0 (0)	0 (0)	0 (0)
Missing	8 (12.3)	2 (3.0)	5 (6.8)
Oxford classification at Month 6, no. (%)			
0	41 (63.1)	41 (61.2)	40 (54.1)
I	18 (27.7)	19 (28.4)	19 (25.7)
II	5 (7.7)	3 (4.5)	12 (16.2)
III	0 (0)	0 (0)	1 (1.4)
IV	0 (0)	0 (0)	0 (0)
V	0 (0)	0 (0)	0 (0)
Missing	1 (1.5 %)	4 (6.0)	2 (2.7)
Temporal region score			
Oxford classification at Month 4.5, no. (%)			
0	43 (66.2)	37 (55.2)	42 (56.8)
I	8 (12.3)	22 (32.8)	17 (23)
II	5 (7.7)	6 (9.0)	10 (13.5)
III	1 (1.5)	0 (0)	0 (0)
IV	0 (0)	0 (0)	0 (0)
V	0 (0)	0 (0)	0 (0)
Missing	8 (12.3)	2 (3.0)	5 (6.8)
Oxford classification at Month 6, no. (%)			
0	43 (66.2)	42 (62.7)	43 (58.1)
I	17 (26.2)	16 (23.9)	19 (25.7)
II	2 (3.10)	5 (7.5)	9 (12.2)
III	2 (3.1)	0 (0)	1 (1.4)
IV	0 (0)	0 (0)	0 (0)
V	0 (0)	0 (0)	0 (0)
Missing	1 (1.5)	4 (6.0)	2 (2.7)
Corneal fluorescein staining			
Oxford classification at Month 4.5, no. (%)			
0	34 (52.3)	32 (47.8)	40 (54.1)
I	19 (27.7)	24 (35.8)	21 (28.4)
II	4 (6.2)	8 (11.9)	8 (10.8)
III	2 (3.1)	1 (1.5)	0 (0)
IV	0 (0)	0 (0)	0 (0)
V	0 (0)	0 (0)	0 (0)
Missing	7 (10.8)	2 (3.0)	5 (6.8)
Oxford classification at Month 6, no. (%)			
0	40 (61.5)	33 (49.3)	40 (54.1)
I	18 (27.7)	20 (29.9)	27 (36.5)
II	5 (7.7)	9 (13.4)	5 (6.8)
III	1 (1.5)	1 (1.5)	0 (0)
IV	0 (0)	0 (0)	0 (0)
V	0 (0)	0 (0)	0 (0)
Missing	1 (1.5)	4 (6.0)	2 (2.7)

Participants appeared to show lower scores over time, with more participants reaching a score of 0 at each time point. ITT, intent to treat.

similar incidence of new TEAEs was found between dosing groups (0.5 % and 1.0 %), with a trend towards a reduced rate of all TEAEs with the 0.5 % concentration. A lower per person-years rate for TEAEs was observed during Months 3–6, relative to Baseline to Month 3, for both doses of AZR-MD-001. This metric is not expected to be heavily influenced by participation discontinuations, as it accounts for varying follow-up durations across study groups and time periods. Dermatologic keratolytic products have also shown that application site pain and irritation are temporary and typically self-resolving [22]. The observation in the present study of a lower incidence of new TEAEs related to the study drug in the extension period, compared to the initial three months of the study [11], is an important observation for clinicians in managing patient expectations when treating MGD if the current treatment becomes commercially available.

In the extension phase of the study, increased meibum quantity, expression, and quality were accompanied by observations of less corneal fluorescein staining over time, and improvements in SPEED and VAS subscale scores. The VAS subscales are useful for considering the breadth of symptomatic expression of MGD, and to measure a spectrum of participant-reported responses to treatment. The proportion of participants with clinically meaningful improvements, and symptom resolution, in this period of the study highlight the potential clinical benefit of AZR-MD-001 treatment, with many participants achieving resolution of MGD signs and symptoms across the extended study period.

Current FDA-approved treatments for signs and patient-reported symptoms of dry eye include Tyrvara, Meibo, Cequa, Xiidra, and Eysuvis [23–29]. While the participant populations and clinical registration trial methodologies differ from the current study, there is currently an absence of evidence that these treatments can yield improvements of similar magnitude in the breadth of MGD signs and symptoms as was found in this Phase 2 extension trial, especially for this duration of use.

Conventional treatments for MGD and related conditions include eyelid hygiene (e.g., eyelid cleansing), artificial tears, oral omega-3 fatty acid supplements (e.g., eicosapentaenoic acid and docosahexaenoic acid), oral omega-6 fatty acid supplements (e.g., linoleic acid and gamma-linolenic acid), topical antibiotics (e.g., bacitracin and erythromycin), topical corticosteroids, topical cyclosporine, oral antibiotics (e. g., doxycycline, minocycline, and tetracycline), and warm compresses and/or massage to the eyelids [23–25,27–29]. Exterior eyelid-warming devices [17,30–33], and other technologically advanced approaches such as intense-pulsed light (IPL), and thermal pulsation therapy have also been developed to treat MGD and/or dry eye [17,34–37].

From a pathophysiological perspective, the material that makes up the secretions from meibomian glands in MGD is an altered mixture of abnormal lipid secretions and keratinized epithelial debris [16]. While lipid secretions are sensitive to temperatures that can be utilized in patients, keratinized epithelial debris is not [16]. Agents that break the disulfide bonds that also cause meibomian gland obstruction, or soften larger keratinized blockages to allow for expression through the glands, may thus be useful in therapeutic approaches in MGD. In dermatology, keratolytics are recommended for the treatment to break disulfide keratin bonds of hyperkeratinized skin cells [38]. There is thus a sound biological rationale for AZR-MD-001 to represent a potentially novel treatment option for MGD that approaches the etiology of MGD from multiple angles, particularly as a convenient twice-weekly, self-administered therapy.

4.1. Limitations

A consideration when interpreting the presented findings is that most study participants were Caucasian, which may limit generalizability to a more diverse patient population with MGD.

The study was powered for the efficacy of the primary endpoints at Month 3, and thus the efficacy endpoints presented are considered exploratory. Safety and efficacy endpoints were not statistically compared from Baseline to Month 3 and Month 3 to Month 6, and require further study for confirmation of findings. Efficacy differences between treatment and vehicle from Baseline to Month 3 were prespecified and were statistically significant in a previous study [11], and results from Months 3–6 are consistent with these findings of a treatment benefit for AZR-MD-001 relative to vehicle. Future studies are needed to fully evaluate treatment changes over time.

Data were not collected beyond six months (after treatment cessation) so it is not known if maintenance of any clinical effects occurs upon withdrawal of the AZR-MD-001 treatment. A vehicle effect was seen for many outcome measures, which is anticipated due to participants being in a clinical trial and undergoing regular diagnostic meibomian gland expression. Efficacy outcomes seen in the vehicle group were consistent with prior ocular surface disease clinical trials [39]. It is possible that participants who did not find the treatment tolerable discontinued during the first three months of the study, affecting the incidence of new

TEAEs during the extension period, however this was accounted for in the per person-years calculations.

5. Conclusions

This study demonstrates that topical treatment with AZR-MD-001, administered twice weekly, results in improvements in both signs and symptoms of MGD that are clinically relevant to the condition. While changes in clinical signs appear earlier in the course of treatment, symptoms of MGD and safety outcomes improve over six months, with both doses of AZR-MD-001 demonstrating a benefit with continued treatment. The 0.5 % concentration of AZR-MD-001 showed the most robust efficacy results and will be used in future clinical trials. AZR-MD-001 is a promising therapeutic agent with a novel mechanism of action that could signify a major advancement in therapy for people living with MGD, and could augment currently available therapeutic approaches for these patients. Phase 3 clinical studies in an expanded population with MGD are planned for AZR-MD-001.

CRediT authorship contribution statement

Laura E. Downie: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Conceptualization. **Jennifer P. Craig:** Writing – review & editing, Visualization, Investigation, Data curation. **Fiona Stapleton:** Writing – review & editing, Visualization, Methodology, Investigation. **Jacqueline Tan:** Writing – review & editing, Visualization, Investigation. **Lyndon W. Jones:** Writing – review & editing, Visualization, Investigation. **Alison Ng:** Writing – review & editing, Visualization, Investigation. **Mark Hinds:** Writing – review & editing, Visualization, Investigation. **Charles Bosworth:** Writing – review & editing, Visualization, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Yair Alster:** Writing – review & editing, Visualization, Resources, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Role of the funding source

Acknowledgements

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