Safety and Efficacy of Topical AZR-MD-001 for the Treatment of Meibomian Gland Dysfunction in a 6-Month Study

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PURPOSE

- Meibomian gland dysfunction (MGD) is a chronic, progressive condition characterized by glandular and meibum changes.[1] Prevalence is highly variable and estimated to be as high as 70% in general population–based studies.[2]
- With currently no approved pharmacotherapies for MGD, suboptimally treated MGD can lead to gland blockage/dilation, decreased meibum quality/quantity, irreversible glandular atrophy/loss, altered tear film composition, ocular surface damage, and evaporative dry eye.[3]
- A phase 2 clinical trial was conducted to investigate the safety and efficacy of AZR-MD-001 (selenium sulfide ophthalmic ointment)—a potent keratolytic and keratostatic agent that induces meibomian gland lipogenesis—versus vehicle for the treatment of MGD.

DEMOGRAPHICS

- 245 patients were included in the safety and the intent-to-treat populations (**Table 1**).

TABLE 1. DEMOGRAPHICS AND BASELINE CHARACTERISTICS (SAFETY POPULATION)

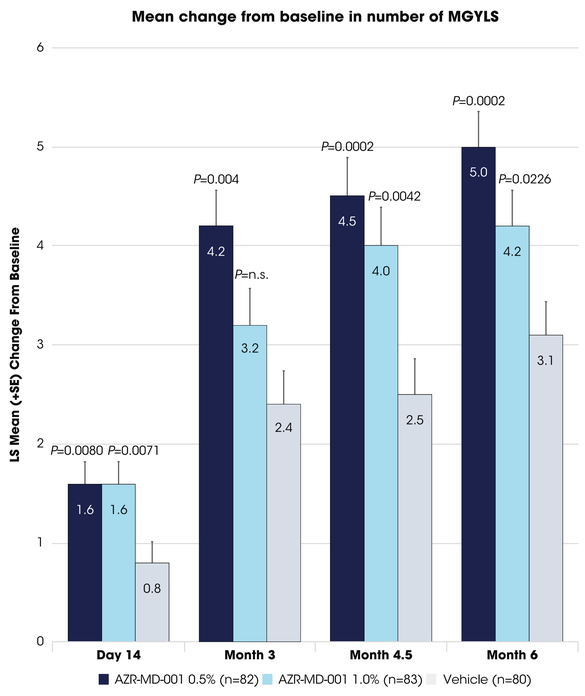
		AZR-MD-001 0.5% (N=82)	AZR-MD-001 1.0% (N=83)	VEHICLE (N=80)
Age (years)	Mean (SD)	52.1 (16.9)	55.6 (17.2)	51.9 (18.5)
	Range	18–80	20–93	20–97
Gender, n (%)	Male	31 (37.8)	27 (32.5)	24 (30.0)
	Female	51 (62.2)	56 (67.5)	56 (70.0)
Race, n (%)	White	57 (69.5)	64 (77.1)	56 (70.0)
	Asian	16 (19.5)	10 (12.0)	21 (26.3)
	Black	3 (3.7)	3 (3.6)	1 (1.3)
	Other	6 (7.3)	6 (7.2)	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)
Number of MGYLS	Mean (SD)	1.7 (1.4)	1.9 (1.4)	1.8 (1.3)
MGS score	Mean (SD)	5.7 (2.8)	6.0 (3.0)	6.0 (2.8)
OSDI total score	Mean (SD)	25.2 (7.5)	24.2 (6.0)	25.0 (6.7)

The safety population included all randomized patients administered ≥1 dose of study drug.
MGD, meibomian gland dysfunction; MGS, Meibomian Gland Secretion; MGYLS, Meibomian Glands Yielding Liquid Secretion; OSDI, Ocular Surface Disease Index; SD, standard deviation.

RESULTS

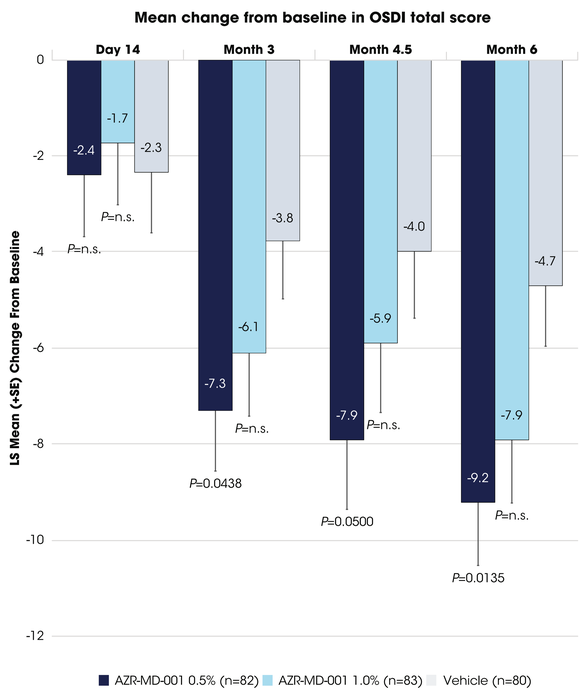
- AZR-MD-001 0.5% met the co-primary endpoints, significantly improving the signs (number of MGYLS; **Figure 1**) and symptoms (OSDI total score; **Figure 2**) of MGD versus vehicle at Month 3.[5]
- Both doses continued to demonstrate statistically significant improvements versus vehicle in the number of MGYLS at Months 4.5 and 6 (**Figure 1**).
- AZR-MD-001 0.5% significantly improved OSDI total score versus vehicle at Months 4.5 and 6, and AZR-MD-001 1.0% did not show a statistically significant difference versus vehicle (**Figure 2**).
- Significant clinical changes were seen as early as Day 14, after a total of four applications of the drug (**Figure 1**).

FIGURE 1. AZR-MD-001 0.5% RESULTED IN MORE FUNCTIONAL MEIBOMIAN GLANDS THAN VEHICLE AT MONTH 6 (ITT POPULATION)



Mean (standard deviation) baseline MGYLS score in total population: 1.8 (1.3).
*P*value vs vehicle (n.s., not significant; *P*>0.05 vs vehicle).
ITT, intent-to-treat (all patients randomized to study drug); MGYLS, Meibomian Glands Yielding Liquid Secretion (higher scores are better).

FIGURE 2. AZR-MD-001 0.5% SIGNIFICANTLY IMPROVED MGD-RELATED DRY EYE SYMPTOMS VS VEHICLE AT MONTHS 4.5 AND 6 (ITT POPULATION)



Mean (standard deviation) baseline OSDI total score in total population: 24.8 (6.7).
*P*value versus vehicle (n.s., not significant; *P*>0.05 vs vehicle).
ITT, intent-to-treat (all patients randomized to study drug); OSDI, Ocular Surface Disease Index (lower scores are better).

SAFETY AND TOLERABILITY

- AZR-MD-001 demonstrated good safety and tolerability during the 6 months of treatment (**Table 2**).
  - There were no TEAEs with an incidence rate ≥5% during Months 4–6 (**Table 2**).
- The most common TEAE was application-site pain (**Table 2**), all events of which were considered related to study drug.
- Most TEAEs (146/152, 96.1%) in the 0.5% group were mild to moderate.
- None of the serious TEAEs were considered related to study drug.
- Five patients discontinued the study due to a TEAE (**Table 2**).

TABLE 2. TEAEs DECREASED IN INCIDENCE WITH CONTINUED USE OF AZR-MD-001 OVER 6 MONTHS (SAFETY POPULATION)

	MONTHS 1–3			MONTHS 4–6		
	0.5% (N=82)	1.0% (N=83)	VEHICLE (N=80)	0.5% (N=82)	1.0% (N=83)	VEHICLE (N=80)
TEAEs (patients, n [%]) reported in ≥5%						
Application-site pain	14 (17.1)	13 (15.7)	0	0	2 (2.4)	0
Lacrimation increased	9 (11.0)	1 (1.2)	0	2 (2.4)	1 (1.2)	0
Superficial punctate keratitis*	5 (6.1)	6 (7.2)	1 (1.3)	0	2 (2.4)	0
Eye pain	5 (6.1)	6 (7.2)	1 (1.3)	2 (2.4)	1 (1.2)	0
Corneal staining*†	4 (4.9)	7 (8.4)	1 (1.3)	1 (1.2)	1 (1.2)	0
Eye irritation‡	4 (4.9)	5 (6.0)	2 (2.5)	1 (1.2)	1 (1.2)	1 (1.3)
Eye inflammation	3 (3.7)	8 (9.6)	1 (1.3)	0	1 (1.2)	0
Application-site irritation	2 (2.4)	5 (6.0)	0	2 (2.4)	2 (2.4)	0
Discontinuations due to TEAEs	2 (2.4)	1 (1.2)	0	2 (2.4)	0	0

*Defined as associated with an increase in corneal staining of ≥2 grades.
†62% baseline incidence of corneal staining Oxford Score 1 or 2 units signifying early moderate inflammation.
‡Eye irritation upon application occurring during first month of study.
TEAE, treatment-emergent adverse event.

SUMMARY

- Six months of biweekly dosing of AZR-MD-001 0.5% significantly improved signs and symptoms of MGD compared to vehicle
- AZR-MD-001 0.5% significantly improved MGYLS and reduced associated symptoms of MGD at Month 6, with improvements in signs observed as early as Day 14 (after only 4 applications)
- AZR-MD-001 was found to be safe through 6 months of therapy, and tolerability improved with prolonged exposure, in alignment with topical selenium dermatology agents
  - Application site pain was the most common TEAE.

METHODS

- **Purpose:** Phase 2, prospective, randomized, double-masked, vehicle-controlled trial evaluating the safety and efficacy of AZR-MD-001 (0.5% or 1.0%) for the treatment of MGD (NCT03652051)
- **Eligible patients:** Male or female, aged ≥18 years, with mild to moderate MGD (Meibomian Gland Secretion [MGS] score ≤12 for 15 glands of the lower lid) and associated ocular symptoms (Ocular Surface Disease Index [OSDI] score 13–33); self-reported dry eye signs and symptoms within 3 months of study entry; and had a Standard Patient Evaluation of Eye Dryness score ≥6, a Tear Break-Up Time <10 seconds in both eyes, and gland dropout <75%
- **Treatment:** Patients randomized (1:1:1) to AZR-MD-001 0.5%, 1.0%, or vehicle applied to the lower eyelid twice weekly at bedtime
  - No conventional treatments allowed during the study
- **Study timepoints:** Baseline, Day 14, Month 1.5, Month 3, Month 4.5, and Month 6
- **Co-primary endpoints:** Change from baseline in number of Meibomian Glands Yielding Liquid Secretion (MGYLS) and in OSDI total score at Month 3, analyzed using a hierarchical approach
- **Analysis:** Changes from baseline evaluated using an analysis of covariance model with continuous baseline score as a covariate and treatment, duration of disease category (<5 or ≥5 years), and baseline MGS score category (<6 or ≥6 and ≤12) as factors

Co-primary efficacy endpoints

MGYLS measures the number of glands yielding liquid secretion through observing 15 glands on the lower lid, following diagnostic expressibility, to determine whether they secrete any liquid (binary outcome); with a score range of 0–15, higher scores are better.[4]

OSDI measures 12 items centered on ocular symptoms, environmental triggers, and vision-related functioning, with each item rated from 0 (none of the time) to 4 (all of the time); with the total score ranging 0–100, lower scores better.[4]

Safety and tolerability

Safety and tolerability were assessed by the nature, incidence, and severity of treatment-emergent adverse events (TEAEs).

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