Nonclinical assessment of repeat dosing of AZR-MD-001 (selenium sulfide, SeS_2, sterile ophthalmic ointment) to the lower eyelid: A novel therapy developed for meibomian gland dysfunction

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BACKGROUND

- Meibomian gland dysfunction (MGD) is a chronic progressive abnormality of the meibomian glands characterized by terminal duct obstruction and changes in glandular secretion (meibum) that, if left untreated, can lead to atrophy and to irreversible loss of glandular structure and ability to maintain healthy tear film.[1] MGD results in alteration of the tear film, symptoms of eye irritation, and associated ocular surface conditions such as evaporative dry eye disease (DED), with potential for corneal damage and visual impairment.[1]
- AZR-MD-001 (selenium sulfide, SeS_2, sterile ophthalmic ointment) is being developed to treat MGD and associated DED. The AZR-MD-001 formulation was designed to maximize local gland exposure on the lid margins. Clinically, the drug (0.5% or 1%) will be applied as a thin layer of ointment over the lower eyelid twice per week before bedtime; blinking helps get the drug to the upper lid margin.
- A nonclinical program to support the clinical development of AZR-MD-001 was conducted. Pivotal repeat dose studies were conducted in dogs for 3 months and in rabbits for 6 months. The weekly ocular safety margins used in these studies exceeded the planned clinical dose by more than 7-fold.

OBJECTIVE

- To evaluate the toxicology profile of AZR-MD-001 in repeat dose toxicology studies in dogs and rabbits

METHODS

AZR-MD-001 toxicity was assessed in 2 pivotal repeat dose toxicology studies, conducted per Good Laboratory Practice regulations at Pharmaron Lab Services LLC (formerly Absorption Systems; San Diego, CA):

- Beagle dogs for 3 months with a 4-week recovery period, 5/sex/group
- Dutch Belted rabbits for 6 months with a 4-week recovery period, 9/sex/group

TREATMENT GROUPS (BOTH DOGS AND RABBITS, BOTH EYES)

- Group 1 – Vehicle, Daily (0 µg/eye)
- Group 2 – 1%, Daily (40 µg/eye)
- Group 3 – 2.5%, Twice weekly (100 µg/eye)
- Group 4 – 2.5%, Daily (100 µg/eye)

MEASUREMENTS

- **Ophthalmic Measurements** (both eyes) – tolerability scale; dermal and ocular Draize; intraocular pressure; ophthalmic examinations (by a Boarded veterinary ophthalmologist) included slit-lamp biomicroscopy (modified McDonald-Shadduck scoring), fluorescein staining, eyelid evaluation, and indirect ophthalmoscopy
- **Systemic Measurements** – general health observations, body weight, electrocardiography (ECG; dogs only), toxicokinetic (TK) analysis, and clinical pathology
- **Necropsy** – at the end of the dosing period and end of recovery period: full necropsy with organ weights
- **Histopathological evaluation** – eyes, ocular adnexa, and nasal turbinates

Descriptive statistics –
SAS® statistical software suite embedded within Provantis™

TK parameters –
non-compartmental analysis on individual profiles using WinNonlin® version 6.3

RESULTS

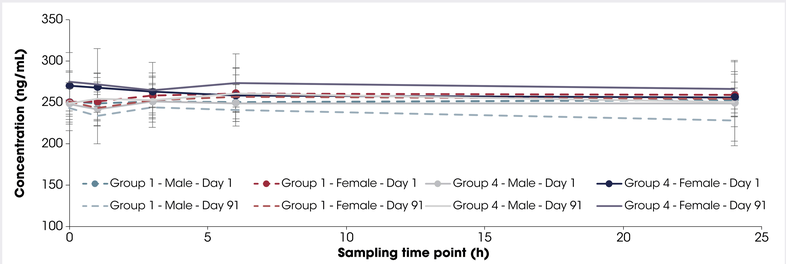
TABLE 1. BEAGLE DOGS (N=40)

	GROUP 1 – VEHICLE, DAILY (0 µg/EYE)	GROUP 2 – 1%, DAILY (40 µg/EYE)	GROUP 3 – 2.5%, TWICE WEEKLY (100 µg/EYE)	GROUP 4 – 2.5%, DAILY (100 µg/EYE)
Ophthalmic Measurements – End of dosing phase, day 91				
Tolerability scale (0–4)	0	0	0	0
Mean ocular Draize (0–110)	0	0	0	0
Mean dermal Draize (0–8)	0	0	0	0
Intraocular pressure (mm Hg)†	M 20.2±3.4 F 18.1±1.6	M 19.3±2.2 F 18.5±2.3	M 19.3±1.7 F 18.1±1.8	M 19.1±1.3 F 18.1±1.1
Ophthalmic Examinations – End of dosing phase, day 91				
Slit-lamp biomicroscopy	0	0	0	0
Indirect ophthalmoscopy	0	0	0	0

†Both eyes (right and left) combined. F, female; M, male.

TK analyses in Beagle dogs demonstrated no effect on endogenous selenium plasma levels in all treated groups

AZR-MD-001 Vehicle (Group 1) vs. 2.5% (100 µg/lid SeS_2; Group 4) following QD dosing, bilateral to the lower eyelids



Presented as mean (± standard deviation) selenium plasma concentration (ng/mL) over time (h) in male and female dogs on Days 1 and 91.

The plasma selenium concentrations following 91 days of AZR-MD-001 dosing, bilaterally, to the lower eyelid margins of dogs at various concentrations and dosing frequencies **demonstrated a lack of systemic selenium elevation above the endogenous levels** during the first 24 hours following administration.

Ophthalmic examinations – Administration of AZR-MD-001 was not associated with any corneal damage, iris damage, or other ophthalmic abnormalities.

Systemic measurements – No systemic effects were found by clinical observations, body weight, ECG, and/or clinical pathology.

Histopathology – No test article–related macroscopic or microscopic findings were observed in animals at scheduled necropsy.

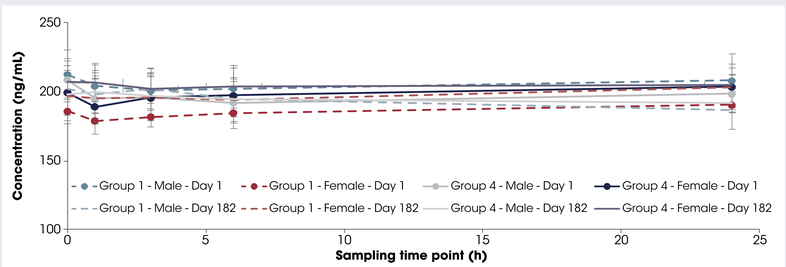
TABLE 2. DUTCH BELTED RABBITS (N=72)

	GROUP 1 – VEHICLE, DAILY (0 µg/EYE)	GROUP 2 – 1%, DAILY (40 µg/EYE)	GROUP 3 – 2.5%, TWICE WEEKLY (100 µg/EYE)	GROUP 4 – 2.5%, DAILY (100 µg/EYE)
Ophthalmic Measurements – End of dosing phase, day 182				
Tolerability scale (0–4)	0	0	0	0
Mean ocular Draize (0–110)	0	0	0	0
Mean dermal Draize (0–8)	0	0	0	0
Intraocular pressure (mm Hg)	M 14.7±2.8 F 16.6±2.4	M 14.9±1.6 F 17.3±1.5	M 16.0±1.4 F 16.8±1.5	M 14.9±2.3 F 17.9±1.5
Ophthalmic Examinations – End of dosing phase, day 182				
Slit-lamp biomicroscopy	0	0	0	0
Indirect ophthalmoscopy	0	0	0	0

F, female; M, male.

TK analyses in Dutch Belted rabbits demonstrated no effect on endogenous selenium plasma levels in all treated groups

AZR-MD-001 Vehicle (Group 1) vs. 2.5% (100 µg/lid SeS_2; Group 4) following QD dosing, bilateral to the lower eyelids



Presented as mean (± standard deviation) selenium plasma concentration (ng/mL) over time (h) in male and female rabbits on Days 1 and 182.

The plasma selenium concentrations following 182 days of AZR-MD-001 dosing, bilaterally, to the lower eyelid margins of rabbits at various concentrations and dosing frequencies **demonstrated a lack of systemic selenium elevation above the endogenous levels** during the first 24 hours following administration.

Ophthalmic examinations – Administration of AZR-MD-001 was not associated with any corneal damage, iris damage, or other ophthalmic abnormalities.

Systemic measurements – No systemic effects were found by clinical observations, body weight, organ weights, and/or clinical pathology.

Histopathology – Minimal or mild mononuclear cell infiltrates of the superficial dermis and epidermal hyperplasia of the eyelid were observed in all groups at the end of the dosing period. There was no dose response seen in either severity or incidence. It was not considered to be adverse. No other pathologies were found.

SUMMARY

- These findings demonstrate that AZR-MD-001 (up to 2.5%) daily in both lower eyelids was well tolerated ocularly and systemically in test animals. The nonclinical toxicology program supported the clinical phase 2 program and supports continuing to phase 3 studies evaluating the safety and efficacy of AZR-MD-001 up to a concentration of 1.0% dosed twice a week in humans.

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Reference

1. Nichols KK, et al. *Invest Ophthalmol Vis Sci.* 2011;52(4):1922-9.

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