

# **A Multicenter, Vehicle-controlled, Randomized Study to Evaluate the Safety, Tolerability and Pharmacodynamics of AZR-MD-001 in Patients with Meibomian Gland Dysfunction (MGD)**

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**Sponsor:** Azura Ophthalmics, Level 9,  
31 Queen Street  
Melbourne, VIC 3000 Australia

Tel: +1 714-559-8435

E-mail:  
Charles.Bosworth@azuraophthalmics.com

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**STATEMENT OF COMPLIANCE**

**INVESTIGATOR:**

**STUDY LOCATION:**

**I agree to:**

- Implement and conduct this study diligently and in strict compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP) and all applicable state, local and federal regulatory requirements.
- The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) for review and approval. Approval of both the protocol and the consent form will be obtained before any participant is enrolled.
- Maintain all information supplied by Azura Ophthalmics in confidence and, when this information is submitted to an Institutional Review Board (IRB), Independent Ethics Committee (IEC) or another group, it will be submitted with a designation that the material is confidential.
- I have read this protocol in its entirety and I agree to all aspects.

\_\_\_\_\_  
Investigator Printed Name

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

## 1 PROTOCOL SUMMARY

### 1.1 SYNOPSIS

**Study Compound(s):** AZR-MD-001 (Selenium Disulfide)

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**Phase:** 2b

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**Objectives:** To evaluate the safety, tolerability and pharmacodynamics of AZR-MD-001 ointment/semi-solid drug applied to the lower lid twice-weekly for up to 3 months compared to its vehicle in patients with meibomian gland dysfunction (MGD).

**Clinical Hypotheses:** AZR-MD-001 ointment/semi-solid drug has an acceptable safety and tolerability profile following twice-weekly, evening peri-ocular administration for the study treatment duration.

AZR-MD-001 ointment/semi-solid drug is more effective than vehicle for treating MGD as measured by the meibum gland secretion score (MGS).

AZR-MD-001 ointment/semi-solid drug is more effective than vehicle for treating symptoms associated with MGD as measured by Total Ocular Surface Disease Index (OSDI) score.

### 1.2 SCHEMA

**Study Design:** *Structure:* Multicenter, investigator-masked, vehicle-controlled, randomized, parallel group study comparing AZR-MD-001 (0.5%) ointment/semi-solid drug and AZR-MD-001 vehicle dosed twice-weekly in the evening.

Patients with MGD will be randomly assigned in a 1:1 ratio to receive either a single concentration of AZR-MD-001 ointment/semi-solid drug (i.e., 0.5%) or AZR-MD-001 vehicle.

For all dose groups a screening visit will be followed by a baseline visit 14 days later (qualification period). At the end of the qualification period patients who still exhibit signs of MGD and who can comply with dosing instructions at the baseline visit will be enrolled into a 3-month treatment period. The study flow is shown in Figure 1.

*Duration:* The total duration of study is approximately 3.5 months (from screening to study completion).

*Study Treatment Groups:* AZR-MD-001 ointment/semi-solid drug (i.e., 0.5%).

*Active Period Control:* AZR-MD-001 Vehicle

*Baseline Visit:* “Vaseline” (AZR-MD-001 Vehicle)

*Dosage/Dose Regimen:* Upon meeting inclusion/exclusion criteria patients will be randomized to AZR-MD-001 ointment/semi-solid drug (0.5%) or AZR-MD-001 vehicle administered twice-weekly, in the evening at bed time for three months.

*Randomization/Stratification:* Patients will be randomized to receive AZR-MD-001 ointment/semi-solid drug (0.5%) or AZR-MD-001 vehicle in a 1:1 treatment allocation ratio at the baseline visit.

Patients will be stratified by duration of MGD diagnosis (i.e., < 5 years or  $\geq$  5 years) and baseline MGS score (MGS score of < 6 or MGS score  $\geq$ 6 and  $\leq$  12) for the qualified eye (i.e., the eye meeting the inclusion/exclusion criteria). If the patient has 2 qualified eyes, the stratification will be based on the eye with the lower numerical MGS score. If the eyes have the same MGS score, then the right eye will be selected as the study eye.

*Visit Schedule:* Up to 6 scheduled visits: screening, randomization, day 14, month 1, month 1.5, and month 3 (exit). For patients who discontinue the study early, the month 3 visit procedures should be completed.

## **Study Population Characteristics**

*Number of Patients:* The total number of randomized patients for the study will be up to approximately 30. Approximately 15 patients should have a baseline MGS score of < 6 and approximately 15 patients should have a baseline MGS score  $\geq$ 6 and  $\leq$  12. Based upon data from ongoing study AZ201801 and the simplified inclusion/exclusion criteria for this study a screen failure rate of ~40% is expected. Thus, ~42 patients will need to be screened to achieve ~30 patients randomized to treatment.

*Condition/Disease:* Meibomian Gland Dysfunction (MGD)

*Key Inclusion Criteria:*

- Male or female, 18 years of age or older at screening visit
- Capable of understanding and willing to provide written informed consent and likely to complete the entire course of study according to instructions
- Written authorization for use and release of health and research study information has been obtained
- Best-corrected visual acuity (BCVA) of 20/40 or better (Snellen equivalent), using the logarithm of the minimum angle of resolution (LogMAR) in each eye at the screening and baseline visits
- Evidence of meibomian gland obstruction (based on a meibomian gland secretion (MGS) score of  $\leq$ 12 for 15 glands of the lower lid) in both eyes at the screening and baseline visits
- Reported dry eye signs and symptoms within the past 3 months

- Prior to starting screening visit procedures, patients are required to have discontinued:
  - Use of systemic antihistamines or isotretinoin for at least 1 month
  - Anti-inflammatory treatments for DED (e.g., cyclosporine ophthalmic emulsion [Restasis® or Ikervis®] or lifitegrast ophthalmic solution [Xiidra®]) for at least 3 months
  - All other prescription medications used for dry eye or MGD (e.g., antibiotics, corticosteroids, and non-steroidal anti-inflammatory drugs) for at least 2 weeks
  - LipiFlow® or other lid-heating therapy, meibomian gland probing, or therapeutic gland expression in either eye within 6 months prior to the screening visit
  - All other MGD treatments (e.g., at-home warm compress therapy, eyelid hygiene, eyelid massage, and manual lid expression) for at least 2 weeks
- And
  - All other topical ophthalmic preparations (including artificial tear substitutes) other than the study drops: 72 hours prior to screening visit. If artificial tear substitutes were used within 72 hours of the screening visit the visit should be rescheduled
- Evidence of active MGD associated signs and symptoms at the screening and baseline visits:
  - Score  $\geq 6$  on the Standard Patient Evaluation of Eye Dryness questionnaire (SPEED)
  - Ocular Surface Disease Index (OSDI) questionnaire score  $\geq 13$
- And
  - TBUT < 10 seconds in both eyes
- Demonstrated ability to follow dosing instructions at the baseline visit
- A negative pregnancy test result for all women at the screening visit
- Women of childbearing potential must have a history of bilateral tubal ligation or use oral contraceptives, implants, injectables, transdermal patch, or intrauterine device for birth control during the study. Abstinence is not considered a reliable method of birth control. If these methods of birth control do not apply, woman of childbearing potential must have a monogamous partner who has had a vasectomy at least 3 months before the screening visit or who is of the same gender.

*Exclusion Criteria:*

- Uncontrolled ocular disease (except for MGD and dry eye disease/keratoconjunctivitis sicca associated with MGD) or uncontrolled systemic disease
- Patient has glaucoma, ocular hypertension, or intraocular pressure (IOP) in either eye at screening  $\geq 24$  mm Hg as determined by Goldman applanation tonometry or has planned insertion/removal of glaucoma filtration shunts/devices during the study
- Corneal abnormality or disorder that impacts normal spreading of the tear film (keratoconus, pterygia, scarring) or corneal integrity
- BCVA worse than 20/40 in either eye at the screening or baseline visit

- Current use of punctal plugs, anticipated insertion during the study, or a history of punctal cautery in either eye at any time prior to the screening visit or anticipate such a procedure during the study
- Keratoconjunctivitis sicca secondary to destruction of conjunctival goblet cells as occurs with vitamin A deficiency or scarring, such as that with cicatricial pemphigoid, alkali burns, Stevens-Johnson syndrome, trachoma, or irradiation
- Keratoconjunctivitis sicca secondary to aqueous deficient DED
- Active ocular infection (bacterial, viral, or fungal) at the screening or baseline visits
- Corneal, conjunctival, or eyelid inflammation (including allergic, vernal, or giant papillary conjunctivitis and mucous membrane pemphigoid) that in the judgment of the investigator may interfere with the study results or the ability of subjects to complete the treatment period
- Recent (within the past 3 months of the screening visit) ocular surgery, trauma, herpes, or recurrent inflammation
- Contact lens use anticipated during the study
- Periocular application of makeup likely to impact meibomian gland function during the study or tattooing of the lids
- Use of any type of scleral lenses or sealed compartment ocular frames within 2 months of the screening visit, or planned use during the study
- Use prohibited medications (topical, topical ophthalmic, systemic and/or injectable) during the appropriate pre-study wash-out period and during the study
- Unwilling to abstain from the use of systemic medications known to cause dryness for the study duration that is not used on a stable dosing regimen for at least 30 days prior to the baseline visit
- Unwilling to abstain from the use of systemic or topical treatments for MGD or dry eye for the study duration (Including over-the-counter [OTC] artificial tears, ocular lubricants, or dietary supplements known to impact ocular surface health)
- Eyelid abnormalities that affect normal lid function in either eye other than those caused by meibomian gland dysfunction
- Diagnosis of hepatitis C infection, human immunodeficiency virus (HIV) infection, sarcoidosis, amyloidosis, active tuberculosis, or graft versus host disease
- History of anterior segment surgery or trauma that could affect corneal sensitivity (e.g., cataract surgery or any surgery involving a limbal or corneal incision) in either eye within the 12 months prior to the screening visit
- Planned anterior segment surgery (e.g., cataract surgery or any surgery involving a limbal or corneal incision) in either eye during the study period
- Meibography score at the screening visit of 4 (greater than 75% partial glands using the gestalt grading system)
- Corneal staining  $\geq 3$  (between 33 and 100 dots) using the Oxford Scheme

- Schirmer's tear test without anesthesia  $\leq 5$  mm in either eye at the baseline visit
- Known allergy or sensitivity to fluorescein, lissamine green, or the study medication or its components
- Use of medicated shampoos containing selenium (e.g., Selsun Blue, Exsel, Selsum, and Seleen) following the screening visit
- Patient is unlikely to follow study instructions or to complete all required study visits or has a condition or situation that in the investigator's opinion, may put the patient at significant risk, may confound the study results, or may interfere significantly with the patient's participation in the study
- Patient is an employee at the investigational site or is related to any member of the study staff
- Pregnant, nursing, or females of childbearing potential and not utilizing adequate birth control measures. Woman of childbearing potential may have a monogamous partner who has had a vasectomy at least 3 months before the screening visit or who is of the same gender.
- Positive urine pregnancy test at the screening visit
- Participation in another clinical trial involving a therapeutic drug or device within the past 30 days

## Response Measures

### *Primary Sign for MGD:*

- Change from Baseline to month 3 in meibum gland secretion score (MGS) (0 to 45 scale)

### *Primary Symptom for MGD:*

- Change from Baseline to month 3 in Total OSDI

### *Other Efficacy Measures:*

- Change from Baseline to day14, month 1 and month 1.5 in MGS (0 to 45 scale)
- MGS score (0 to 45 scale) at each visit
- Proportion of patients with a MGS score  $> 12$  at each visit
- Change from Baseline to day14, month 1, month 1.5 and month 3 in the number of Meibomian Glands Yielding Liquid Secretion (MGYLS) (0 to 15 scale)
- MGYLS (0 to 15 scale) at each visit
- Change from Baseline to day 14, month 1, month 1.5, and month 3 in TBUT
- TBUT at each visit
- Proportion of patients with a TBUT score  $> 5$  at each visit
- Change from Baseline to day 14, month 1, month 1.5 and month 3 in Standard Patient Evaluation of Eye Dryness (SPEED)
- SPEED at each visit
- Proportion of patients with a SPEED  $< 6$  at each visit
- Change from Baseline to day 14, month 1, month 1.5 and month 3

- in average visual analogue scale (VAS)
- Average VAS at each visit
  - Change from Baseline to day 14, month 1, month 1.5 and month 3 in worst VAS
  - Worst VAS at each visit
  - Change from Baseline to day 14, month 1 and month 1.5 in Total OSDI
  - Total OSDI, OSDI sub-scales, and individual items from the OSDI across visits
  - Proportion of patients with a Total OSDI change from baseline > 4.5, the known minimally important clinical difference (MICD) for early to moderate disease, at month 3
  - Proportion of patients with a Total OSDI < 13 at each visit
  - Number of expressible glands yielding clear meibum at day14, month 1, month 1.5, and month 3
  - Eyelid margin erythema/telangiectasias at day14, month 1, month 1.5, and month 3
  - Corneal and conjunctival staining (0 to 5 scale) at each visit

*Safety:*

- Adverse events
- Vital signs
- Study medication tolerability as measured by the Ocular Comfort Questionnaire
- Urine pregnancy test
- Best-corrected visual acuity (BCVA; Logarithmic visual acuity chart)
- Biomicroscopy
- Ophthalmoscopy
- Intraocular pressure (IOP)

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**General Statistical**

**Methods and Types of Analyses:**

The safety population will include all treated patients. For safety variables, patients in the safety population will be analyzed by the treatment actually received. The modified intent-to-treat (mITT) population will be comprised of all patients randomized and, who have values at randomization, and at least 1 post-randomization value for MGS at a regularly scheduled visit (i.e., Day 14 or Month 1). All patients in the mITT population will be analyzed by the treatment received. This population will be used for the primary and the secondary efficacy analyses.

The modified intent-to-treat 2 (mITT2) population will be comprised of patients who are included in the mITT and have the randomization MGS score in the study eye  $\geq 6$  and  $\leq 12$ . The mITT2 population will be analyzed by the treatment received.

In general, continuous data will be summarized with descriptive statistics (number of patients, mean, standard deviation, median, minimum, and maximum) and will be analyzed using analysis of variance (ANOVA) techniques or 2-sample t-tests for between-group comparisons, and paired t-tests for within-group analyses. Categorical variables will be summarized by sample size (N), frequency count,

and percent, and they will be analyzed using Pearson's chi-square test or Fisher's exact test (if the expected cell count is less than 5 in 25% or more of the cells). Ordinal variables will be analyzed using the Cochran-Mantel-Haenszel (CMH) or the Wilcoxon rank-sum test for between-treatment comparisons and the sign-rank test for within-treatment comparisons.

*Primary Efficacy (MGD):*

The primary efficacy sign for MGD is change from baseline in MGS. The visit for the primary variable is month 3 and the primary analysis population is mITT. Statistical testing will be performed for the AZR-MD-001 group versus vehicle group.

The primary efficacy symptom for MGD is change from baseline in Total OSDI. The visit for the primary variable is month 3 and the primary analysis population is mITT. Statistical testing will be performed for the AZR-MD-001 group versus vehicle group.

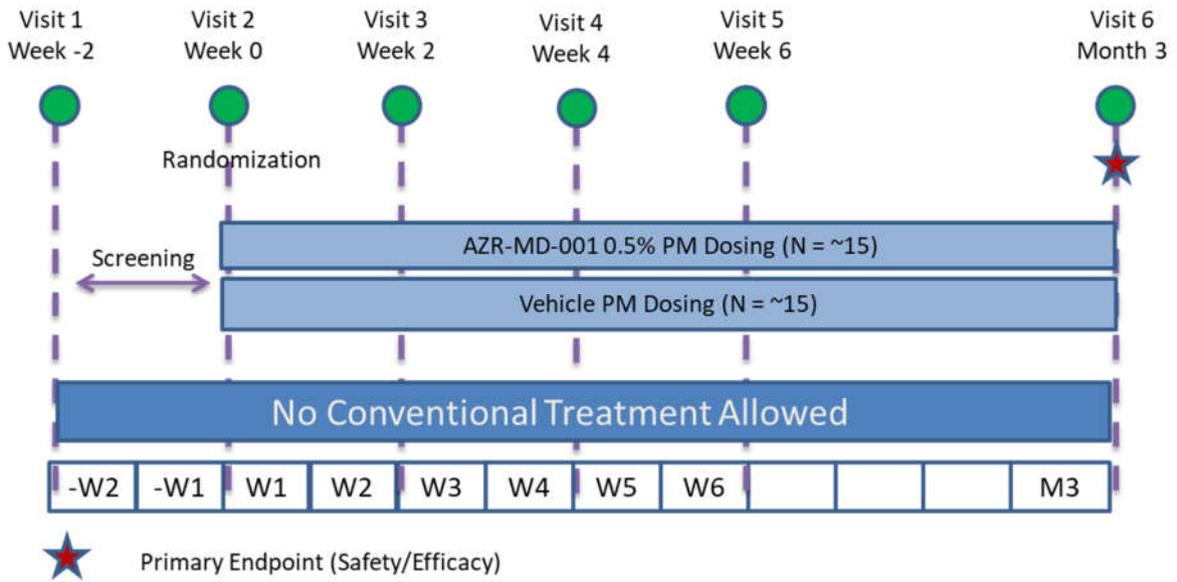
*Safety:* Safety measures will be analyzed using the safety population. Medical Dictionary for Regulatory Activities (MedDRA) nomenclature will be used to code adverse events. Incidence rates of each treatment-emergent adverse event will be summarized by primary system organ class and preferred term. Summary tables will be generated for all treatment-emergent adverse events regardless of causality as well as for those considered to be treatment-related.

*Sample Size Calculation:* Estimates for sample size calculations are from the first interim analysis from Azura Clinical Protocol AZ201801. The standard deviation for MGS was 3.35 units for an ineffective dose and 9.48 units for the high dose. A sample size of 12 subjects per group will have 90% power to detect a difference of 10.4 units between the active treatment group and the vehicle group using a two-sample t-test at a significance level of 0.05. The standard deviation for Total OSDI was 13.01 units for an ineffective dose and 6.79 units for the high dose. A sample size of 11 subjects per group will have 90% power to detect a difference of 15.9 units between the active treatment group and the vehicle group using a two-sample t-test at a significance level of 0.05.

*Multiplicity Consideration:* To address the multiple primary endpoints defined in this study, the primary endpoints have been prioritized into a hierarchical structure. In order to test the primary symptom endpoint of Total OSDI, the primary sign endpoint of MGS must be statistically significantly higher in the 0.5% AZR-MD-001 treatment group compared to the vehicle treatment group using a two-sided significance level of 0.05. Using this strategy, the family-wise Type I error rate will be maintained at the 0.05 significance level for the two primary endpoints.

*Interim Analysis:* None Planned

**Figure 1 Study Flow – Multicenter, investigator-masked, vehicle-controlled, randomized, parallel group study**



### 1.3 SCHEDULE OF ACTIVITIES (SOA) COHORT 1 AND EXPANSION COHORT

**Table 1 Schedule of Visits and Procedures**

Study Period	Qualification Period		Investigator-Masked Period			
	Screening <sup>a</sup> (Day -14)	Baseline Day 0 Randomization	Day 14	Month 1	Month 1.5	Month 3 (Exit)
Visit Window	$\pm 2$ Days	N/A	$\pm 2$ Days	$\pm 7$ Days	$\pm 7$ Days	$\pm 7$ Days
Informed consent/authorization	X					
Contact IVRS/IWRS for patient number assignment (screening number)	X					
Demographics (including height and weight)	X					
Inclusion/exclusion criteria	X	X				
Medical and ophthalmic history	X	X				
Medication history	X					
Washout medications	X					
Vital signs (pulse rate, blood pressure) <sup>f</sup>	X	X		X		X
Pregnancy test (urine) for female patients <sup>b, f</sup>	X					X
OSDI <sup>f</sup>	X	X	X	X	X	X
SPEED <sup>f</sup>	X	X	X	X	X	X
Patient Ocular Symptoms (VAS) <sup>f</sup>	X	X	X	X	X	X
Best-corrected visual acuity (BCVA) <sup>f</sup>	X <sup>c</sup>	X	X	X	X	X
Slit-lamp biomicroscopy (includes eyelid margin erythema/telangiectasias and do not touch the lids) <sup>f</sup>	X	X	X	X	X	X
Tear Break Up Time (TBUT) <sup>e, f</sup>	X	X	X	X	X	X
Sodium fluorescein corneal staining, Oxford scale <sup>f</sup>	X	X	X	X	X	X
Lissamine green conjunctival staining, Oxford scale <sup>f</sup>	X	X	X	X	X	X

Study Period	Qualification Period		Double-Masked Period			
	Screening <sup>a</sup> (Day -14)	Baseline Day 0 Randomization	Day 14	Month 1	Month 1.5	Month 3 (Exit)
Visit Window	$\pm 2$ Days	N/A	$\pm 2$ Days	$\pm 7$ Days	$\pm 7$ Days	$\pm 7$ Days
Meibomian gland evaluation (MGE) <sup>e, f</sup>	X	X	X	X	X	X
Schirmer without anesthesia <sup>f</sup>	X	X		X		X
Intraocular pressure (IOP) <sup>f</sup>	X					X
Ophthalmoscopy exam <sup>d</sup>	X					X
Meibography <sup>f</sup>	X					X
Study medication Tolerability/Comfort Questionnaire <sup>f</sup>		X <sup>g</sup>	X	X	X	X
Adverse events/medications/procedures <sup>f</sup>	X	X	X	X	X	X <sup>h</sup>
Discontinue concomitant medication(s) impacting inclusion/exclusion	X					
Contact IVRS/IWRS for patient randomization number		X				
Medication dispensing/return		X	X	X	X	X
Physician Observation of Drug Application Methods		X				

BCVA = Best Corrected Visual Acuity; OSDI = Ocular Surface Disease Index; SPEED = Standard Patient Evaluation of Eye Dryness; TBUT = tear break up time;

VAS = Visual Analogue Scale; PM = Evening

*a* Screening diagnostic procedures are not required to be performed on the same day, and can be performed across multiple days from days -14 to -2. At screening, patients will be asked to report use of artificial tears and all other treatments for MGD and/or associated DED. Patients should wash out from all medication listed in the inclusion/exclusion criteria.

*b* For females of childbearing potential.

*c* Manifest refraction performed at screening will be used at each visit to obtain BCVA.

*d* Ophthalmoscopy examination will be dilated at screening and undilated for month 3 visit unless dilation is necessary

*e* TBUT and MGE should be performed by the same individual for a given patient.

*f* The individual performing the measurement will not be involved in drug dispensing or accountability and should remain masked to the treatment received by the patient.

<sup>g</sup> The tolerability questionnaire at BSL is completed based on participants experience with the “practice dose” using Vaseline. At other visits, participants are to complete it referring back to their last evening dose

<sup>h</sup> A follow up telephone call will occur 1 week (+/- 2 days) after the participant has attended the final on site 3 Month visit. This is a safety follow up call.

## 2 INTRODUCTION

### 2.1 BACKGROUND

Meibomian gland dysfunction (MGD) is a chronic, diffuse abnormality of the meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion. Terminal duct obstruction is caused by hyperkeratinization of the ductal epithelium (Nichols et al, 2011). This may result in alteration of the tear film, symptoms of eye irritation, and ocular surface disease such as evaporative dry eye. The principal clinical consequence of obstructive MGD is evaporative dry eye syndrome and large population based studies (i.e., Bangkok Study and the Shihpai Eye Study) estimate that over 60% of patients with dry eye symptoms also have MGD (Schaumberg et al, 2011).

MGD may be diagnosed by meibomian gland expression alone, with demonstration of an altered quality of expressed secretions, and/or by a loss of gland functionality (Nelson et al, 2011). Population based studies have estimated the prevalence of MGD to vary between 3.5% and 70% of the general population. The prevalence of MGD appears higher in Asian populations (i.e., 46.5% to 69.3%) and increases with age (Schaumberg et al, 2011). Risk factors in the pathogenesis of obstructive MGD include age, hormonal disturbances and environmental influences (e.g., contact lenses).

Meibomian glands are large sebaceous glands that are located as separate gland strands in parallel arrangement within the tarsal plates of the eyelids. Meibomian glands produce meibum via a holocrine mechanism during which meibocytes are transformed into the meibum. Following production in the gland acini, meibum is transported through the ductal system via the connecting duct and the central duct towards the orifice at the free eyelid margin close to the inner eyelid border (Knop et al, 2011).

Meibum is a complex mixture of various polar and nonpolar lipids containing cholesteryl esters, triacylglycerol, free cholesterol, free fatty acids, phospholipids, wax esters, diesters, and minor protein components. Normal meibum is a clear liquid at body temperature (Green-Church et al, 2011). It is transported within the gland by the force of secretory pressure from continuous secretion and by muscular action of the orbicularis muscle and riolans muscles during blinking. After it is delivered onto the posterior eyelid margin, meibum moves from the posterior eyelid margin reservoir onto the tear meniscus and is pulled as a thin layer onto the pre-ocular tear film every time the eyelid opens. During closure of the eyelid, it is compressed and a small part

is continuously renewed. Meibum forms the outer lipid layer of the tear film which functions to slow evaporation of the aqueous component of the tear film, preserves the clear optical surface, and forms a barrier to protect the eye from microbial agents and organic matter (e.g., dust and pollen) (Green-Church et al, 2011).

Conventional treatments of obstructive MGD entail eyelid hygiene (e.g., lid washing and use of preservative-free artificial tears), omega-3 dietary supplementation (e.g., eicosapentaenoic acid and docosahexaenoic acid), topical antibiotics (e.g., bacitracin and erythromycin), topical corticosteroids, topical cyclosporine, oral antibiotics (e.g., doxycycline, minocycline, and tetracycline), oral omega-6 fatty acids (e.g., linoleic acid and gamma-linolenic acid), as well as unclogging of glands that are blocked, which can be achieved by applying warm compresses to the eyelid or gentle lid massaging (Olson et al, 2003; Romero et al, 2004; Yoo et al, 2005; Perry et al, 2006; Pinna et al, 2007; Souchier et al, 2008; and Foster et al, 2009). Moreover, eyelid-warming devices have also been employed in the treatment of patients with MGD (Goto et al, 2002; Mitra et al, 2005; Matsumoto et al, 2006; Geerling et al, 2011; Lane et al, 2012).

## 2.2 STUDY RATIONAL & KNOWN POTENTIAL BENEFITS

The recognition that terminal duct obstruction from hyperkeratinization of the ductal epithelium on meibomian glands is a core mechanism behind meibomian gland dysfunction (MGD) is consistent with clinical experience demonstrating that effective treatments for MGD require resolution of ductal obstruction and evacuation of glandular contents (Nichols et al, 2011; Lane et al, 2012; Blackie et al, 2015). Warm compresses and thermal/mechanical devices (e.g., LipiFlow) are used in an attempt to raise the internal temperature of the meibomian glands over the normal melting point for meibum (i.e., 32°C to 40°C) resolving the terminal duct obstruction (Lane et al, 2012). Unfortunately, warm compresses are unable to achieve this benefit for severely obstructed glands which can have a melting point > 40°C.

Finis and colleagues (2014), conducted a prospective, randomized, observer-masked trial in 40 patients with MGD: 19 patients were randomized to LipiFlow and 16 patients were randomized to standard of care (i.e., twice-daily lid warming, massage, and cleaning of the lid margin) for 3 months. LipiFlow and standard of care demonstrated significant improvements from baseline in symptoms, measured by SPEED, and in the number of expressible glands by 1 month. Consistently observed benefits for devices designed to treat glandular obstruction include:

- 1) Improvement in the meibum gland score (MGS) (0 to 45 scale);
- 2) Increases in the number of meibomian glands yielding liquid secretion (MGYLS) (0 to 15 scale);

3) Increased Tear Break-up Time (TBUT); and

- 4) Improved Total OSDI, SPEED and eye dryness scores (measured using a visual analogue scale [VAS]) (Blackie et al, 2015).

While there are no approved pharmacological treatments for terminal duct obstruction from hyperkeratinization associated with MGD, compounds that reduce disulfide bonds (S-S) have shown promise. Akyol-Salman and colleagues (2010) used N-acetyl-cysteine (NAC) in 20 patients with MGD and demonstrated a statistically significant improvement in TBUT and symptoms (e.g., itching) by 1 month (Akyol-Salman et al, 2010; Akyol-Salman et al, 2012). Selenium sulfide as a 0.5% ointment has also been applied to the lid margin as a treatment for seborrheic blepharitis (Bahn, 1954).

Azura Ophthalmics is evaluating AZR-MD-001 ointment/semi-solid drug (selenium disulfide) as a potential treatment for MGD and associated evaporative DED. Selenium sulfide exists as a mixture of selenium monosulfide and selenium disulfide. AZR-MD-001 uses the same API as commercially available marketed products (i.e., Selsun Blue, Exsel, Selsum, and Seleen). In these shampoos selenium disulfide is used as an anti-fungal and anti-dandruff ingredient. It is marketed at a 1% concentration in non-prescription products and at a 2.5% concentration in prescription products.

Clinical study MGSS1 was a prospective, interventional, non-randomized, contra-lateral eye controlled pilot study of selenium disulfide shampoo (2.5%) in 18 MGD patients. Patients were treated under additional safety measures, twice-weekly for 34 weeks and then had a single treatment on day 44. Selenium disulfide shampoo (2.5%) was safe and well tolerated with controlled dosing. One patient (FHT,002) developed conjunctivitis and superficial punctate keratitis and one patient (MCG,006) developed superficial punctate keratitis. The adverse events could be attributed to the surfactant in the shampoo (Sodium Lauryl Sulphate). Both patient's symptoms resolved upon cessation of treatment. Significant improvements in TBUT ( $p = 0.0008$ ), meibum quality ( $p = 0.002$ ), and patency ( $p=0.02$ ) for the drug treated eye over the contra-lateral eye were observed by day 22.

Clinical Protocol AZ201801 was a multicenter, double-masked, vehicle-controlled, randomized, parallel group study carried out in 2 sequentially overlapping cohorts (Cohort 1: sequential rising concentrations of AZR-MD-001 ointment/semi-solid drug (i.e., 0.1%, 0.5%, 1.0%, or a top dose up to 2.5%) and AZR-MD-001 vehicle dosed twice-weekly and/or once daily in the evening; Expansion Cohort: parallel doses of up to two concentrations of AZR-MD-001 ointment/semi-solid drug (i.e., two of four available concentrations: 0.1%, 0.5%, 1.0%, or 2.5%) and AZR-MD-001 vehicle dosed either twice-weekly or once daily in the evening. The first pre-planned Interim Analysis covered all patients up to the 10th enrolled patient in Cohort 1, Group 3 completing the Month 3 Visit and

who met all protocol inclusion and exclusion criteria and had at least one post-baseline visit.

Eleven patients were randomized to Cohort 1, Group 1 (0.1%, twice-weekly) between September 10th, 2018 and October 19th, 2018 in ongoing clinical study AZ201801. Twelve patients were randomized to Cohort 1, Group 2 (0.5%, twice-weekly) between October 19th, 2018 and February 20th, 2019. Ten patients were randomized to Cohort 1, Group 3 (1.0%, twice-weekly) between April 22nd, 2019 and June 19th, 2019.

As specified in Protocol Amendment # 2 dated January 2019, the primary efficacy variables for MGD included change from baseline to month 3 in Meibomian Gland Score (MGS) and measures of Total Ocular Surface Disease Index (OSDI). Least Square (LS) mean changes from baseline (larger scores signal improvement) for MGS at month 3 were  $4.5 \pm 2.0$  ( $p = 0.025$ ) for the Vehicle Group;  $1.2 \pm 2.0$  ( $p = 0.56$ ) for the AZR-MD-001 0.1% Group (sub-therapeutic dose);  $4.9 \pm 2.1$  ( $p = 0.02$ ) for the AZR-MD-001 0.5% Group; and  $12.2 \pm 2.4$  ( $p < 0.0001$ ) for the AZR-MD-001 1.0% Group. Total OSDI showed the same pattern of results. Least square (LS) mean changes from baseline (smaller scores signal improvement) for Total OSDI at month 3 were  $0.0 \pm 3.4$  ( $p = 0.99$ ) for the Vehicle Group;  $9.5 \pm 3.8$  ( $p = 0.01$ ) for the AZR-MD-001 0.1% Group;  $-6.9 \pm 4.0$  ( $p = 0.08$ ) for the AZR-MD-001 0.5% Group; and  $-12 \pm 5.1$  ( $p < 0.01$ ) for the AZR-MD-001 1.0% Group. The difference of 12 between the Vehicle and AZR-MD-001 1.0% Groups was statistically significant ( $p = 0.03$ ) and the results appear dose responsive.

Based upon positive efficacy and safety results from clinical study MGSS1 for the ocular application of selenium disulfide shampoo (2.5%) and from Clinical Protocol AZ201801 for AZR-MD-001 (0.5% and 1.0%), Azura Ophthalmics is further evaluating the safety, tolerability and effectiveness of AZR-MD-001 (0.5%) ointment/semi-solid drug, surfactant free, in patients with MGD.

## 2.3 RISK/BENEFIT ASSESSMENT

### 2.3.1 KNOWN POTENTIAL RISKS

Selenium sulfide is used as an anti-fungal and anti-dandruff ingredient in commercially available shampoo (i.e., Selsun Blue, Exsel, Selsun, and Seleen). Selenium sulfide is not absorbed through the skin following topical use and is considered safe for topical use. In 15 people who applied 2.5% selenium sulfide to the torso overnight no appreciable levels of selenium sulfide were measured in the serum or in the urine (Kalivas, 1993). Additionally, in a 1-year exposure study, 16 people who washed their hair weekly with 1% shampoo monthly did not demonstrate urine selenium levels that were different from 8 control subjects (Cummins and Kimura, 1971). These data support the conclusion that selenium is not absorbed through intact skin. Systemic absorption of selenium has been reported with open lesions on the scalp (Sternberg et al, 1964). Based upon these findings, systemic exposure to selenium disulfide following topical, ocular dosing of AZR- MD-001 ointment/semi-solid drug is considered a minimal risk.

Selenium can have inhibitory effects on proteins and enzymes by reacting with thiol or sulfhydryl groups in proteins. Specifically, selenium sulfide, in vitro, was shown to inactivate the free sulfhydryl groups on human epidermis and mouse liver (Flesch, 1953).

Ocular toxicity studies with selenium sulfide have been completed in rabbits. Selenium sulfide was administered to the conjunctival sac of rabbits to compare the toxicity of 0.5% selenium disulfide ophthalmic ointment to that of 2.5% selenium sulfide shampoo (Rosenthal and Adler, 1962). Administration of the 0.5% selenium disulfide ophthalmic ointment was not associated with any ocular toxicity while 2.5% selenium sulfide shampoo was associated with chemosis, redness, corneal clouding, edema, and “total staining” in all eyes within 2 hours of administration. It is unclear if 2.5% selenium sulfide or if another ingredient of the shampoo is bothersome to the ocular surface.

To further evaluate the ocular tolerability and ocular toxicity of selenium disulfide, Azura Ophthalmics evaluated AZR-MD-001 ointment/semi-solid drug in a preclinical study at three concentrations (i.e., 0.5%, 1.0%, and 2.5%) over three dosing frequencies (i.e., twice weekly once daily and twice daily) with a standard clinical dosing volume (i.e 5  $\mu$ L) and with an exaggerated dosing volume (i.e., 25  $\mu$ L) for the highest concentration of 2.5%. Thirty-nine female albino rabbits (New Zealand White strain) were included across 10 groups (see Table 2–1). All groups were treated for 7 days. During the study, eyes were evaluated macroscopically (Draize’s scale) and under the slit-

lamp (McDonald-Shadduck’s scale). At the end of the study, eye globes were histopathologically examined.

Table 2–1 Dose Groups Included in the Pre-Clinical Evaluation of AZR-MD-001 Ointment/semi-solid Drug

Group n°	Treatment (concentration)	Dose Regimen (Right eye)	Number of animals		
			Series 1	Series 2	Series 3
4	AZR149 (0.5% - 5 µL)	Twice weekly (q3.5d ± 1d) ocular topical application from Day 1 to Day 7 onto the lower lid margin	--	3	--
3	AZR150 (1% - 5 µL)		--	3	--
1	AZR141 (2.5% - 25 µL)		3	--	--
2	AZR140 (Placebo - 25 µL)		3	--	--
8	AZR149 (0.5% - 5 µL)	Once daily ocular topical application from Day 1 to Day 7 onto the lower lid margin	--	6	--
7	AZR150 (1% - 5 µL)		--	3	--
5	AZR141 (2.5% - 25 µL)		6	--	--
6	AZR140 (Placebo - 25 µL)		6	--	--
9	AZR149 (0.5% - 5 µL)	Twice daily (7h ± 1h) ocular topical application from Day 1 to Day 7 onto the lower lid margin	--	6	--
10	AZR141 (2.5% - 5 µL)	Once daily ocular topical application from Day 1 to Day 7 onto the lower lid margin	--	--	3*

\*Note 1: These 3 animals were already treated once daily with AZR149 0.5% during 7 days before joining the series 3 (without wash-out period).

No clinical or microscopic findings were observed for any tested concentration, (i.e., 0.5%, 1.0% or 2.5%) or dosing regimen (i.e., twice weekly or once daily) with the intended clinical dose volume of 5 µL. Animals treated with 2.5% at an exaggerated dosing volume (i.e., 25 µL), presented with signs of conjunctival redness from Day 5 in 6/6 animals through Day 7 in 5/6 animals, conjunctival chemosis from Day 6 in 6/6 animals through Day 7 in 3/6 animals, slight corneal opacity for 5/6 animals on Day 3 through day 7 in 3/6 animals (1 slight, 2 moderate), and red and swollen eyelids. All signs self-resolved within 14 days of treatment cessation with no particular management. On ocular histopathology examinations, no microscopic changes were observed for any dosing group including the 2.5% exaggerated dosing volume. Thus, AZR-MD-001 ointment/semi-solid drug up to a concentration of 2.5% using the intended clinical dosing volume of 5 µL is both macroscopically and microscopically well tolerated in these experimental conditions.

Clinically, ocular irritation, conjunctivitis, and epithelial keratitis have been reported in humans dosed with selenium sulfide as a 0.5% ophthalmic ointment with Sodium Lauryl Sulphate applied to the lid margin (Bahn, 1954). The most severe AE reported in all prior topical ophthalmic studies using selenium sulfide was self-limiting keratitis which resolved upon cessation of treatment. Thus, published literature has established the ocular safety and tolerability of selenium sulfide up to a maximal daily exposure of 0.5% dosed twice-daily (BID) for 1 month (see the Investigator's Brochure for more detail). In clinical study MGSS1, selenium disulfide shampoo (2.5%) was safe and well tolerated with controlled dosing. One patient (FHT,002) developed conjunctivitis and superficial punctate keratitis and one patient (MCG,006) developed superficial punctate keratitis. Both patient's symptoms resolved upon cessation of drug treatment. The observed ocular signs could be attributed to the surfactant, Sodium Lauryl Sulphate, in the shampoo.

Ocular irritation, conjunctivitis, and epithelial keratitis were observed in clinical protocol AZ201801. Data review from study AZ201801, up to the Interim Analysis, did not identify any significant and/or unexpected safety or tolerability findings for AZR-MD-001 0.1%, 0.5% or 1.0% (see the Investigator's Brochure for more detail).

### 2.3.2 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The predominate conventional treatments for obstructive MGD entail eyelid hygiene (e.g., lid washing and use of preservative-free artificial tears), applying warm compresses to the eyelid, and gentle lid massaging (Olson et al, 2003; Romero et al, 2004; Yoo et al, 2005; Perry et al, 2006; Pinna et al, 2007; Souchier et al, 2008; and Foster et al, 2009). Eyelid-warming devices have also been employed in the treatment of patients with MGD (Goto et al, 2002; Mitra et al, 2005; Matsumoto et al, 2006; Geerling et al, 2011; Lane et al, 2012). Unfortunately, these treatments are relatively invasive, time consuming and uncomfortable for patients. There are currently no approved pharmacologic treatments for MGD. Thus, there is a medical need for a less invasive, pharmacologic treatment for MGD and associated evaporative DED.

Given the high unmet medical need, the reversibility of ocular findings with selenium disulfide shampoo (2.5%) in clinical study MGSS1, and the observed safety and efficacy for both MGD and evaporative DED in clinical protocol AZ201801, the risk/benefit profile of AZR-MD-001 ointment/semi-solid drug supports continued development in the proposed study design.

### 3 OBJECTIVES AND ENDPOINTS

Table 3–1 Table of Objectives, Endpoint, and Endpoint Justification

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
<b>Cohort 1 and Expansion Cohort</b>		
<p>To evaluate the safety, tolerability and pharmacodynamics of AZR-MD-001 ointment/semi-solid drug applied to the lower lid twice-weekly for up to 3 months compared to its vehicle in patients with meibomian gland dysfunction (MGD).</p>	<p><b>Safety/Adverse Events:</b></p> <ul style="list-style-type: none"> <li>● Incidence rates of each treatment-emergent adverse event summarized by primary system organ class and preferred term.</li> <li>● Tables for all treatment-emergent adverse events regardless of causality.</li> <li>● Tables for all treatment-emergent adverse events considered to be treatment-related.</li> <li>● Shift tables for safety variables (e.g., IOP, biomicroscopy, and ophthalmoscopy).</li> </ul> <p><b>Signal of Efficacy:</b> <i>Primary Efficacy for MGD:</i></p> <ul style="list-style-type: none"> <li>● Change from Baseline to Month 3 in meibum gland secretion score (MGS) (0 to 45 scale)</li> <li>● Change from Baseline to Month 3 in Total OSDI</li> </ul>	<p>The endpoints for safety and tolerability are all commonly used in ophthalmic drug trials.</p> <p>Consistently observed benefits for devices designed to treat glandular obstruction and for AZR-MD-001 ointment/semi-solid drug include:</p> <ul style="list-style-type: none"> <li>● Improvement in the meibum gland secretion score (MGS) (0 to 45 scale);</li> <li>● Improved Total OSDI (Blackie et al, 2015).</li> </ul>

## **4 STUDY DESIGN**

### **4.1 OVERALL DESIGN**

This is a multicenter, investigator-masked, vehicle-controlled, randomized, parallel group study comparing AZR-MD-001 (0.5%) ointment/semi-solid drug and AZR-MD-001 vehicle dosed twice-weekly in the evening.

Patients with MGD will be randomly assigned in a 1:1 ratio to receive either a single concentration of AZR-MD-001 ointment/semi-solid drug (i.e., 0.5%) or AZR-MD-001 vehicle.

For all dose groups a screening visit will be followed by a baseline visit 14 days later (qualification period). At the end of the qualification period patients who still exhibit signs of MGD and who can comply with dosing instructions will be enrolled into a 3-month treatment period. The study flow is shown in Figure 1.

### **4.2 PROCEDURES**

#### **4.2.1 Screening**

Participants will be identified by the sites and brought in for screening visits. Participants may be provided with the Participant information sheet in advance, though will only sign consent during the visit with the study team. Written informed consent will be obtained from each participant prior to commencing any study related activities. Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing: the exact nature of the trial; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. The participant must personally sign and date the latest approved version of the Informed Consent form.

It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, without affecting their legal rights and with no obligation to give the reason for withdrawal.

The following data will be collected at the screening visit – which may be conducted over one day, or multiple days in the window before the baseline visit:

- Medical History (including ophthalmic)
- Demographics (date of birth, gender, race, ethnicity)
- Vital Signs – height, weight, pulse rate and blood pressure
- Urine pregnancy test for women of childbearing potential
- Current medications (including any washout required)
- Questionnaires completed by the participant: OSDI, SPEED, VAS
- Slit -lamp Biomicroscopy
- Tear Break up Time

- Sodium Fluorescein corneal staining
- Lissamine green conjunctival staining
- Meibomian gland evaluation
- Schirmer's test – without anesthesia
- Intraocular Pressure
- Ophthalmoscopy Examination (dilated)
- Meibography

#### 4.2.2 Baseline (Day 0)

Participants will return to the clinical site up to 14 days from screening visit. Assessments will be conducted as per the Schedule of Assessment table. If the participant is still eligible based upon results of BCVA, TBUT and meibomian gland score, the participant will be asked to “practice dose” with Vaseline in order for the study doctor to confirm their suitability and compliance with being able to self-dose. The tolerability questionnaire will be provided to participants to complete based upon this “practice dose”.

The study doctor observing the participants application of dose is required to confirm that they will be able to consistently administer the medication themselves at home by answering some specific questions about the self-dosing. If the participant is confirmed as eligible at this stage, they will be randomized into one of the 2 arms, and provided with the appropriate medication to take home, with instruction for storage and the requirement to keep and return all used and unused containers.

In order to main the blind, the person performing the Randomization and dispensing the medication must not be involved in performing any assessments with the participants.

Participants will be required to dose twice per week at bedtime. Patients will take their first at-home dose in the evening of the Baseline Visit and then 2 or 3 days of “rest” before taking the next dose (i.e., twice weekly dosing).

For example, if a patient is dosed for the first time on Monday evening, then they can dose again on Thursday or Friday. It is recommended they keep dosing on the same two days of each week. If the participant misses a dose on their “scheduled” day, they should dose the next day and then go back to the same schedule for the following weeks.

#### 4.2.3 Day 14/Month 1/Month 1.5/Month 3 (plus follow up call)

Participants will return to site at Day 14 (+/- 2 days), Month 1 (+/- 7 days), Month 1.5 (+/- 7 days) and Month 3 (+/- 2 days).

Assessments will be conducted as per the Schedule of Assessment table. Note the Ophthalmoscopy examination will be conducted undilated, unless dilation is necessary.

Participants are expected to return all used and unused containers for compliance check at each visit, with new medication dispensed.

Month 3 is the final on site study visit for participants. For any participant that withdraws early, the Month 3 assessments should be conducted at the next study visit.

The participants will be called one week (+/- 2 days) after their month 3 visit, to assess adverse events and address any issues noted since ceasing the study medication.

### 4.3. SCIENTIFIC RATIONALE FOR STUDY DESIGN

While there are no approved pharmacological treatments for terminal duct obstruction from hyperkeratinization associated with MGD, compounds that reduce disulfide bonds (S-S) have shown promise. Akyol-Salman and colleagues (2010) used N-acetyl-cysteine (NAC) in 20 patients with MGD and demonstrated a statistically significant improvement in TBUT and symptoms (e.g., itching) by 1 month (Akyol-Salman et al, 2010; Akyol-Salman et al, 2012). Selenium sulfide as a 0.5% ointment dosed up to a total daily dose of 1.0% has also been applied to the lid margin as a treatment for seborrheic blepharitis (Bahn, 1954, see the Investigator's Brochure for more detail).

Azura Ophthalmics is evaluating AZR-MD-001 ointment/semi-solid drug (selenium disulfide) as a potential treatment for MGD and associated evaporative DED. Selenium sulfide exists as a mixture of selenium monosulfide and selenium disulfide. AZR-MD-001 uses the same API as commercially available marketed products (i.e., Selsun Blue, Exsel, Selsum, and Seleen). In these shampoos selenium disulfide is used as an anti-fungal and anti-dandruff ingredient. It is marketed at a 1% concentration in non-prescription products and at a 2.5% concentration in prescription products.

Four clinical studies of topical ocular formulations of selenium sulfide have been completed in seborrheic blepharitis (Bhan GC, 1954; Thygeson P & Vaughan DG, 1954; Cohen LB, 1954; Wong AS, Fasanella RM, Haley LD et al, 1956). Bhan GC (1954) evaluated selenium sulfide 0.5% applied twice-weekly for 2 weeks followed by once-weekly administration for 6 weeks in 100 subjects. He reported resolution of signs and symptoms of seborrheic blepharitis in 97% of treated patients. Thygeson P & Vaughan DG (1954) evaluated selenium sulfide 0.5% applied twice-weekly for a period of between 2 months to 1 year in 89 seborrheic blepharitis patients and reported improvement in all eyes and a cure in 75%. Cohen LB (1954) evaluated selenium sulfide 0.625% ointment (assuming 25% of 2.5% shampoo) applied every other night for four applications then repeated whenever the seborrheic blepharitis flared in 40 seborrheic blepharitis patients. He reported resolution of signs and symptoms in 92% of patients. Finally, Wong AS et al (1956) evaluated selenium sulfide 0.5% vs Ammoniated Mercury (control) applied twice-daily (BID) for 4 weeks in combination with daily eyelid cleaning in 76 seborrheic blepharitis eyes. They reported improvement of sign and symptoms in 80% of seborrheic blepharitis patients. Across all studies topical ocular application of selenium sulfide up to maximal daily exposure of 0.5% BID was safe and well tolerated. The most severe AE reported across studies was self-limiting keratitis which resolved upon cessation of treatment.

Clinical study MGSS1 was a prospective, interventional, non-randomized, contra-lateral eye controlled pilot study of selenium disulfide shampoo (2.5%) in 18 MGD patients. Patients were treated under additional safety measures, twice-weekly for 34 weeks and then had a single treatment on day 44. Selenium disulfide shampoo (2.5%) was safe and well tolerated with controlled dosing. One patient (FHT,002) developed conjunctivitis and superficial punctate keratitis and one patient (MCG,006) developed superficial punctate keratitis. The adverse events could be attributed to the surfactant in the shampoo (Sodium Lauryl Sulphate). Both patient's symptoms resolved upon cessation of drug treatment. Significant improvements in TBUT ( $p = 0.0008$ ), meibum quality ( $p = 0.002$ ), and patency ( $p=0.02$ ) for the drug treated eye over the contra-lateral eye were observed by day 22.

Clinical Protocol AZ201801 was a multicenter, double-masked, vehicle-controlled, randomized, parallel group study carried out in 2 sequentially overlapping cohorts. Significant, dose responsive improvements for both MGS and total OSDI were observed.

Based upon positive efficacy and safety results from both clinical study MGSS1 and Clinical Protocol AZ201801, Azura Ophthalmics is further evaluating the safety, tolerability and effectiveness of AZR-MD-001 (0.5%) ointment/semi-solid drug, surfactant free, in patients with MGD.

#### **4.4 DATA REVIEW COMMITTEE (DRC)**

This study does not use a DRC.

#### **4.5 END OF STUDY DEFINITION**

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

### **5 STUDY POPULATION**

The study will consist of patients with Meibomian Gland Dysfunction (MGD).

#### **5.1 INCLUSION CRITERIA**

- Male or female, 18 years of age or older at screening visit

- Capable of understanding and willing to provide written informed consent and likely to complete the entire course of study according to instructions
- Written authorization for use and release of health and research study information has been obtained
- Best-corrected visual acuity (BCVA) of 20/40 or better (Snellen equivalent), using the logarithm of the minimum angle of resolution (LogMAR) in each eye at the screening and baseline visits
- Evidence of meibomian gland obstruction (based on a meibomian gland secretion (MGS) score of  $\leq 12$  for 15 glands of the lower lid) in both eyes at the screening and baseline visits
- Reported dry eye signs and symptoms within the past 3 months
- Prior to starting screening visit procedures, patients are required to have discontinued:
  - Use of systemic antihistamines or isotretinoin for at least 1 month
  - Anti-inflammatory treatments for DED (e.g., cyclosporine ophthalmic emulsion [Restasis® or Ikervis®] or lifitegrast ophthalmic solution [Xiidra®]) for at least 3 months
  - All other prescription medications used for dry eye or MGD (e.g., antibiotics, corticosteroids, and non-steroidal anti-inflammatory drugs) for at least 2 weeks
  - LipiFlow® or other lid-heating therapy, meibomian gland probing, or therapeutic gland expression in either eye within 6 months prior to the screening visit
  - All other MGD treatments (e.g., at-home warm compress therapy, eyelid hygiene, eyelid massage, and manual lid expression) for at least 2 weeks

And

- All other topical ophthalmic preparations (including artificial tear substitutes) other than the study drops: 72 hours prior to screening visit. If artificial tear substitutes were used within 72 hours of the screening visit the visit should be rescheduled
  - Evidence of active MGD associated signs and symptoms at the screening and baseline visits:
    - Score  $\geq 6$  on the Standard Patient Evaluation of Eye Dryness questionnaire (SPEED)
    - Ocular Surface Disease Index (OSDI) questionnaire score  $\geq 13$
- And
- TBUT  $< 10$  seconds in both eyes
  - Demonstrated ability to follow dosing instructions at the baseline visit
  - A negative pregnancy test result for all women at the screening visit
  - Women of childbearing potential must have a history of bilateral tubal ligation or use oral contraceptives, implants, injectables, transdermal patch, or intrauterine device for

birth control during the study. Abstinence is not considered a reliable method of birth control. If these methods of birth control do not apply, woman of childbearing potential must have a monogamous partner who has had a vasectomy at least 3 months before the screening visit or who is of the same gender.

## 5.2 EXCLUSION CRITERIA

- Uncontrolled ocular disease (except for MGD and dry eye disease/keratoconjunctivitis sicca associated with MGD) or uncontrolled systemic disease
- Patient has glaucoma, ocular hypertension, or intraocular pressure (IOP) in either eye at screening  $\geq 24$  mm Hg as determined by Goldman applanation tonometry or has planned insertion/removal of glaucoma filtration shunts/devices during the study
- Corneal abnormality or disorder that impacts normal spreading of the tear film (keratoconus, pterygia, scarring) or corneal integrity
- BCVA worse than 20/40 in either eye at the screening or baseline visit
- Current use of punctal plugs, anticipated insertion during the study, or a history of punctal cautery in either eye at any time prior to the screening visit or anticipate such a procedure during the study
- Keratoconjunctivitis sicca secondary to destruction of conjunctival goblet cells as occurs with vitamin A deficiency or scarring, such as that with cicatricial pemphigoid, alkali burns, Stevens-Johnson syndrome, trachoma, or irradiation
- Keratoconjunctivitis sicca secondary to aqueous deficient DED
- Active ocular infection (bacterial, viral, or fungal) at the screening or baseline visits
- Corneal, conjunctival, or eyelid inflammation (including allergic, vernal, or giant papillary conjunctivitis and mucous membrane pemphigoid) that in the judgment of the investigator may interfere with the study results or the ability of subjects to complete the treatment period
- Recent (within the past 3 months of the screening visit) ocular surgery, trauma, herpes, or recurrent inflammation
- Contact lens use anticipated during the study
- Periocular application of makeup likely to impact meibomian gland function during the study or tattooing of the lids
- Use of any type of scleral lenses or sealed compartment ocular frames within 2 months of the screening visit, or planned use during the study
- Use prohibited medications (topical, topical ophthalmic, systemic and/or injectable) during the appropriate pre-study wash-out period and during the study
- Unwilling to abstain from the use of systemic medications known to cause dryness for the study duration that is not used on a stable dosing regimen for at least 30 days prior to the baseline visit
- Unwilling to abstain from the use of systemic or topical treatments for MGD or dry eye for the study duration (Including over-the-counter [OTC] artificial tears, ocular lubricants, or dietary supplements known to impact ocular surface health)
- Eyelid abnormalities that affect normal lid function in either eye other than those caused by meibomian gland dysfunction
- Diagnosis of hepatitis C infection, human immunodeficiency virus (HIV) infection, sarcoidosis, amyloidosis, active tuberculosis, or graft versus host disease
- History of anterior segment surgery or trauma that could affect corneal sensitivity (e.g., cataract surgery or any surgery involving a limbal or corneal incision) in either eye within the 12 months prior to the screening visit

- Planned anterior segment surgery (e.g., cataract surgery or any surgery involving a limbal or corneal incision) in either eye during the study period
- Meibography score at the screening visit of 4 (greater than 75% partial glands using the gestalt grading system)
- Corneal staining  $\geq 3$  (between 33 and 100 dots) using the Oxford Scheme
- Schirmer's tear test without anesthesia  $\leq 5$  mm in either eye at the baseline visit
- Known allergy or sensitivity to fluorescein, lissamine green, or the study medication or its components
- Use of medicated shampoos containing selenium (e.g., Selsun Blue, Exsel, Selsum, and Seleen) following the screening visit
- Patient is unlikely to follow study instructions or to complete all required study visits or has a condition or situation that in the investigator's opinion, may put the patient at significant risk, may confound the study results, or may interfere significantly with the patient's participation in the study
- Patient is an employee at the investigational site or is related to any member of the study staff
- Pregnant, nursing, or females of childbearing potential and not utilizing adequate birth control measures. Woman of childbearing potential may have a monogamous partner who has had a vasectomy at least 3 months before the screening visit or who is of the same gender.
- Positive urine pregnancy test at the screening visit
- Participation in another clinical trial involving a therapeutic drug or device within the past 30 days

### 5.3 LIFESTYLE CONSIDERATIONS

To be eligible for this study patient must comply with the following:

- Patients should not have LipiFlow<sup>®</sup> or other lid-heating therapy, meibomian gland probing, or therapeutic gland expression in either eye within 6 months of the screening visit or during the study.
- Patients must have discontinued (2 weeks before screening) and be willing to remain off other MGD treatments (e.g., at-home warm compress therapy, eyelid hygiene, eyelid massage, and manual lid expression) during the study.
- Patients should not have punctal plugs or plan to have punctal plugs inserted during the study.
- Patients must have discontinued (1 month before screening) and be willing to remain off antihistamines or isotretinoin during the study.
- Patients must have discontinued (3 months before screening) and be willing to remain off Anti-inflammatory treatments for DED (e.g., cyclosporine ophthalmic emulsion [Restasis<sup>®</sup> or Ikervis<sup>®</sup>] or lifitegrast ophthalmic solution [Xiidra<sup>®</sup>]).
- Patients should avoid the use of medicated shampoos containing selenium (e.g., Selsun Blue, Exsel, Selsum, and Seleen) following the screening visit.
- Patients must have discontinued (2 weeks before screening) and be willing to remain off all other prescription medications used for dry eye or MGD (e.g., antibiotics, corticosteroids, and non-steroidal anti-inflammatory drugs) during the study.

- Patients must have discontinued all other topical ophthalmic preparations (including artificial tear substitutes) other than the study drops 72 hours prior to the screening visit. If artificial tear substitutes were used within 72 hours of the screening visit the visit should be rescheduled.
- Patients must avoid periocular application of makeup during the study

Patients should be instructed to strictly follow the visit schedule and to report any changes in condition to the investigative site personnel.

The patients should be instructed to maintain a stable dose of any concomitant medication used chronically, or any new medication initiated during the study if possible. Patients should be instructed to communicate any changes to their medication at their next study visit. Patients should also be reminded to contact the study site if they experience difficulties during their study participation.

Patients should refrain from using any ophthalmic preparations other than study treatment in order to obtain an accurate assessment of their signs and symptoms. Patients should be instructed to communicate any changes to their ophthalmic preparations other than study treatment at their next study visit.

#### 5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing

requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of normal variability in safety or efficacy measures (e.g., minimally important clinical difference for OSDI) may be rescreened one additional time. Rescreened participants should be assigned a new screening number and the original number should not be reused.

## 5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

The total number of randomized patients for the study will be up to approximately 30. Approximately 15 patients should have a baseline MGS score of < 6 and approximately 15 patients should have a baseline MGS score  $\geq 6$  and  $\leq 12$ . Based upon data from ongoing study AZ201801 and the simplified inclusion/exclusion criteria for this study a screen failure rate of ~40% is expected. Thus, ~42 patients will need to be screened to achieve ~30 patients randomized to treatment.

Individual study sites may choose to advertise the study in order to facilitate patient recruitment. All advertisements will be approved by the sponsor Azura Ophthalmics, submitted to their IEC, and approved by the IEC before they are used by the site.

## 6 STUDY INTERVENTION

### 6.1 STUDY INTERVENTION(S) ADMINISTRATION

#### 6.1.1 STUDY TREATMENT(S)/ FORMULATION(S)/ MEDICAL DEVICE COMPOSITION OR DESIGN

AZR-MD-001 Ophthalmic Ointment contains the drug product, AZR-MD-001 (0.5%), and suitable excipient. The only excipient in the formulation is Petrolatum white. The AZR-MD-001 vehicle and product labelled "Vaseline" for use at the baseline visit contain only Petrolatum white. The formulations will be supplied in identical unit dose containers (see Table 6.1.1–1).

Table 6.1.1–1 Investigational Product and Packaging / Labelling Characteristics

<b>Product name:</b>	AZR-MD-001 (Selenium disulfide API in ointment/semi-solid Petrolatum white)	Vaseline	Vehicle
<b>Formulation description:</b>	AZR-MD-001 is an orange opaque dispersion ointment with an odor faintly of hydrogen sulfide	Ointment will match AZR-MD-001's texture	Ointment will match AZR-MD-001's texture
<b>Dosage form:</b>	Ophthalmic ointment/semi-solid drug	Ophthalmic ointment/semi-solid drug	Ophthalmic ointment/semi-solid drug
<b>Unit dose strength(s)/Dosage level(s):</b>	0.5%/5mg	Placebo Petrolatum, white	Placebo Petrolatum, white
<b>Route of Administration</b>	Topical	Topical	Topical
<b>Dosing instructions:</b>	Store between 2 – 8°C until opened. <b>Refrigerate.</b> Do not <b>freeze.</b> Discard 4 weeks (30 days) after opening. Protect from light	Store between 2 – 8°C until opened. <b>Refrigerate.</b> Do not <b>freeze.</b> Discard 4 weeks (30 days) after opening. Protect from light	Store between 2 – 8°C until opened. <b>Refrigerate.</b> Do not <b>freeze.</b> Discard 4 weeks (30 days) after opening. Protect from light
<b>Physical description:</b>	An orange opaque ointment packaged in a multi-use tube	A white opaque ointment packaged in a multi-use tube	A white opaque ointment packaged in a multi-use tube
<b>Device:</b>	Multi -use white tube with cap	Multi -use white tube with cap	Multi -use white tube with cap
<b>Method for individualizing dosage:</b>	Each container/tube is placed in an individual package and appropriately labelled.	Each container/tube is placed in an individual package and appropriately labelled.	Each container/tube is placed in an individual package and appropriately labelled.

API = Active pharmaceutical ingredient

### 6.1.2 SELECTION OF DOSES IN THE STUDY

Azura Ophthalmics is further evaluating the safety, tolerability and effectiveness of AZR-MD-001

ointment/semi-solid drug, surfactant free, at an effective concentration of 0.5% based upon positive results from clinical studies MGSS1 and AZ201801 (see the Investigators' Brochure for more detail) that demonstrated the safe and effective treatment of MGD with selenium sulfide exposures up to 1.0% twice-weekly, pre-clinical safety data with exaggerated dosing up to 2.5% with the clinical formulation and concentrations up to 2.5% fulfil the criteria for a low risk Schedule 2 (Pharmacy medicine) classification as specified in the Australian Poisons Standard October 2017 (Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP), No. 18) (see Table 6.1.2-1).

Table 6.1.2-1: Australian Poisons Standard for Selenium

Australian Poisons Standard Dated 26th September 2017			
Schedule	Description	Topical	Oral
1	Schedule is intentionally blank.		
2	<b>Pharmacy Medicine</b> -Safe use may require advice from a pharmacist or licensed person.	For human topical use of 3.5% or less	For human oral use with a recommended dose of 150 micrograms or less
3	<b>Pharmacist Only Medicine</b> -Safe use requires advice from a pharmacist without a prescription.		
4	<b>Prescription Only Medicine</b> -Use should be ordered by persons permitted by State or Territory legislation to prescribe and should be available from a pharmacist on prescription.		For human oral use with a recommended dose of 300 micrograms or more
6	<b>Poison</b> -Substances with a moderate potential for causing harm, the extent of which can be handled through distinctive packaging and strong safety labeling.	In this schedule if it occurs with an "arsenic" (i.e., selenium arsenide)	

Azura Ophthalmics believes that the use of AZR-MD-001 ointment/semi-solid drug with selenium disulfide at a concentration of 0.5% is likely to safely and effectively treat MGD.

### 6.1.3 DOSING AND ADMINISTRATION

Patients (or a caregiver) will dispense a dose of approximately 3.5mm (0.14inch, 4mg) using a dosing aid supplied by Azura Ophthalmics. Patients will then use their washed index finger to apply the drug to the tarsus of the lower lid of both eyes in the evening just before bedtime. They will be instructed to press the ointment strip against their index finger to leave a thin and uniform ointment layer over the finger. The patient will then apply the thin drug film and blink several times to transfer a portion of the drug from the lower eyelid to the upper eyelid (see the Dosing Instruction Sheet for more detail).

Multi-dose tubes of the masked study medication are each to be used for only 30 days to both eyes. The patient should be instructed to place the used tube in the used tube bag after use and should return used and unused tubes at the next study visit.

## 6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

### 6.2.1 ACQUISITION AND ACCOUNTABILITY

Subjects will be instructed on proper instillation and storage of study drug at the end of the baseline, day 14, month 1, and month 1.5 visits, will be given written instructions and may also

watch an instructional video. The used and unused study drug tubes will be collected at each visit from day 14 up to and including month 3 to assess dosing and symptom assessment compliance. Dosing compliance will be based off of the used and unused tube count.

#### 6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

The study packaging will be performed by PCI Pharma Services. All packaging and labeling operations will be performed according to Good Manufacturing Practice for Medicinal Products and the relevant regulatory requirements.

Details of packaging and labeling are in final study documentation provided by PCI Pharma Services.

#### 6.2.3 PRODUCT STORAGE AND STABILITY

The study medication must be stored in a secure area accessible only to the investigator and his/her designees. The study medication will be administered only to patients entered into the clinical study, in accordance with the conditions specified in this protocol.

The study medication is to only be prescribed by the principal investigator or his/her named sub-investigator(s) or a pharmacist, and is to only be used in accordance with this protocol. The study medication must only be distributed to patients properly qualified under this protocol to receive study medication.

The investigator must keep an accurate accounting of the study medication received from the supplier. This includes the amount of study medication dispensed to patients, amount of study medication returned to the investigator by the patients, and the amount returned or disposed upon the completion of the study. A detailed inventory must be completed for the study medication.

All study medication will be returned to the sponsor or their designee or destroyed at the study site. The return or disposal of study medication will be specified in writing. AZR-MD-001 is to be refrigerated between 2 – 8°C until opened and protected from light. Maintenance of a temperature log (manual or automated) is required at the clinical sites.

#### 6.2.4 PREPARATION

Patients should let the study tube equilibrate at room temperature below 25°C for up to 15 minutes before dosing. Patients will use the study medication directly from the dose container in accordance with the protocol and should return the dose container to refrigeration between 2 – 8°C following successful dosing. For the next day of dosing, this process should be repeated.

This in use pattern should continue for 30 days at which time the dose container should be used for a final day of dosing and then discarded.

### 6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Patients (or a caregiver) will apply approximately 3.5mm (0.14inch, 4mg) using a dosing aid supplied by Azura Ophthalmics. Patients will use their washed index finger to apply the drug to the tarsus of the lower lid of both eyes in the evening just before bedtime. The patient will then blink several times to transfer a portion of the drug from the lower eyelid to the upper eyelid.

To minimize the risk for noncompliance with the dosing instructions patients enrolled into the clinical study will be given dosing instructions and will have access to instructional dosing videos. Additionally, site personnel will observe patients applying ointment from a tube labelled "Vaseline" at the baseline visit, and will have access to instructional dosing videos.

Only patients demonstrating an understanding with the provided dosing instructions can be enrolled into the clinical study.

Following the qualification period, the patient, staff members performing all safety and efficacy assessments, site personnel (with the exception of designated personnel who are responsible for drug accountability) and the sponsor study team will be masked to the treatment assignment for the 3 month treatment period. All study medication will be provided in identical tubes and cartons to maintain masking of the study. Due to the difference in color between the active and control treatments, which are in opaque tubes, designated personnel who are responsible for drug accountability will not perform any safety or efficacy assessments and will not discuss assigned treatment(s) with staff members who are performing safety or efficacy assessments.

To obtain a screening number at the screening visit the site will access an electronic data capture (EDC) system and complete the appropriate electronic Case Report Form (eCRF). The numbers will be assigned sequentially by site.

The automated IWRS system will provide the site with the specific medication kit number(s) to use for each qualified patient at the baseline visit. At the baseline/randomization visit, patients meeting all inclusion/exclusion criteria, will be placed in one of the strata. A randomization number will be assigned to each patient corresponding to the treatment arm they are assigned to. The numbers will be assigned sequentially in order of enrollment within the patient's stratum. The IWRS system will report a medication kit number to use for each patient corresponding to the randomization number.

The site will dispense the study medication kit assigned by the IWRS system. Sites will log onto the IWRS system at all subsequent study visits to obtain medication kit number for dispensing study medication. Sites will receive an IWRS confirmation notice for each transaction. All notifications are to be maintained with the study source documents.

## 6.4 CONCOMITANT THERAPY

Not-applicable: Patients must have discontinued and be willing to remain off all other ophthalmic preparations including artificial tears during the study.

### 6.4.1 RESCUE MEDICINE

In the event that rescue medication is required for clinically relevant worsening of keratitis, patients will be provided a concomitant regimen the investigator/treating clinician can initiate:

- Flarex® 0.1% dosed four times a day for up to 10 days as recommended by the prescribing physician.

and

- Instillation of Hylo-Forte® in each eye 5 minutes prior to applying the study ointment. This can be maintained for the duration of the study as recommended by the prescribing physician.

Patients responding to treatment may remain in the study. Patients not-responding to treatment and who are still demonstrating clinically significant keratitis may be temporally discontinued from treatment or discontinued from the study at the investigator/treating clinician's discretion.

## 7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

### 7.1 DISCONTINUATION OF STUDY INTERVENTION

Patients can voluntarily withdraw from the study at any time. The investigator and Azura Ophthalmics can withdraw a patient from the study at any time for any reason. Additionally, patients can be discontinued from the study by an investigator if any of the following criteria are met:

- patient develops (or had an exacerbation of) any medical condition that, in the opinion of the investigator, would have put the patient at an unacceptable medical risk or compromised the patient's ability to participate in the study
- patient is unwilling or unable to continue to comply with study procedures

- patient becomes pregnant

The study can be stopped at the study site(s) at any time by the site investigator(s). Azura Ophthalmics can also stop the study (and/or the study site[s]) with appropriate notification.

If a patient discontinues participation in the study early, every attempt must be made to complete the exit procedures. Notification of early patient discontinuation from the study and the reason for discontinuation should be made to Azura Ophthalmics and should be clearly documented on the appropriate eCRF.

## 7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

The investigator and Azura Ophthalmics have the right to withdraw a patient from the study at any time for any reason. When possible, the decision to withdraw a patient from the study should be discussed with Azura Ophthalmics.

Patients who are withdrawn early from the study should have early exit visit procedures completed at the time of withdrawal, or at their next scheduled visit, whenever possible.

## 7.3 LOST TO FOLLOW-UP

A patient will be considered lost to follow-up if he or she fails to return for 2 consecutive scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within the specified visit window (see Table 1.3) and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record or study file.
- Should the patient continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

## 8 STUDY ASSESSMENTS AND PROCEDURES

### 8.1 EFFICACY ASSESSMENTS

#### 8.1.1 PRIMARY EFFICACY MEASURES

*Primary Sign for MGD:*

- Change from Baseline to month 3 in meibum gland secretion score (MGS) (0 to 45 scale)

*Primary Symptom for MGD:*

- Change from Baseline to month 3 in Total OSDI

#### 8.1.2 SECONDARY EFFICACY MEASURES

*Secondary efficacy measures include:*

- Change from Baseline to day14, month 1 and month 1.5 in MGS (0 to 45 scale)
- MGS score (0 to 45 scale) at each visit
- Proportion of patients with a MGS score > 12 at each visit
- Change from Baseline to day14, month 1, month 1.5 and month 3 in the number of Meibomian Glands Yielding Liquid Secretion (MGYLS) (0 to 15 scale)
- MGYLS (0 to 15 scale) at each visit
- Change from Baseline to day 14, month 1, month 1.5, and month 3 in TBUT
- TBUT at each visit
- Proportion of patients with a TBUT score > 5 at each visit
- Change from Baseline to day 14, month 1, month 1.5 and month 3 in Standard Patient Evaluation of Eye Dryness (SPEED)
- SPEED at each visit
- Proportion of patients with a SPEED < 6 at each visit
- Change from Baseline to day 14, month 1, month 1.5 and month 3 in average visual analogue scale (VAS)
- Average VAS at each visit
- Change from Baseline to day 14, month 1, month 1.5 and month 3 in worst VAS
- Worst VAS at each visit
- Change from Baseline to day 14, month 1 and month 1.5 in Total OSDI
- Total OSDI, OSDI sub-scales, and individual items from the OSDI across visits
- Proportion of patients with a Total OSDI change from baseline > 4.5, the known minimally important clinical difference (MICD) for early to moderate disease, at month 3
- Proportion of patients with a Total OSDI < 13 at each visit
- Number of expressible glands yielding clear meibum at day14, month 1, month 1.5, and month 3
- Eyelid margin erythema/telangiectasias at day14, month 1, month 1.5, and month 3
- Corneal and conjunctival staining (0 to 5 scale) at each visit

### 8.1.3 DATA REVIEW COMMITTEE (DRC)

Not applicable.

## 8.2 SAFETY AND OTHER ASSESSMENTS

### 8.2.1 SAFETY MEASURES

*The following safety measures will be examined:*

- Adverse events
- Vital signs
- Study medication tolerability as measured by the Ocular Comfort Questionnaire
- Urine pregnancy test
- Best-corrected visual acuity (BCVA; Logarithmic visual acuity chart)
- Biomicroscopy
- Ophthalmoscopy
- Intraocular pressure (IOP)

## 8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Adverse events occurring during the study will be recorded on an adverse event case report form (CRF). If adverse events occur, the first concern will be the safety of the study participants.

All adverse events that are drug-related and unexpected (not listed as treatment-related in the current Investigator's Brochure) must be reported to the governing Institutional Review Board/Independent Ethics Committee (IRB/IEC) as required by the IRB/IEC, local regulations, and the governing health authorities. Any adverse event that is marked 'ongoing' at the exit visit must be followed-up as appropriate.

### 8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

An AE is defined as any untoward medical occurrence in a clinical study subject administered a medicinal product which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not it is related to the medicinal (investigational) product. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction or the significant worsening of the indication under investigation that is not recorded elsewhere in the CRF under specific efficacy assessments. Anticipated fluctuations of pre-existing conditions, including the disease under study that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

It is the responsibility of the investigator to document all AEs that occur during the study. AEs will be elicited by asking the subject a nonleading question, for example, "Have you experienced any new or changed symptoms since we last asked/since your last visit?". AEs should be reported on the appropriate page of the CRF.

Some illustrate examples follow to help understand the difference between events meeting the definition of an AE and those that don't.

**Events meeting AE definition include:**

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae).
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

**Events NOT meeting definition of an AE include:**

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

### 8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

An SAE is any untoward medical occurrence or effect that, at any dose,

- Results in death.
- Is life-threatening (an AE is life-threatening if the subject was at immediate risk of death from the event as it occurred, i.e., it does not include a reaction that might have caused death if it had occurred in a more serious form).
- Requires or prolongs inpatient hospitalization. (Complications occurring during hospitalization are AEs and are SAEs if they cause prolongation of the current hospitalization. Hospitalization for elective treatment of a pre-existing non-worsening condition is not, however, considered an AE. The details of such hospitalizations must be recorded on the medical history or physical examination page of the CRF).
- Results in persistent or significant disability/incapacity. (An AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions).
- Results in a congenital anomaly/birth defect.

In addition, medical and scientific judgement is required to decide if prompt notification is required in situations other than those defined for SAEs above. This may include any event that the investigator regards as serious that did not strictly meet the criteria above but may have jeopardized the subject or required intervention to prevent one of the outcomes listed above, or that would suggest any significant hazard, contraindication, side effect, or precaution that may be associated with the use of the investigational product.

#### 8.3.2.1 REPORTING OF SERIOUS ADVERSE EVENTS

Any SAE must be reported by the investigator if it occurs during the clinical study or within 30 days of receiving the study drug, whether or not the SAE is considered to be related to the investigational product. An SAE report consists of the SAE form, the AE form, medical history and the concomitant medication form. A copy of these forms must be faxed or e-mailed within 24 hours for the attention of the CRO. The appropriate pages in the eCRF must be completed as soon as possible. The CRO will handle the SAE as per the Safety Management Plan and ensure

appropriate review and onward reporting to the Sponsor, with oversight of reporting to the ethics committees and competent authority as per local regulatory requirements:

For medical emergencies contact: Peter McCluskey

Phone: 02 9382 7300

E-Mail: [peter.mccluskey@sydney.edu.au](mailto:peter.mccluskey@sydney.edu.au)

The investigator should not wait to receive additional information to document fully the event before notification of a SAE, though additional information may be requested. Where applicable, information from relevant laboratory results, hospital case records, and autopsy reports should be obtained.

Instances of death, congenital abnormality, or an event that is of such clinical concern as to influence the overall assessment of safety, if brought to the attention of the investigator at any time after cessation of study drug administration and linked by the investigator to this study, should be reported to the study monitor.

The sponsor and/or CRO will promptly notify all relevant investigators and the regulatory authorities of findings that could adversely affect the safety of subjects, impact on the conduct of the study or alter the independent ethics committee (IEC)/institutional review board (IRB) approval/favorable opinion of the study. In addition, CRO, on behalf of the sponsor, will expedite the reporting to all concerned investigators, to the IECs/IRBs, where required, and to the regulatory authorities of all adverse reactions that are both serious and unexpected.

Details of the procedures to be followed if a pregnancy occurs are provided in Section 8.3.7.

### 8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

#### 8.3.3.1 SEVERITY OF EVENT

A clinical determination will be made of the intensity of an adverse event. The severity assessment for a clinical adverse event must be completed using the following definitions as guidelines:

Mild	Awareness of sign or symptom, but easily tolerated
Moderate	Discomfort enough to cause interference with usual activity
Severe	Incapacitating with inability to work or do usual activity

#### 8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

A determination will be made of the relationship (if any) between an adverse event and the study drug or study procedure, as applicable. A causal relationship is present if a determination is made that there is a reasonable possibility that the adverse event may have been caused by the drug or study procedure. Causality should be assessed using the following categories:

- **Unrelated:** Clinical event with an incompatible time relationship to study drug administration, and that could be explained by underlying disease or other drugs or chemicals or is incontrovertibly not related to the study drug.
- **Unlikely:** Clinical event whose time relationship to study drug administration makes a causal connection improbable, but that could plausibly be explained by underlying disease or other drugs or chemicals.
- **Possible:** Clinical event with a reasonable time relationship to study drug administration, but that could also be explained by concurrent disease or other drugs or chemicals.
- **Probable:** Clinical event with a reasonable time relationship to study drug administration, and is unlikely to be attributed to concurrent disease or other drugs or chemicals.
- **Very Likely/Certain:** Clinical event with plausible time relationship to study drug administration, and that cannot be explained by concurrent disease or other drugs

or chemicals.

### 8.3.3.3 ACTION TAKEN

The investigator will describe the action taken in the appropriate section of the CRF, as follows:

- None
- Study drug stopped
- Study drug temporarily interrupted
- Concomitant medication
- Other, specify.

### 8.3.4 TIME PERIOD & FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

All investigators should follow up subjects with AEs until the event is resolved or until, in the opinion of the investigator, the event is stabilized or determined to be chronic. Details of AE resolution must be documented in the CRF.

Subjects should be followed up for 30 days (check time limit with sponsor) after receiving the last dose of study drug, and any AEs that occur during this time should be reported according to the procedures outlined above.

#### 8.3.4.1 DOCUMENTATION AND REPORTING OF ADVERSE EVENTS

AEs should be reported and documented in accordance with the procedures outlined below. All AEs occurring during the study must be documented on the relevant CRF pages. The following data should be documented for each AE:

- Description of the symptom event
- Classification of 'serious' or 'not serious'
- Severity
- Date of first occurrence and date of resolution (if applicable)
- Action taken
- Causal relationship
- Outcome of event (unknown, recovered, not yet recovered, recovered with sequelae, death [with date and cause reported])

### 8.3.5 REPORTING EVENTS TO PARTICIPANTS

When necessary for the safety and proper treatment of the patient, the investigator can unmask the patient's treatment assignment to determine which treatment has been assigned and institute appropriate follow-up care. The Randomization and Unblinding Plan should be followed in any instance of request for unblinding. When possible, the sponsor (Azura Ophthalmics) should be notified prior to unmasking study medication. The investigator should inform the sponsor (Azura Ophthalmics) of the unmasking if there is no notification prior to the unmasking.

The reason for breaking the code must be recorded in the patient's source documents.

A report of the results of this study may be published, sent to the appropriate health authorities in any country in which the study drug may ultimately be marketed, and published in part as required by appropriate health authorities (e.g., Clinical Trials posting and disclosure), but the patient's name will not be disclosed in these documents.

Patients will be informed that the study is posted and the results eventually disclosed by appropriate health authorities (e.g., Clinical Trials posting or freedom of information by the FDA).

### 8.3.6 EVENTS OF SPECIAL INTEREST

#### 8.3.6.1 UNEXPECTED ADVERSE REACTION DEFINITION

An unexpected adverse reaction is any untoward and unintended response that is related to the administration of the study drug at any dose that is not consistent with the applicable product information (e.g., investigators brochure for an unauthorized investigational medicinal product or summary of product characteristics for an authorized product).

All suspected unexpected serious adverse reactions (SUSARs) will be the subject of expedited reporting. The sponsor and/or CRO shall ensure that all relevant information about a SUSAR that is fatal or life-threatening is reported to the relevant competent authorities and IEC/IRB within 7 days after knowledge by the sponsor of such a case and that relevant follow up information is communicated within an additional 8 days. All other SUSARs will be reported to the relevant competent authorities and IEC/IRB within 15 days after knowledge by the sponsor of such a case. All investigators should follow up SUSARs until the event is resolved or until, in the opinion of the investigator, the event is stabilized or determined to be chronic. Post study SUSARs that occur after the subject has completed the clinical study must be reported by the investigator to the sponsor.

### 8.3.7 REPORTING OF PREGNANCY

If a female becomes pregnant during the study, the investigator will notify Azura Ophthalmics

immediately after the pregnancy is confirmed and the patient will be exited from the study after appropriate safety follow-up. The investigator will (1) notify the patient's physician that the patient was being treated with an investigational drug, and (2) follow the progress of the pregnancy. The investigator must document the outcome of the pregnancy and provide a copy of the documentation to Azura Ophthalmics.

## 9 STATISTICAL CONSIDERATIONS

The statistical analysis plan (SAP) will provide a detailed description of the planned statistical analysis.

### 9.1 SAMPLE SIZE DETERMINATION

**Sample Size Calculation:** Estimates for sample size calculations are from the first interim analysis from Azura Clinical Protocol AZ201801. The standard deviation for MGS was 3.35 units for an ineffective dose and 9.48 units for the high dose. A sample size of 12 subjects per group will have 90% power to detect a difference of 10.4 units between the active treatment group and the vehicle group using a two-sample t-test at a significance level of 0.05. The standard deviation for Total OSDI was 13.01 units for an ineffective dose and 6.79 units for the high dose. A sample size of 11 subjects per group will have 90% power to detect a difference of 15.9 units between the active treatment group and the vehicle group using a two-sample t-test at a significance level of 0.05.

**Multiplicity Consideration:** To address the multiple primary endpoints defined in this study, the primary endpoints have been prioritized into a hierarchical structure. In order to test the primary symptom endpoint of Total OSDI, the primary sign endpoint of MGS must be statistically significantly higher in the 0.5% AZR-MD-001 treatment group compared to the vehicle treatment group using a two-sided significance level of 0.05. Using this strategy, the family-wise Type I error rate will be maintained at the 0.05 significance level for the two primary endpoints.

### 9.2 POPULATIONS FOR ANALYSES

The safety population will include all treated patients. For safety variables, patients in the safety population will be analyzed by the treatment actually received. The modified intent-to-treat (mITT) population will be comprised of all patients randomized and, have values at randomization, and at least 1 post-randomization value for MGS at a regularly scheduled visit (i.e., Day 14 or Month 1). All patients in the mITT population will be analyzed by the treatment received. This population will be used for the primary and the secondary efficacy analyses.

The method of Last Observation Carried Forward (LOCF) will be used for efficacy on the mITT

population. In these analyses, non-missing values recorded at visit 3 (i.e., Day 14) or later will be used to replace missing data at visits where data are not recorded.

Additional imputation methods will be used for sensitivity analysis and will be outlined in the Statistical Analysis Plan (SAP).

### 9.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to the sponsor or their designee. Protocol deviations must be sent to the reviewing IEC per their policies. The site investigator is responsible for knowing and adhering to the reviewing IEC requirements.

### 9.4 STATISTICAL ANALYSES

#### 9.4.1 GENERAL APPROACH

In general, continuous data will be summarized with descriptive statistics (number of patients, mean, standard deviation, median, minimum, and maximum) and will be analyzed using analysis of variance (ANOVA) techniques or 2-sample t-tests for between-group comparisons, and paired t-tests for within-group analyses. Categorical variables will be summarized by sample size (N), frequency count, and percent, and they will be analyzed using Pearson's chi-square test or Fisher's exact test (if the expected cell count is less than 5 in 25% or more of the cells). Ordinal variables will be analyzed using the Wilcoxon rank-sum test for between-treatment comparisons and the sign-rank test for within-treatment comparisons.

*Efficacy (MGD):*

*Primary Sign for MGD:*

- Change from Baseline to month 3 in meibum gland secretion score (MGS) (0 to 45 scale)

*Primary Symptom for MGD:*

- Change from Baseline to month 3 in Total OSDI

*Other Efficacy Measures:*

- Change from Baseline to day14, month 1 and month 1.5 in MGS (0 to 45 scale)
- MGS score (0 to 45 scale) at each visit
- Proportion of patients with a MGS score > 12 at each visit
- Change from Baseline to day14, month 1, month 1.5 and month 3 in the number of Meibomian Glands Yielding Liquid Secretion (MGYLS) (0 to 15 scale)
- MGYLS (0 to 15 scale) at each visit
- Change from Baseline to day 14, month 1, month 1.5, and month 3 in TBUT
- TBUT at each visit
- Proportion of patients with a TBUT score > 5 at each visit
- Change from Baseline to day 14, month 1, month 1.5 and month 3 in Standard Patient Evaluation of Eye Dryness (SPEED)
- SPEED at each visit
- Proportion of patients with a SPEED < 6 at each visit
- Change from Baseline to day 14, month 1, month 1.5 and month 3 in average visual analogue scale (VAS)
- Average VAS at each visit
- Change from Baseline to day 14, month 1, month 1.5 and month 3 in worst VAS
- Worst VAS at each visit
- Change from Baseline to day 14, month 1 and month 1.5 in Total OSDI
- Total OSDI, OSDI sub-scales, and individual items from the OSDI across visits
- Proportion of patients with a Total OSDI change from baseline > 4.5, the known minimally important clinical difference (MICD) for early to moderate disease, at month 3
- Proportion of patients with a Total OSDI < 13 at each visit
- Number of expressible glands yielding clear meibum at day14, month 1, month 1.5, and month 3
- Eyelid margin erythema/telangiectasias at day14, month 1, month 1.5, and month 3
- Corneal and conjunctival staining (0 to 5 scale) at each visit

*Safety:* Safety measures will be analyzed using the safety population. Medical Dictionary for Regulatory Activities (MedDRA) nomenclature will be used to code adverse events. Incidence rates of each treatment-emergent adverse event will be summarized by primary system organ class and preferred term. Summary tables will be generated for all treatment-emergent adverse events regardless of causality as well as for those considered to be treatment-related.

#### 9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary efficacy variables (see Section 8.1.1) will be analyzed at month 3 using an analysis of covariance [ANCOVA] model with baseline MGS score and duration of disease as covariates and treatment (AZR-MD-001 ointment/semi-solid drug or vehicle) as factors in the model. Pairwise comparisons will be performed for each AZR-MD-001 ointment/semi-solid drug treatment group versus vehicle using t-tests of the least square means from this model. Two-sided confidence intervals (95%) will be provided for the differences between treatments.

Details of other efficacy analyses will be provided in the statistical analysis plan.

### 9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The secondary efficacy variables (see Section 8.1.2) will be analyzed using an analysis of covariance [ANCOVA] model with baseline MGS score and duration of disease as covariates and treatment (AZR-MD-001 ointment/semi-solid drug or vehicle) as factors in the model. Pairwise comparisons will be performed for each AZR-MD-001 ointment/semi-solid drug treatment group versus vehicle using t-tests of the least square means from this model. Two-sided confidence intervals (95%) will be provided for the differences between treatments.

Descriptive statistics (change from baseline variables) will be tabulated for the following within treatment group changes in the mITT population:

- Patients in the AZR-MD-001 ointment/semi-solid drug treatment group: changes from baseline to days 14, month 1, month 1.5 and month 3
- Patients in the AZR-MD-001 vehicle group: changes from baseline to days 14, month 1, month 1.5 and month 3

Within each treatment group, shift tables for complete treatment response (yes/no) in the study eye will be presented for patients in the mITT population for endpoint signifying a “clinical cure” (Proportion of patients with a MGS score > 12; Proportion of patients with a MGYLS score of >2; Proportion of patients with a MGYLOS score of >2; Proportion of patients with a TBUT > 5 seconds at each visit; Proportion of patients with a Schirmer’s test  $\geq$  10 mm at each visit; Proportion of patients with a Total OSDI < 13 at each visit; and Proportion of patients with a SPEED Score < 6.

- Patients in the AZR-MD-001 ointment/semi-solid drug treatment group: changes from baseline to days 14, month 1, month 1.5 and month 3.
- Patients in the AZR-MD-001 vehicle group: changes from baseline to days 14, month 1, month 1.5 and month 3.

The Logistic Regression method for general association, stratified by baseline MGS score and duration of disease will be used to compare treatments with respect to the proportion of patients achieving a “clinical cure” in the study eye. Odds ratio along with 95% CI will be obtained by pairwise comparisons will be performed for each AZR-MD-001 treatment groups versus vehicle..

### 9.4.4 SAFETY ANALYSES

Safety measures will be analyzed using the safety population. Medical Dictionary for Regulatory Activities (MedDRA) nomenclature will be used to code adverse events. Treatment-emergent

adverse events will be summarized. The adverse events will be classified into ocular and nonocular types and will be summarized separately. Detailed methods for the analyses of adverse events and other safety variables will be described in the analysis plan.

#### 9.4.5 BASELINE DESCRIPTIVE STATISTICS

In general, continuous data will be summarized with descriptive statistics (number of patients, mean, standard deviation, median, minimum, and maximum) and will be analyzed using analysis of variance (ANOVA) techniques or 2-sample t-tests for between-group comparisons, and paired t-tests for within-group analyses. Categorical variables will be summarized by sample size (N), frequency count, and percent, and they will be analyzed using Pearson's chi-square test or Fisher's exact test (if the expected cell count is less than 5 in 25% or more of the cells). Ordinal variables will be analyzed using the Cochran-Mantel-Haenszel (CMH) or the Wilcoxon rank-sum test for between-treatment comparisons and the sign-rank test for within-treatment comparisons.

#### 9.4.6 PLANNED INTERIM ANALYSES

None planned.

#### 9.4.7 SUB-GROUP ANALYSES

Patients will be stratified by duration of MGD diagnosis (i.e., < 5 years or  $\geq$  5 years) and baseline MGS score for the qualified eye (i.e., the eye meeting the inclusion/exclusion criteria). If the eyes have the same MGS score the right eye will be selected as the study eye.

Thus, subgroup analyses are planned for the 4 groups defined by the 2 stratification factors:

1. MGD diagnosis < 5 years and MGS score for the qualified eye < 6
2. MGD diagnosis < 5 years and MGS score for the qualified eye  $\geq$  6 and  $\leq$  12
3. MGD diagnosis  $\geq$  5 years and MGS score for the qualified eye < 6
4. MGD diagnosis  $\geq$  5 years and MGS score for the qualified eye  $\geq$  6 and  $\leq$  12.

#### 9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will be listed by measure and time point.

#### 9.4.9 EXPLORATORY ANALYSES

The statistical analysis plan (SAP) will provide a detailed description of the planned exploratory statistical analysis.

## **10 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS**

### **10.1 INDEPENDENT ETHICS COMMITTEE**

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the subjects, and any other relevant study documentation will be submitted to the appropriate IEC/IRB. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the study drug is released to the investigator. Any necessary extensions or renewals of IEC/IRB approval must be obtained for changes to the study such as amendments to the protocol, the ICF or other study documentation. The written approval of the IEC/IRB together with the approved ICF must be filed in the study files. The investigator will report promptly to the IEC/IRB any new information that may adversely affect the safety of the subjects or the conduct of the study. The investigator will submit written summaries of the study status to the IEC/IRB as required. On completion of the study, the IEC will be notified that the study has ended.

### **10.2 REGULATORY AUTHORITIES**

Relevant study documentation will be submitted to the regulatory authority according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authority will be notified that the study has ended.

### **10.3 ETHICAL CONDUCT OF THE STUDY**

The investigator(s) and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines, and the applicable national and local laws and regulatory requirements.

### **10.4 INFORMED CONSENT PROCESS**

The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s) and must adhere to GCP.

The investigator is responsible for ensuring that no subject undergoes any study related examination or activity before that subject has given written informed consent to participate in the study.

The investigator or designated personnel will inform the subject of the objectives, methods, anticipated benefits and potential risks and inconveniences of the study. The subject should

be given every opportunity to ask for clarification of any points s/he does not understand and, if necessary, ask for more information. At the end of the interview, the subject will be given ample time to consider the study. Subjects will be required to sign and date the ICF. After signatures are obtained, the ICF will be kept and archived by the investigator in the investigator's study file. A signed and dated copy of the subject ICF will be provided to the subject or their authorized representative.

It should be emphasized that the subject may refuse to enter the study or to withdraw from the study at any time, without consequences for their further care or penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give or who withdraw written informed consent should not be included or continue in the study.

If new information becomes available that may be relevant to the subject's willingness to continue participation in the study, a new ICF will be approved by the IRB/IEC(s) (and regulatory authorities, if required). The study subjects will be informed about this new information and re-consent will be obtained.

## 10.5 SUBJECT CONFIDENTIALITY

Monitors, auditors, and other authorized agents of the sponsor and/or its designee, the IEC(s) approving this research, and the United States (US) FDA, as well as that of any other applicable agency(ies), will be granted direct access to the study subjects' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the subjects' identity will remain confidential

## 11 QUALITY ASSURANCE

### 11.1 AUDIT AND INSPECTION

Study centers and study documentation may be subject to Quality Assurance audit during the course of the study by the sponsor or its nominated representative. In addition, inspections may be conducted by regulatory authorities at their discretion.

### 11.2 MONITORING

Data for each subject will be recorded on a CRF. Data collection must be completed for each subject who signs an informed consent form (ICF) and is administered study drug.

In accordance with GCP and ICH guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the CRF are accurate and reliable.

The investigator must permit the monitor, the IEC, the sponsor's internal auditors, and representatives from regulatory authorities direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the CRFs.

### 11.3 DATA MANAGEMENT AND CODING

Study centers will enter data directly into an electronic data capture (EDC) system by completing the CRF via a secure internet connection. Data entered into the eCRF must be verifiable against source documents at the study center. Data to be recorded directly on the eCRF will be identified and the eCRF will be considered the source document. Any changes to the data entered into the EDC system will be recorded in the audit trail and will be FDA CFR 21 Part 11 compliant.

Medical coding will use Medical Dictionary for Regulatory Activities (MedDRA) for concomitant diseases and AEs and WHO Drug for medications. Missing or inconsistent data will be queried in writing to the investigator for clarification. Subsequent modifications to the database will be documented.

Missing or inconsistent data will be queried to the investigator for clarification. Subsequent modifications to the database will be documented.

## 12 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

### 12.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigator, IRB, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements

- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or applicable regulatory agencies.

## 12.2 FUTURE USE OF STORED SPECIMENS AND DATA

### 12.2.1 HANDLING OF BIOLOGICAL SPECIMENS

None are planned for collection during the study.

## 12.3 KEY ROLES AND STUDY GOVERNANCE

<b>Medical Monitor</b>	<b>DRC Chair</b>
Peter McCluskey	N/A
Phone: 02 9382 7300	N/A
E-mail: peter.mccluskey@sydney.edu.au	N/A

## 12.4 RETENTION OF DOCUMENTATION

For countries falling within the scope of the ICH guidelines, Azura Ophthalmics-specific essential documents, all study related correspondence, patient records, consent forms, patient privacy documentation, records of the distribution and use of all investigational products, and copies of CRFs should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product or as per local regulation if longer. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by Azura Ophthalmics.

In addition, for countries not falling within the scope of the ICH guidelines, local regulatory requirements should be followed regarding the retention of clinical study documentation.

It is the responsibility of Azura Ophthalmics to inform the study center when these documents no longer need to be retained. The investigator must contact the sponsor before destroying any study related documentation. In addition, all subject medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

Azura Ophthalmics requires that it be notified in writing if the investigator wishes to relinquish ownership of the data so that mutually agreed-upon arrangements can be made for transfer of ownership to a suitably qualified, responsible person.

## 12.5 SOURCE DOCUMENTS

All study related correspondence, patient records, consent forms, patient privacy documentation, records of the distribution and use of all investigational products, and copies of CRFs should be maintained on file.

In addition, for countries not falling within the scope of the ICH guidelines, local regulatory requirements should be followed regarding the retention of clinical study documentation.

Azura Ophthalmics requires that it be notified in writing if the investigator wishes to relinquish ownership of the data so that mutually agreed-upon arrangements can be made for transfer of ownership to a suitably qualified, responsible person.

## 12.6 STUDY SUMMARY

An investigator's summary will be provided to Azura Ophthalmics within a short time after the completion of the study, or as designated by Azura Ophthalmics. A summary is also to be provided to the responsible IRB/IEC.

## 12.7 INSTITUTIONAL REVIEW BOARD /INDEPENDENT ETHICS COMMITTEE (IEC) RECORDS RETENTION

The IRB should retain all relevant records such as standard operating procedures (SOPs), membership lists (including qualifications of the members), submitted documents, minutes of meetings, and correspondence until either item 1 or 2 listed below, whichever is later.

1. The date of approval for manufacturing and marketing applications of the relevant investigational products (in case of discontinuing its development, until at least 3 years after the date of development discontinuation)
2. The day at least 3 years after the date of the termination or completion of the clinical study

When the study site or Azura Ophthalmics requests the SOPs and membership lists, the IRB should comply with the request.

## 12.8 PUBLICATION AND DATA SHARING POLICY

Azura Ophthalmics as the sponsor, has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and Azura Ophthalmics personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Azura Ophthalmics.

## 12.9 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the DRC has established policies and

procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

## 12.10 ADDITIONAL CONSIDERATIONS

None

## 12.11 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
BCVA	Best-corrected visual acuity
CFR	Code of Federal Regulations
CMH	Cochran-Mantel-Haenszel
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DED	Dry Eye Disease
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICH GCP	International Conference on Harmonisation Good Clinical Practice
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IOP	Intraocular pressure
IRB	Institutional Review Board
LOCF	Last Observation Carried Forward
LogMAR	Logarithm of the minimum angle of resolution
MedDRA	Medical Dictionary for Regulatory Activities
MGD	Meibomian gland dysfunction
MGE	Meibum gland evaluation
MGS	Meibum gland secretion score
MGYLS	Meibomian Glands Yielding Liquid Secretion
mITT	The modified intent-to-treat
MOP	Manual of Procedures
NAC	N-acetyl-cysteine
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OSDI	Ocular Surface Disease Index
PI	Principal Investigator
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOA	Schedule of Activities
SOP	Standard Operating Procedure
SPEED	Eye Dryness questionnaire
TBUT	Tear Break-up Time
US	United States
VAS	Visual analogue scale

### 12.12 PROTOCOL AMENDMENT HISTORY

<b>Version</b>	<b>Date</b>	<b>Description of Change</b>	<b>Brief Rationale</b>

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## 14 SUBJECTIVE STUDY SCALES

### 14.1 VISUAL ANALOG SCALE (VAS)

Patients will be asked the following questions regarding their ocular discomfort (unrelated to study drug instillation).

The patient will be asked to subjectively rate each symptom (OU) by placing a vertical mark on the horizontal line to indicate the level of discomfort. 0% corresponds to “no discomfort” and 100% corresponds to “maximal discomfort.”

<b>Burning/Stinging</b>	0%	50%	100%
	-----		
<b>Itching</b>	0%	50%	100%
	-----		
<b>Foreign body sensation</b>	0%	50%	100%
	-----		
<b>Eye Discomfort</b>	0%	50%	100%
	-----		
<b>Eye Dryness</b>	0%	50%	100%
	-----		
<b>Photophobia</b>	0%	50%	100%
	-----		
<b>Pain</b>	0%	50%	100%
	-----		

## 14.2 OCULAR SURFACE DISEASE INDEX (OSDI)

The OSDI questionnaire consists of 12 questions regarding ocular symptoms, environmental triggers, and vision-related functioning in patients with DED. The patient will be asked to rate each symptom using a 5-point scale (0 to 4), where 0 = none of the time; 1 = some of the time; 2

= half of the time; 3 = most of the time; and 4 = all of the time. Seven questions related to visual functioning allow a response of "N/A" (not applicable). The total OSDI will be calculated by EDC from the raw scores of each of the 12 questions based on the formula:  $([\text{sum of scores for all questions answered}^a] \times 100) / ([\text{total number of questions answered}^a] \times 4)$ .

<sup>a</sup> Questions answered with N/A will be excluded in the calculation of total OSDI.

**OCULAR SURFACE DISEASE INDEX ©**  
 (US English version of the OSDI)

**Please answer the following questions by checking the box that best represents your answer.**

Have you experienced any of the following during the last week:

	All of the time	Most of the time	Half of the time	Some of the time	None of the time
1 Eyes that are sensitive to light?					
2 Eyes that feel gritty?					
3 Painful or sore eyes?					
4 Blurred vision?					
5 Poor vision?					

Have problems with your eyes limited you in performing any of the following during the last week:

	All of the time	Most of the time	Half of the time	Some of the time	None of the time	Not applicable
6 Reading?						
7 Driving at night?						
8 Working with a computer or bank machine (ATM)?						
9 Watching TV?						

Have your eyes felt uncomfortable in any of the following situations during the last week:

	All of the time	Most of the time	Half of the time	Some of the time	None of the time	Not applicable
10 Windy conditions?						
11 Places or areas with low humidity (very dry)?						
12 Areas that are air conditioned?						

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### 14.3 STANDARD PATIENT EVALUATION OF EYE DRYNESS (SPEED)

## SPEED™ QUESTIONNAIRE

**Name:** \_\_\_\_\_ **Date:** \_\_\_/\_\_\_/\_\_\_ **Sex:** M F (Circle) **DOB:** \_\_\_/\_\_\_/\_\_\_

*For the Standardized Patient Evaluation of Eye Dryness (SPEED) Questionnaire, please answer the following questions by checking the box that best represents your answer. Select only one answer per question.*

**1. Report the type of SYMPTOMS you experience and when they occur:**

Symptoms	At this visit		Within past 72 hours		Within past 3 months	
	Yes	No	Yes	No	Yes	No
Dryness, Grittiness or Scratchiness						
Soreness or Irritation						
Burning or Watering						
Eye Fatigue						

**2. Report the FREQUENCY of your symptoms using the rating list below:**

Symptoms	0	1	2	3
Dryness, Grittiness or Scratchiness				
Soreness or Irritation				
Burning or Watering				
Eye Fatigue				

**0 = Never    1 = Sometimes    2 = Often    3 = Constant**

**3. Report the SEVERITY of your symptoms using the rating list below:**

Symptoms	0	1	2	3	4
Dryness, Grittiness or Scratchiness					
Soreness or Irritation					
Burning or Watering					
Eye Fatigue					

**0 = No Problems**  
**1 = Tolerable - not perfect, but not uncomfortable**  
**2 = Uncomfortable - irritating, but does not interfere with my day**  
**3 = Bothersome - irritating and interferes with my day**  
**4 = Intolerable - unable to perform my daily tasks**

**4. Do you use eye drops for lubrication?**     YES     NO    If yes, how often? \_\_\_\_\_

Cornea. 2013 Sep;32(9):1204-10  
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 13-ADV-123 A

For office use only  
 Total SPEED score (Frequency + Severity) = \_\_\_/28

## 14.4 STUDY MEDICATION TOLERABILITY/COMFORT QUESTIONNAIRE

Patients will use a visual analog scale ranging from 0 to 100 to answer 8 questions assessing the acute overall comfort of the study drug (in both eyes together). Questions 1 through 4 assess to what degree the drops felt comfortable, felt soothing, were moistening/lubricating, and enhanced clear vision, respectively. Questions 5 through 8 assess to what degree the drops caused stickiness, blur, burning/stinging, and discomfort, respectively. Higher scores represented greater comfort for questions 1 to 4 (i.e., 100% corresponds to “comfortable” and 0% corresponds to “not comfortable”), while lower scores represented greater comfort for questions 5 to 8. (i.e., 0% corresponds to “no discomfort” and 100% corresponds to “maximal discomfort”).

Ratings should commence ~5 ± 1 minutes after eye drop administration.

<b>Drug Felt</b>	0%	100%
	Uncomfortable <span style="float: right;">Comfortable</span>	
<b>Drug Felt</b>	0%	100%
	Not Soothing <span style="float: right;">Soothing</span>	
<b>Drug Felt</b>	0%	100%
	Not Moistening/Lubricating <span style="float: right;">Moistening/Lubricating</span>	
<b>Drug Enhanced</b>	0%	100%
	Did not Enhance Clear Vision <span style="float: right;">Clear Vision</span>	
<b>Drug Caused</b>	0%	100%
	No Stickiness <span style="float: right;">Stickiness</span>	
<b>Drug Caused</b>	0%	100%
	No Blur <span style="float: right;">Blur</span>	
<b>Drug Caused</b>	0%	100%
	No Burning/Stinging <span style="float: right;">Burning/Stinging</span>	
<b>Drug Caused</b>	0%	100%
	No Discomfort <span style="float: right;">Discomfort</span>	

## 15 SPONSOR APPROVAL(S)

**Protocol Title:** A Multicenter, Vehicle-controlled, Randomized Study to Evaluate the Safety, Tolerability and Pharmacodynamics of AZR-MD-001 in Patients with Meibomian Gland Dysfunction (MGD)

**Protocol Number:** AZ202001

**Final Date:** 12Mar2020

This clinical study protocol was subject to critical review and has been approved by the sponsor. The following personnel contributed to writing and/or approving this protocol.

Signed:  
Chief Medical Officer Azura  
Ophthalmics

Date: \_ Charles Bosworth Ph.D.