# A Single-center, Vehicle-controlled, Study to Evaluate the Safety, Tolerability, and Pharmacodynamics of AZR-MD-001 as Adjunctive Therapy to Conventional Therapeutic Treatment for Meibomian Gland Dysfunction (MGD) or Contact Lens Discomfort (CLD).

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| **Short Title:** | Evaluation of AZR-MD-001 as Adjunctive Therapy to Conventional Therapeutic Treatment for Meibomian Gland Dysfunction (MGD) |
| **Protocol Number:** | SOVS2019-070 |
| **National Clinical Trial (NCT) Identified Number:** | TBD |
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| **Funded by:** | Azura Ophthalmics, Level 9,<br>31 Queens Street<br>Melbourne, VIC 300 Australia |
| **Version and Version Number:** | Final, 6.0 |
| **Date:** 17Feb2020 | |

## Summary of Changes from Previous Version:

| Affected Section(s) | Summary of Revisions Made | Rationale |
|---|---|---|
| Sections 1, 5, 7.2, 8.3.2.1, 8.3.7 | Minor modifications/ clarification to wording in these Sections | To satisfy UNSW HREC queries regarding the Study Population, Participant Discontinuation/Withdrawal, Reporting of SAEs and Reporting of Pregnancy |
| Sections 9.3, 10.5, 11.1, 12.1 | Modifications to the wording in these Sections | To satisfy UNSW HREC queries regarding the duties and responsibilities of the Study Sponsor |
| Sections 1.2, 3, 4.1, and 6.1.1 | Delete 0.5% dose concentration of AZR-MD-001 planned to be evaluated in this study | The 1.0% AZR-MD-001 concentration has been selected for evaluation in this study |
| Sections 1.2 and 1.3 | Addition of lipid layer thickness measurement using the LipiView II and associated exclusion criteria | To include measurement of an additional tear film parameter that may demonstrate changes following treatment with AZR-MD-001 |
| Section 1.3 | Addition of tear meniscus height measurement and tear collection | To include evaluation of additional tear film parameters that may demonstrate changes following treatment with AZR-MD-001 |
| Sections 1.2, 5.2, 5.3, 6.1 and 6.3 | Addition of: (i) study ointment to be applied at night only; (ii) instillation of a commercially available artificial tear eye drop in each eye (Hylo-Forte®) 5 minutes prior to applying the study ointment; (iii) include the 0.5% dose of AZR-MD-001 to allow participants to be dispensed with the lower concentration of study IP by an unmasked investigator (where applicable); (iv) allow the study IP to be removed 15 mins after application using a cotton wipe moistened with saline. | To reduce the risk of ocular toxicity events and improve participant tolerability to the study ointment upon application, the proposed actions are to be initiated in a stepped approach. This will enable the method of ointment application to be optimized to meet the participants' needs. |

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| Sections 1.1, 1.2, 3, 4.1, 4.2, 5, 8.1 and 9.4 | Deletion of the MGD group from this study. | As recruitment has not yet begun for the MGD group, this group will be removed from this study and a new research study protocol proposed. |

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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 |
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# 1 PROTOCOL SUMMARY

## 1.1 SYNOPSIS

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

**Phase:** 2

**Objectives:**

To evaluate the reliability and sensitivity to change for novel methods of measuring meibomian gland expression (MGE) and associated instructions for measurement.

To determine if therapy with AZR-MD-001 is more effective than vehicle for treating contact lens discomfort (CLD).

**Clinical Hypotheses:**

Novel methods of measuring meibomian gland expression (MGE) and associated instructions for measurement can be easily implemented by site personnel and are sensitive to conventional therapeutic treatment.

Therapy with AZR-MD-001 is more effective than vehicle for treating contact lens discomfort (CLD).

## 1.2 SCHEMA

**Study Design:**

*Structure:* Single-center, single-masked (the individual(s) performing efficacy measures will be masked to treatment assignment for the patient(s) they are assessing), vehicle-controlled, randomized, parallel group study. Patients diagnosed with CLD will be enrolled into this study . Patients with CLD will be randomly assigned in a 2:1 ratio to receive either a single concentration of AZR-MD-001 ointment/semi-solid drug (1.0%) or AZR-MD-001 vehicle for 4 months. A single concentration (1.0%) and dose frequency of administration (twice weekly or once daily) declared safe by the data review committee (DRC) from study AZ201801 will be included in this study at randomization. (The concentration of AZR-MD-001 may be reduced to 0.5% if the 1.0% dose is not well tolerated – see Dosage/Dose Regimen below). At the month 1 visit the patients will receive conventional therapeutic treatment in both eyes (i.e., debridement in one eye and debridement plus therapeutic expression of the meibomian glands in the other eye [randomly allocated]) and continue their assigned dosing regimen for three more months. The study flow is shown in Figure 1.

*Duration:* The total duration of study is approximately 4 months (from baseline to study completion).

*Study Treatment Groups:* AZR-MD-001 ointment/semi-solid drug (1.0%).

*Controls:* AZR-MD-001 Vehicle

*Dosage/Dose Regimen*: Upon meeting inclusion/exclusion criteria patients will be randomized to AZR-MD-001 ointment/semi-solid drug (1.0%) or AZR-MD-001 vehicle administered either twice-weekly or once-daily for four months at night-time only. If the regimen is well tolerated, the patients will receive conventional therapeutic treatment and will also be asked to continue their assigned dosing regimen at the end of the month 1 visit. If the regimen is not well tolerated, but the participant is willing to continue in the study, the investigator will offer the following modified treatment regimens in the order as listed:

i. A single drop of commercially available eye drop Hylo-Forte® (AFT Pharmaceuticals; sodium hyaluronate 2mg/mL) will be instilled in each eye 5 minutes prior to application of the study ointment;
ii. Dispense the lower concentration 0.5% dose AZR-MD-001 in lieu of the 1% dose (this will be conducted where applicable by an unmasked investigator);
iii. Wipe the lower eyelid with a cotton wipe moistened with saline to remove the study ointment 15 minutes after application.

If the regimen is still not well tolerated or the participant wishes to withdraw at any time, they will be discontinued from the study.

*Randomization/Stratification:* Patients will be randomized to receive AZR-MD-001 ointment/semi-solid drug (1.0%) or AZR-MD-001 vehicle in a 2:1 treatment allocation ratio.

Patients will be stratified by average (i.e., across both eyes) baseline MGS score (MGS score of $< 6$ or MGS score $\geq 6$ and $\leq 12$). Both eyes should qualify for the study (i.e., meet the inclusion/exclusion criteria).

*Visit Schedule*: Up to 8 scheduled visits: randomization, day 14, month 1, month 1 + 48hrs, month 1.5, month 2, month 3, and month 4 (exit). For patients who discontinue the study early, the month 4 visit procedures should be completed.

**Study Population Characteristics**

*Number of Patients*: The total number of randomized patients for the study will be up to 15 patients with CLD. Based upon data from the LipiFlow® development program a screen failure rate of ~ 40% is expected for new patients. Thus, ~up to 21 patients will need to be screened to achieve ~up to 15 patients randomized to treatment.

*Condition/Disease*: Contact Lens Discomfort (CLD)

*Key Inclusion Criteria*:

<u>New CLD Patients</u>:

- Evidence of meibomian gland obstruction (based on a meibomian gland secretion (MGS) score of ≤12 for 15 glands of the lower lid) in both eyes at the baseline visit
- A history of wearing soft contact lenses for at least 6 months
- Wearing of the soft contact lenses for at least 3 weeks before the baseline visit and wore or attempted to wear lenses at least 4 times a week before the baseline visit.
- Symptomatic as defined by an answer of "No" at baseline to the question, "Are you able to comfortably wear your lenses as long as you want?"
- Self-reported history of contact lens dryness/intolerance in the 6 months preceding the baseline visit. Baseline CLDEQ-8 score >12
- Contact lenses may be used during the study as long as they are removed 15 minutes before dosing and not reinserted until at least 15 minutes after dosing.

<u>All Patients</u>:

- Male or female, 18 years of age or older at baseline 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 baseline visit
- Prior to the baseline visit patients are required to discontinue:
    - 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 baseline 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

baseline visit. If artificial tear substitutes were used within 72 hours of the baseline visit the visit should be rescheduled

- A negative pregnancy test result for all women of childbearing potential at the baseline 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 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 baseline visit.

*Exclusion Criteria*:

All Patients:

- Uncontrolled ocular disease (except for MGD or CLD) or uncontrolled systemic disease
- Patient has glaucoma or ocular hypertension as demonstrated by an intraocular pressure (IOP) in either eye at baseline of ≥24 mm Hg 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 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 baseline 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 baseline visit
- 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 baseline visit) ocular surgery, trauma, herpes, or recurrent inflammation
- Periocular application of makeup 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 baseline 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, dry eye, or CLD for the study duration (Including over-the-counter [OTC] artificial tears, ocular lubricants, or dietary supplements known to impact ocular surface health [e.g., Omega 3 supplements] except those prescribed for use as part of the study)
- 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 baseline 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
- 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 baseline 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, or planning pregnancy
- Positive urine pregnancy test at the baseline visit
- Participation in another clinical trial involving a therapeutic drug or device within the past 30 days (except for AZR-MD-001)
- Epilepsy or history of migraines exacerbated by flashing, strobe-like lights

<u>New Patients</u>:

- Meibography score at the baseline visit of 4 (greater than 75% partial glands using the gestalt grading system)
- Corneal staining ≥ 3 (between 33 and 100 dots) using the Oxford Scheme
- Schirmer's tear test without anesthesia ≤ 5 seconds in either eye at the baseline visit

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| **Response Measures** | *Evidence for a treatment effect of AZR-MD-001 (AZR-MD-001 compared to Vehicle in the study eye):*<br><br>•<br><br>*Primary Efficacy for CLD:*<br><br>• Change from Baseline to day 14 and month 1 in meibum gland secretion score (MGS) (lower lid: 0 to 45 scale; upper lid: 0 to 45 scale, or upper and lower lids combined)<br>• Change from Baseline to day 14 and month 1 in the number of Meibomian Glands Yielding Liquid Secretion (MGYLS) (lower lid: 0 to 15 scale; upper lid: 0 to 15 scale, or upper and lower lids combined)<br>• Change from Baseline to day 14 and month 1 in eyelid markers for CLD (e.g., lid margin redness, lid margin thickness, lid-wiper epitheliopathy, and lid-parallel conjunctival folds)<br>• Change from Baseline to day 14 and month 1 in subjective vision ratings (VAS), CLDEQ-8 and comfortable wear time<br><br>*Evidence for Enhancement of conventional therapeutic treatment (AZR-MD-001 compared to Vehicle by eye):*<br><br>*Primary Efficacy:*<br><br>• Change from month 1 to month 1 + 48 hours, month 1.5 and month 2, in meibum gland secretion score (MGS) (lower lid: 0 to 45 scale; upper lid: 0 to 45 scale, or upper and lower lids combined)<br>• Ratio in change from baseline to day 14 and month 1 and from month 1 to month 1.5 and month 2, in meibum gland secretion score (MGS) (lower lid: 0 to 45 scale; upper lid: 0 to 45 scale, or upper and lower lids combined) (e.g., (baseline – day 14)/(month 1 – month 1.5) and (baseline – month 1)/(month 1 – month 2))<br>• Change from month 1 to month 1 + 48 hours and month 2 in the number of Meibomian Glands Yielding Liquid Secretion (MGYLS) (lower lid: 0 to 15 scale; upper lid: 0 to 15 scale, or upper and lower lids combined)<br>• Ratio in change from baseline to day 14 and month 1 and from month 1 to month 1.5 and month 2, in the number of Meibomian Glands Yielding Liquid Secretion (MGYLS) (lower lid: 0 to 15 scale; upper lid: 0 to 15 scale, or upper and lower lids combined) (e.g., (baseline – day 14)/(month 1 – month 1.5) and (baseline – month 1)/(month 1 – month 2))<br>• Change from month 1 to month 1 + 48 hours and month 2 in staining of Marx's line |

- Ratio in change from baseline to day 14 and month 1 and from month 1 to month 1.5 and month 2, in staining of Marx's line (e.g., (baseline – day 14)/(month 1 – month 1.5) and (baseline – month 1)/(month 1 – month 2))
- Change from month 1 to month 1 + 48 hours and month 2 in eyelid markers for CLD (e.g., lid margin redness, lid margin thickness, lid-wiper epitheliopathy, and lid-parallel conjunctival folds)
- Ratio in change from baseline to day 14 and month 1 and from month 1 to month 1.5 and month 2, in eyelid markers for CLD (e.g., lid margin redness, lid margin thickness, lid-wiper epitheliopathy, and lid-parallel conjunctival folds) (e.g., (baseline – day 14)/(month 1 – month 1.5) and (baseline – month 1)/(month 1 – month 2))

*Evidence for prolongation of conventional therapeutic treatment (AZR-MD-001 compared to Vehicle by eye):*

*Primary Efficacy:*

- Change from month 1 to month 3 and month 4, in meibum gland secretion score (MGS) (lower lid: 0 to 45 scale; upper lid: 0 to 45 scale, or upper and lower lids combined)
- Slope of change from month 1 to month 4 in meibum gland secretion score (MGS) (lower lid: 0 to 45 scale; upper lid: 0 to 45 scale, or upper and lower lids combined)
- Change from month 1 to month 3 and month 4 in the number of Meibomian Glands Yielding Liquid Secretion (MGYLS) (lower lid: 0 to 15 scale; upper lid: 0 to 15 scale, or upper and lower lids combined)
- Slope of change from month 1 to month 4 in the number of Meibomian Glands Yielding Liquid Secretion (MGYLS) (lower lid: 0 to 15 scale; upper lid: 0 to 15 scale, or upper and lower lids combined)
- Change from month 1 to month 3 and month 4 in staining of Marx's line
- Slope of change from month 1 to month 4 in staining of Marx's line
- Change from month 1 to month 3 and month 4, in in eyelid markers for CLD (e.g., lid margin redness, lid margin thickness, lid-wiper epitheliopathy, and lid-parallel conjunctival folds)
- Slope of change from month 1 to month 4 in eyelid markers for CLD (e.g., lid margin redness, lid margin thickness, lid-wiper epitheliopathy, and lid-parallel conjunctival folds)

*Validating methods of measuring meibomian gland expression (MGE) (Vehicle group only by eye):*

- Azura Ophthalmics observation of novel methods of measuring meibomian gland expression (MGE) and associated instructions for measurement.

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| | • Ratio in change from baseline to month 1 and from month 1 to month 2, in meibum gland secretion score (MGS) (lower lid: 0 to 45 scale; upper lid: 0 to 45 scale, or upper and lower lids combined) (e.g., (baseline – month 1)/(month 1 – month 2))<br>• Ratio in change from baseline to month 1 and from month 1 to month 2, in the number of Meibomian Glands Yielding Liquid Secretion (MGYLS) (lower lid: 0 to 15 scale; upper lid: 0 to 15 scale, or upper and lower lids combined) (e.g., (baseline – month 1)/(month 1 – month 2))<br><br>*Safety:*<br><br>• Adverse events<br>• Urine pregnancy test<br>• Best-corrected visual acuity (BCVA; Logarithmic visual acuity chart)<br>• Biomicroscopy<br>• Ophthalmoscopy<br>• Intraocular pressure (IOP) |
| **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 for MGS. 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.<br><br>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.<br><br>*Efficacy (CLD)*: The primary efficacy variables for CLD are change from baseline to day 14, month 1, month 1 + 48 hours, month 2, month 3, and month 4 in MGS, number of MGYLS, lid markers for CLD (see Table 1 in Siddireddy et al, 2018), and subjective vision ratings (VAS), CLDEQ-8 and comfortable wear time. A patient will be considered to be a meibum quality responder at a post-randomization visit if the MGS score in the study eye is > 3. The visit for the primary variable is month 1 for AZR-MD-001, month 2 for enhancement of conventional therapeutic treatment, and month 4 for prolongation of conventional |

therapeutic treatment. The primary analysis population is mITT. Statistical tests will be performed for each AZR-MD-001 group versus vehicle group, slope of change relative to an expected slope of 0 and ratio of pre and post conventional therapeutic treatment relative to an expected ratio of 1. Pairwise comparisons of the proportion of responders will be performed using the CMH method stratifying by average baseline MGD score. There will be no alpha adjustment for the multiple tests for the pairwise comparisons.

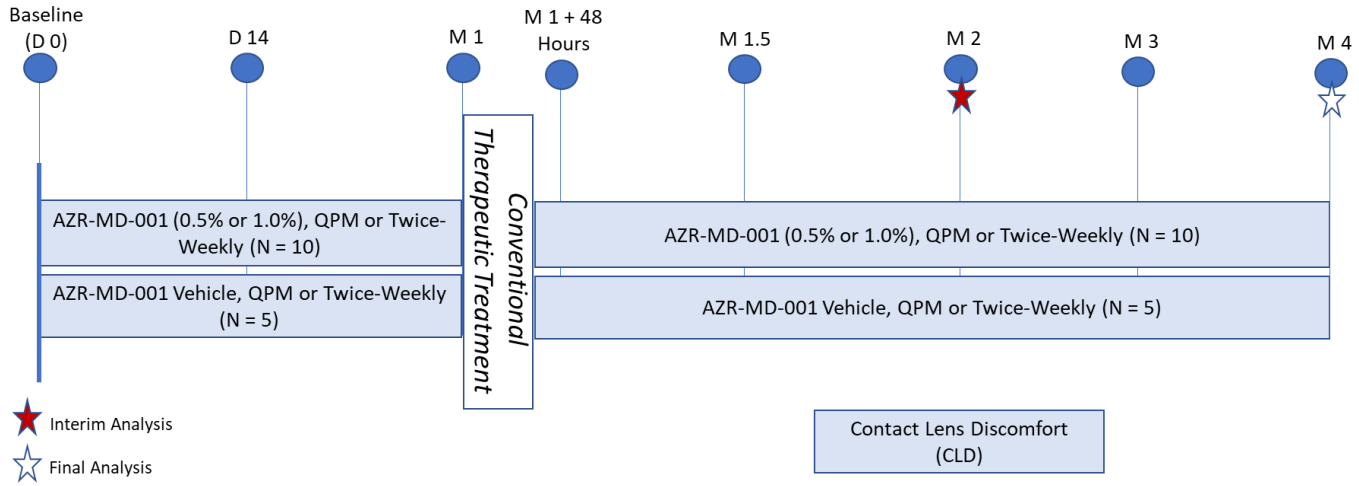
*Validating methods of measuring meibomian gland expression (MGE) (Vehicle group only):*

The efficacy variables are the ratio of change from baseline to month 1 and change from month 1 to month 2 in meibum gland secretion score (MGS) (lower lid: 0 to 45 scale; upper lid: 0 to 45 scale, or upper and lower lids combined) (e.g., (baseline – month 1)/(month 1 – month 2)) and number of Meibomian Glands Yielding Liquid Secretion (MGYLS) (lower lid: 0 to 15 scale; upper lid: 0 to 15 scale, or upper and lower lids combined). The primary analysis population is mITT. Statistical tests will be performed for the vehicle group. There will be no alpha adjustment for multiple tests for the pairwise comparisons.

*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*: The sample size is determined empirically.

**Figure 1** **Single-center, single-masked, vehicle-controlled, randomized, parallel group study**




Note: Participants will be randomized to receive AZR-MD-001 1.0% or vehicle at Baseline. However, the concentration of AZR-MD-001 may be reduced to 0.5% by an unmasked investigator if the 1.0% dose is not well tolerated.

## 1.3 SCHEDULE OF ACTIVITIES (SOA)

***Table 1 Schedule of Visits and Procedures***

| | Baseline /Day 0 | Day 14 | Month 1 | End of Month 1 | Month 1 + 48 Hours, Months 1.5, 2, & 3 | Month 4 (Exit) |
|---|---|---|---|---|---|---|
| Visit Window | N/A | *± 2 Days* | *± 7 Days* | | *± 7 Days* | *± 2 Days* |
| Informed consent/authorization | X | | | | | |
| Demographics (including height and weight) | X | | | | | |
| Inclusion/exclusion criteria | X | | | | | |
| Medical and ophthalmic history | X | | | | | |
| Medication history | X | | | | | |
| Washout medications | X | | | | | |
| Pregnancy test (urine) for female patients | X | | | *Conventional Therapeutic Treatment* | | X |
| Contact Lens Dry Eye Questionnaire-8 (CLDEQ-8) | X | | X | | | X |
| Best-corrected visual acuity (BCVA) | X | X | X | | X | X |
| Subjective questionnaires including visual analogue scales (VAS), and Berkeley Dry Eye Flow Chart (DEFC) and comfortable wearing time for CLD | X | X | X | | X | X |
| Tear evaporation rate | X | X | X | | X | X |
| Meibum collection | X | X | X | | X | X |
| Non-Invasive Tear Break Up Time (TearScope) | X | X | X | | X | X |
| Lipid layer thickness (LipiView II) | X | X | X | | X | X |
| Tear meniscus height (Oculus Keratograph 5M) | X | X | X | | X | X |
| Tear collection | X | | X | | X[b] | X |
| Tear Break Up Time (TBUT) | X | X | X | | X | X |
| Sodium fluorescein corneal staining, Oxford scale | X | X | X | | X | X |
| Sodium fluorescein staining (Eyelid margin and mucocutaneous junction evaluation) | X | X | X | | X | X |
| Meibomian gland evaluation (all) & methods observation (selected) patients | X | X | X | | X | X |
| Slit-lamp biomicroscopy (includes eyelid margin) [a] | X | X | X | | X | X |
| Lissamine green conjunctival staining, Oxford scale | X | | X | | | X |
| Lissamine green staining (Eyelid margin and mucocutaneous junction evaluation) | X | X | X | | X | X |
| Schirmer without Anesthesia | X | | X | | | X |
| Intraocular pressure (IOP) | X | | | | | X |
| Ophthalmoscopy exam | X | | | | | X |
| Meibography | X | | | | | X |
| Adverse events/medications/tolerability + dosing observation (Selected Patients) | X | X | X | | X | X |
| Medication dispensing/return | X | X | X | | X | X |

[a]- photographs and video recording of any interesting/unusual findings may also be made for documentation and/or follow-up purposes
[b] at the monthly visits only (month 2 and month 3)

# 2 INTRODUCTION

## 2.1 BACKGROUND MGD

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., Bankok 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).

## 2.2 BACKGROUND CLD

Contact lens discomfort (CLD) is a condition characterized by episodic or persistent adverse ocular sensations related to lens wear, either with or without visual disturbance, resulting from reduced compatibility between the contact lens and the ocular environment, which can lead to decreased wearing time and discontinuation of contact lens wear. CLD patients present with symptoms of ocular discomfort (e.g., dryness, irritation, discomfort, fatigue, and so forth), these symptoms increase in severity over the day while the patient is wearing the contact lenses. The CLD Workshop recognizes that CLD occurs while a contact lens is worn, and that the removal of contact lenses mitigates the condition (Nichols et al, 2013).

CLD remains a major reason for discontinuation of contact lens wear. There are currently more than 140 million contact lens wearers worldwide and studies report that between 12% and 51% of lens wearers ‘‘drop out’’ of contact lens wear citing CLD as the primary reason for discontinuation (Nichols et al, 2013). Soft contact lenses comprise approximately 90% of the market with rigid lenses making up the remainder of the market. Soft silicone hydrogel lenses make up the majority of the soft contact lenses market. While practitioners and scientists have questioned the influence of polymer chemistry, and various other material attributes on CLD, almost none of these attributes, with the possible exception of friction, appears to be associated directly with CLD. Likewise, contact lens care solutions, contact lens care practices, and contact lens wear schedules are not clearly indicated as increasing CLD or with improving contact lens comfort.

CLD is primarily diagnosed by symptomatology as opposed to observation signs (e.g., altered quality of expressed secretions and/or by a loss of gland functionality for MGD). Thus, the CLD Workshop concluded that the use of symptoms as an outcome measure is appropriate because they relate directly to the patients’ experience with contact lenses and the motivation to seek and use treatment (Nichols et al, 2013). The Contact Lens Dry Eye Questionnaire (CLDEQ) has been well received and is widely used for CLD assessment. The McMonnies and CLDEQ questionnaires have both been used as assessment tools in studies of CLD (Nichols et al, 2002; McMonnies C, 1986); however, a short version of the CLDEQ has been reported to be more accurate in predicting CLD and better at discriminating a contact lens–related dry eye diagnosis than the McMonnies’ questionnaire (Dumbleton et al, 2013). Using the full model parameters for the CLDEQ there appears to be a predictive efficiency of 1.50, with a sensitivity of 83% and specificity of 67% (Nichols et al, 2002). More recently, a revised version of the CLDEQ has been developed, the CLDEQ-8. The scores from the CLDEQ-8 have been shown to correlate well

with baseline CLD status and to be capable of measuring changes in CLD scores associated with refitting with different contact lens materials (Chalmers et al, 2012).

The TFOS subcommittee on Contact Lens Interactions with the Ocular Surface and Adnexa concluded that two specific sines are potentially linked to CLD: alterations to the meibomian glands and alterations to the leading edge of the palpebral conjunctiva (the so-called ‘‘lid-wiper’’ zone) (Efron et al, 2013). Contact lens wear impacts the function of the meibomian glands and reduced meibomian gland function has been associated with contact lens wear. Alterations to the lid-wiper area (i.e., lid wiper epitheliopathy (LWE)) are more common in contact lens wearers who are symptomatic and some studies have related these tissue changes to CLD.

There is a long-standing clinical impression that CL wear increases the risk of meibomian gland alterations. Korb and Henriquez (Korb and Henriquez, 1980; Henriquez and Korb, 1981) investigated the meibomian glands of individuals with a primary complaint of contact lens (CL) intolerance. They described clinical and cytological evidence indicating that the syndrome is due to obstruction of the meibomian gland orifices by desquamated epithelial cells that tend to aggregate in keratotic clusters, resulting in changes in the meibomian gland contribution to the precorneal tear film. Arita and colleagues (Arita et al, 2009) provided direct evidence that CL wear may affect the morphology of meibomian glands. Morphological observation of the meibomian glands revealed that the frequency of meibomian gland loss was significantly higher in CL wearers compared with non–lens wearers. These results strongly suggest that CL wear is a potential cause of alteration in meibomian glands.

More specifically, Arita and colleagues (2008) used a noninvasive meibography system that allowed observation of the meibomian glands in both upper and lower eyelids. They found that CL wear likely affects the morphology of meibomian glands throughout the upper eyelid with a lesser effect in the lower eyelid. This is in contrast to the diagnosis of MGD which centers on the lower eyelid. 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; Lane et al, 2012).

Korb and Henriquez (Korb and Henriquez, 1980) found that foaming on the lower lid margins was apparent in 66.2% of symptomatic contact lens (CL) wearers but in only 3.7% of asymptomatic CL wearers ($P < 0.0001$). Hypersecretory CL-associated gland dysfunction is characterized by the release of a large volume of meibomian lipid (meibum) at the lid margin (foaming) in response to pressure on the tarsus. It remains unclear, however, whether the increased amount of lipid is the result of true hypersecretion, or the damming back of mildly obstructed secretions (Efron and Veys, 1992). Long-standing cases of CL-associated gland

dysfunction may be linked to lid margin abnormalities, such as vascularization, morphological irregularity of the lid margin, blockage (plugging) of orifices, and damage to the mucocutaneous junction (Knob and Knob, 2009).

The lid-wiper region is a thickened epithelial ‘‘lip’’ that has a conjunctival mucosal morphology that extends from the tarsal conjunctiva up to the crest of the posterior lid border and helps to distribute the precorneal tear film. The lid wiper, because it is conceivably the only part of the lid margin that is in direct contact with the globe, will be in contact with the CL surface and is thus subjected to mechanical friction during the blink (Efron et al, 2013). Thus, it is of obvious importance during lens wear. The line of Marx extends from the crest of the posterior lid border and is seen at the bottom of the tear meniscus (Efron et al, 2013). A thin band of stainable epithelial cells directly behind the mucocutaneous junction is the basis for Marx’s line. Previously, the line of Marx was assumed to be the zone in touch with the globe and to represent the wiping surface of the lid border.

A thickened epithelium at the posterior lid margin was first observed by Sattler (1877) and later by Virchow and Saemisch (1910). Its functional implication was not recognized until the mid-1960s by Ehlers (1965). He noticed that this ‘‘bead gliding over the cornea’’ must be assumed to be a perfect ‘‘windscreen wiper (see Efron et al, 2013).’’ Korb and colleagues (Korb et al, 2002; Korb et al, 2005 Korb et al, 2010) linked changes in this region of the lid in subjects who are symptomatic of dryness. The authors postulate that when the tear film is thinned or becomes unstable, or a lens surface is not stable and wettable, there is an increased mechanical/frictional effect on the lid-wiper region, as the lid travels across the ocular or lens surface during blinking. This process may lead to lid-wiper trauma and epitheliopathy (LWE), which can be viewed clinically by staining the marginal conjunctiva with ophthalmic dyes (Korb et al, 2002; Korb et al, 2005 Korb et al, 2010).

LWE is found in 67% to 80% of symptomatic CL wearers, but in only 13% to 32% of asymptomatic subjects (Korb et al, 2002; see Efron et al, 2013). Significantly different LWE scores between symptomatic and asymptomatic subjects are found only in the upper eyelid (Berry et al, 2008; see Efron et al, 2013)). By histology it has been verified in selected cases that cells with atypical keratinization (para-keratinization) increase in number and extend from the natural stainable line of Marx, where they physiologically occur, over the surface of the lid wiper epithelium (Knop et al, 2011). LWE may be one of the few clinical signs truly associated with dryness in lens wearers (Efron et al, 2013).

Common treatments for CLD include the periodic use of rewetting drops, contact lens removal, contact lens refitting (using different lens designs or materials or replacement schedules), and

changes in the contact lens care solutions or regimens, in addition to other less commonly used approaches including topical or systemic medications, alterations in diet, and punctal plugs. Ultimately, CLD is the primary factor associated with permanent discontinuation from contact lens wear (Nichols et al, 2013).

## 2.3 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) and contact lens discomfort (CLD) 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 devises (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 having a melting point > 40°C.

In-office procedures used to either remove keratinized lid margin material (i.e., mechanical debridement-scaling of the line of Marx) (Korb and Blackie, 2013) or open clogged meibomian glands (i.e., therapeutic expression of the meibomian glands) are known to provide symptom relief and short-term improvement in meibomian gland function (Korb and Blackie, 2013; Downie and Craig, 2017). These procedures while effective can be associated with discomfort that limits their level of success especially in severely obstructed glands (Korb and Blackie, 2011). To both improve comfort and to soften keratinized lid margin material before conducting procedures like debridement-scaling topical anesthetics (e.g., benoxinate hydrochloride, 0.4%) are sometimes employed (Downie and Craig, 2017).

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 (see Table 2).

***Table 2: Topical ophthalmic use of selenium disulfide as a treatment for seborrheic blepharitis***

| Study | No. of Subjects | Selenium Disulfide Concentration | Exposure | Efficacy Outcome |
|---|---|---|---|---|
| Bahn (1954) | 100 | 0.50% | Twice-weekly for 2 weeks then once-weekly for 6 weeks. | Resolution of signs and symptoms in 97% of subjects. |
| Thygeson and Vaughan (1954) | 89 | 0.50% | Twice-weekly for a period of between 2 months and 1 year. | Improvement in all eyes and a cure in 75% of subjects. |
| Cohen (1954) | 40 | 0.63% | Every other night for 4 applications then repeated whenever disease flared. | Resolution of signs and symptoms in 92% of subjects. |
| Wong et al. (1956) | 76 (eyes) | 0.50% | Twice-daily for 4 weeks + daily eyelid cleaning. | Improvement of signs and symptoms in 80% of subjects. |

Azura Ophthalmics is evaluating AZR-MD-001 ointment/semi-solid drug (selenium sulfide) 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 sulfide 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. Selenium sulfide works as a keratolytic agent by softening keratinized material.

Clinical study MGSS1 was a prospective, interventional, non-randomized, contra-lateral eye controlled pilot study of selenium sulfide 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 sulfide 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.

Based upon positive efficacy and safety results from clinical study MGSS1 for the ocular application of selenium sulfide shampoo (2.5%), Azura Ophthalmics, is further evaluating the safety, tolerability and effectiveness of AZR-MD-001 ointment/semi-solid drug, surfactant free, in patients with MGD and associated evaporative DED in study AZ201801 entitled, "A Multicenter, Vehicle-controlled, Randomized Study to Evaluate the Safety, Tolerability, Systemic Pharmacokinetics, and Pharmacodynamics of AZR-MD-001 in Patients with Meibomian Gland Dysfunction (MGD) and Evaporative Dry Eye Disease (DED)."

Given the known use of topical anesthetics (e.g., benoxinate hydrochloride, 0.4%) as weak keratolytic agents to soften keratinized lid margin material before conducting procedures like debridement-scaling (Downie and Craig, 2017) and the known ability of this procedure to be conducted without topical anesthetic (Korb and Blackie, 2013), there is a potential for known keratolytic agents such as selenium sulfide when formulated into an ophthalmic preparation (AZR-MD-001) to both improve the efficacy of conventional therapeutic treatment (debridement or therapeutic expression of the meibomian glands) for Meibomian Gland Dysfunction (MGD) and to potentially improve the safety and tolerability of these procedures by reducing the force required to either remove keratinized material or open clogged glands.

## 2.4 RISK/BENEFIT ASSESSMENT

### 2.4.1 KNOWN POTENTIAL RISKS

***Selenium sulfide:***

Selenium sulfide is used as an anti-fungal and anti-dandruff ingredient in commercially available shampoo (i.e., Selsun Blue, Exsel, Selsum. 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. Ocular irritation, conjunctivitis, and epithelial keratitis have been reported in humans dosed with selenium sulfide as a 0.5% ophthalmic ointment and Sodium Lauryl Sulphate applied to the lid margin (Bahn, 1954). In clinical study MGSS1, selenium sulfide 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.

To date ongoing study AZ201801 has evaluated AZR-MD-001 ointment/semi-solid drug (0.1% and 0.5%) either twice weekly or once daily without any obvious, significant ocular safety or tolerability findings (see the AZR-MD-001 Investigator's Brochure for a more detailed description of the AZR-MD-001 safety profile).

***Conventional therapeutic treatment (debridement or therapeutic expression of the meibomian glands):***

The debridement–scaling procedure can be performed in 2 steps using a stainless steel golf club spud (e.g., Katena K2-4000 Golf Club Foreign Body Spud) and either no anesthetic or topical anesthetic (e.g., benoxinate hydrochloride, 0.4%). This procedure is intended to remove tissue that can be removed with gentle motion and mild pressure of the golf club spud.

The patients typically experience no to mild discomfort, and when done correctly there is no observable tissue damage after the procedure is completed. Although not proposed for this study, a safety lens can be placed on the eye to protect the cornea in the case of an erroneous slip of the golf club spud during the procedure; a soft contact lens or a more robust scleral lens could easily be used as a safety lens during debridement-scaling for clinicians less experienced in the procedure (Korb and Blackie, 2013).

Therapeutic expression refers to the assisted flow of meibum from the meibomian glands, achieved by pressing the eyelid between two objects, typically cotton tipped applicators, fingers and/or dedicated expression devices, for example Mastrota paddle or Collins Expressor Forceps. Clinical benefits have been demonstrated by practitioner-applied therapeutic expression, but it can be a painful procedure for the patient due to the discomfort of squeezing the lid (Korb and Blackie, 2011; Downie and Craig, 2017).

### 2.4.2 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The predominate conventional treatments for obstructive MGD 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 pharmacologic treatments for MGD that can work synergistically with conventional therapeutic treatment (debridement or therapeutic expression of the meibomian glands) to potentially improve effect size, duration of clinical benefit, and potentially reduce the amount of force required to achieve positive efficacy outcomes with these procedures resulting in an improved safety profile.

Given the high unmet medical need, the reversibility of ocular findings with selenium sulfide shampoo (2.5%) in clinical study MGSS1, the observed effectiveness for selenium sulfide in

both MGD and evaporative DED, and the known synergy of weak keratolytic agents with conventional therapeutic treatment, the risk/benefit profile of AZR-MD-001 ointment/semi-solid drug supports evaluation in combination with conventional therapeutic treatment(s) in the proposed study design.

# 3 OBJECTIVES AND ENDPOINTS

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

| OBJECTIVES | ENDPOINTS | JUSTIFICATION FOR ENDPOINTS |
|---|---|---|
| | | |
| To evaluate the safety, tolerability and efficacy of AZR-MD-001 ointment/semi-solid drug (1.0%) applied to the lower lid (either twice-weekly or once every evening) for up to 4 months as adjunctive therapy with conventional therapeutic treatment(s) for CLD. | **Safety/Adverse Events**:<br>• Incidence rates of each treatment-emergent adverse events.<br>• Tables for all treatment-emergent adverse events regardless of causality.<br>• Tables for all treatment-emergent adverse events considered to be treatment-related.<br>• Shift tables for safety variables (e.g., IOP, biomicroscopy, and ophthalmoscopy).<br><br>**Signal of Efficacy:**<br>•<br><br>*Primary Efficacy for CLD:*<br>The efficacy variables are<br>• Change from Baseline to day 14 and month 1 in meibum gland secretion score (MGS) (lower lid: 0 to 45 scale; upper lid: 0 to 45 scale, or upper and lower lids combined)<br>• Change from Baseline to day 14 and month 1 in the number of Meibomian Glands Yielding Liquid Secretion (MGYLS) | The endpoints for safety and tolerability are all commonly used in ophthalmic drug and devise trials.<br><br>Observed benefits for conventional therapeutic treatments for glandular obstruction include:<br>1) Improvement in the meibum gland secretion score (MGS) (0 to 45 scale);<br>2) Increases in the number of meibomian glands yielding liquid secretion (MGYLS) (0 to 15 scale); |

| OBJECTIVES | ENDPOINTS | JUSTIFICATION FOR ENDPOINTS |
|---|---|---|
| | (lower lid: 0 to 15 scale; upper lid: 0 to 15 scale, or upper and lower lids combined)<br>• Change from Baseline to day 14 and month 1 in eyelid markers for CLD (e.g., lid margin redness, lid margin thickness, lid-wiper epitheliopathy, and lid-parallel conjunctival folds) and subjective vision ratings (VAS), CLDEQ-8 and comfortable wear time.<br><br>For all endpoints the visit for the primary variable is month 1 for AZR-MD-001, month 2 for enhancement of conventional therapeutic treatment, and month 4 for prolongation of conventional therapeutic treatment. | 3) Increased Tear Break-up Time (TBUT). |

# 4 STUDY DESIGN

## 4.1 OVERALL DESIGN

Single-center, single-masked (the individual(s) performing efficacy measures will be masked to treatment assignment for the patient(s) they are assessing), vehicle-controlled, randomized, parallel group study. Patients diagnosed with CLD will be enrolled . Patients with CLD will be randomly assigned in a 2:1 ratio to receive either a single concentration of AZR-MD-001 ointment/semi-solid drug (1.0%) or AZR-MD-001 vehicle for 4 months. A single concentration (1.0%) and dose frequency of administrations (twice weekly or once daily) declared safe by the data review committee (DRC) from study AZ201801 will be included in this study. At the month 1 visit the patients will receive conventional therapeutic treatment in both eyes (i.e., debridement in one eye and debridement plus therapeutic expression of the meibomian glands in the other eye) and continue their assigned dosing regimen for three more months. The study flow is shown in Figure 1.

## 4.2 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 has also been applied to the lid margin as a treatment for seborrheic blepharitis (see Table 2).

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 sulfide 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 sulfide 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 sulfide 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 study AZ201801, Amendment 2 is an ongoing 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., Cohort 1, Group 1-0.1%, Cohort 1, Group 2-0.5%, Cohort 1, Group 3-1.0%, and Group 4-0.1%, 0.5%, 1.0%, or 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. For Cohort 1 patients will be randomized in a 4:1 ratio (AZR-MD-001: Vehicle) and in the Expansion Cohort patients will be randomized in a 1:1:1 ratio.

Eleven patients were randomized to Cohort 1, Group 1 (0.1%, twice-weekly) between September 10th, 2018 and October 19th, 2018. Patient 101-012 discontinued treatment before the Month 1 visit with irritated eyelids, grittiness and foreign body sensation. All other patients completed

Month 3 by January, 10th, 2019 and exited the study. The principal investigator for the site that enrolled Cohort 1, Group 1 considered an increase in dosing frequency from twice-weekly to once-daily acceptable for 8 of the 10 patients (80%) who completed the Month 1 visit: patient 101-008 had moderate superficial punctate keratopathy (SPK) associated with ocular dryness observed in the left eye and patient 101-011 had moderate SPK observed in the right eye. SPK is an eye disorder caused by the death of small groups of cells on the surface of the cornea (the clear layer in front of the iris and pupil). SPK is commonly associated with dry eye disease and is observed with corneal fluorescein staining. No trend toward increased corneal staining was observed during the study and by Month 3 (study exit) all corneal staining resolved while patients 101-008 and 101-011 remained on treatment. No other significant safety findings were observed for Cohort 1, Group 1 and the DRC made the recommendation to initiate Cohort 1, Group 2 with no modifications to the approved protocol design. Thus, AZR-MD-001 0.1% dosed either twice-weekly or once-daily are considered safe and well tolerated.

Nine patients were randomized to Cohort 1, Group 2 (0.5%, twice-weekly) between October 19th, 2018 and January 18th, 2019. Screening is continuing for Cohort 1, Group 2 and as of February 3rd, 2019 4 patients completed the Month 3 Visit, 4 patients completed the Month 1.5 Visit, 1 patient completed the Day 14 Visit, and 4 patients are in Screening. To date no patient has discontinued dosing in Cohort 1, Group 2. The principle investigator for the site that enrolled all patients for Cohort 1, Group 2 considered an increase in dosing frequency from twice-weekly to once-daily acceptable for 5 of the 8 patients (63%) who completed the Month 1 visit: patient 101-014 had mild SPK and grade 2 oxford corneal staining, patient 101-016 reported some blurring of vision and mild grittiness in the 2 days following drug application, and patient 101-024 reported burning and stinging on the day after application. No trend toward increased corneal staining was observed during the study and by Month 3 (study exit) all corneal staining resolved while patient 101-014 remained on treatment. No significant safety findings have been observed to date for Cohort 1, Group 2.

Based upon positive results from clinical study MGSS1 and good safety and tolerability across 5 completed clinical studies with doses of selenium sulfide up to 2.5% twice weekly or 0.5% BID and the known utility of potential keratolytic agents with conventional therapeutic treatments such as debridement the current study is proposing to evaluate the safety, tolerability and effectiveness of AZR-MD-001 ointment/semi-solid drug, surfactant free in combination with conventional therapeutic treatments in patients with CLD.

## 4.3 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all scheduled visits 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 Contact Lens Discomfort (CLD).

## 5.1 INCLUSION CRITERIA

New CLD Patients:

- Evidence of meibomian gland obstruction (based on a meibomian gland secretion (MGS) score of ≤12 for 15 glands of the lower lid) in both eyes at the baseline visit
- A history of wearing soft contact lenses for at least 6 months
- Wearing of the soft contact lenses for at least 3 weeks before the baseline visit and wore or attempted to wear lenses at least 4 times a week before the baseline visit.
- Symptomatic as defined by an answer of "No" at baseline to the question, "Are you able to comfortably wear your lenses as long as you want?"
- Self-reported history of contact lens dryness/intolerance in the 6 months preceding the baseline visit.
- Baseline CLDEQ-8 score >12
- Contact lens may be use during the study as long as they are removed 15 minutes before dosing and not reinserted until at least 15 minutes after dosing.

All Patients:

- Male or female, 18 years of age or older at baseline 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 baseline visit
- Prior to the baseline visit patients are required to discontinue:
    - 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 baseline 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 baseline visit. If artificial tear substitutes were used within 72 hours of the baseline visit the visit should be rescheduled
- A negative pregnancy test result for all women of childbearing potential at the baseline 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 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 baseline visit.

## 5.2 EXCLUSION CRITERIA

All Patients:

- Uncontrolled ocular disease (except for MGD or CLD) or uncontrolled systemic disease
- Patient has glaucoma or ocular hypertension as demonstrated by an intraocular pressure (IOP) in either eye at baseline of ≥24 mm Hg 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 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 baseline 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 baseline visit
- 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 baseline visit) ocular surgery, trauma, herpes, or recurrent inflammation
- Periocular application of makeup 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 baseline 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, dry eye, or CLD for the study duration (Including over-the-counter [OTC] artificial tears, ocular lubricants, or dietary supplements known to impact ocular surface health [e.g., Omega 3 supplements] except those prescribed for use as part of the study)
- 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 baseline 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
- 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 baseline 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, or planning pregnancy
- Positive urine pregnancy test at the baseline visit
- Participation in another clinical trial involving a therapeutic drug or device within the past 30 days (except for AZR-MD-001)
- Epilepsy or history of migraines exacerbated by flashing, strobe-like lights

New Patients:

- Meibography score at the baseline visit of 4 (greater than 75% partial glands using the gestalt grading system)
- Corneal staining ≥ 3 (between 33 and 100 dots) using the Oxford Scheme
- Schirmer's tear test without anesthesia ≤ 5 seconds in either eye at the baseline visit

## 5.3 LIFESTYLE CONSIDERATIONS

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

- Patients should not have LipiFlow® or other lid-heating therapy, meibomian gland probing, or therapeutic gland expression in either eye within 6 months of the baseline visit or during the study.
- Patients must have discontinued (2 weeks before baseline) 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 (except those prescribed for use as part of 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 baseline) and be willing to remain off antihistamines or isotretinoin during the study.

- Patients must have discontinued (3 months before baseline) and be willing to remain off Anti-inflammatory treatments for DED (e.g., cyclosporine ophthalmic emulsion [Restasis® or Ikervis®] or lifitegrast ophthalmic solution [Xiidra®]).
- Patients should avoid the use of medicated shampoos containing selenium (e.g., Selsun Blue, Exsel, Selsum, and Seleen) following the baseline visit.
- Patients must have discontinued (2 weeks before baseline) 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 baseline visit. If artificial tear substitutes were used within 72 hours of the baseline 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 measures may be rescreened one additional time. Rescreened participants should be assigned the same participant number as for the initial screening.

### 5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

The total number of randomized patients for the study will be up to 15 patients with CLD. Based upon data from the LipiFlow® development program a screen failure rate of ~ 40% is expected for new patients. Thus, ~up to 21 patients will need to be screened to achieve ~up to 15 patients randomized to treatment.

All advertisements, if required for subject recruitment, will be submitted to the IEC and approved by the IEC before they are used.

## 6 STUDY INTERVENTION

### 6.1 STUDY INTERVENTION(S) ADMINISTRATION

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

All concentrations of AZR-MD-001 Ophthalmic Ointment contain the drug product, AZR-MD-001 (1.0% or 0.5%), and suitable excipient. The only excipient in the formulation is White Soft Paraffin. The formulations will be supplied in unit dose containers (see Table 6.1.1–1).

Table 6.1.1–1 Investigational Product and Packaging / Labelling Characteristics

| | Investigational Product | |
|---|---|---|
| **Product name:** | MGT001C1 (Selenium disulfide API in suspension) | Vehicle |
| **Formulation description:** | AZR-MD-001 is an orange opaque dispersion ointment with an odour faintly of hydrogen sulfide | Placebo ointment will match AZR-MD-001's texture |
| **Dosage form:** | Ophthalmic ointment/semi-solid drug | Ophthalmic ointment/semi-solid drug |
| **Unit dose strength(s)/Dosage level(s):** | 1.0%10mg<br>0.5% 5mg | Placebo<br>Petrolatum, white |
| **Route of Administration** | Topical | Topical |
| **Dosing instructions:** | Store between 2 – 8°C until opened. **Refrigerate**. Do not **freeze**. Stop use 4 weeks (30 days) after opening. Protect from light | Store between 2 – 8°C until opened. **Refrigerate**. Do not **freeze**. Stop use 4 weeks (30 days) after opening. Protect from light. |
| **Physical description:** | An orange opaque ointment packaged in a multi-use tube | A white opaque ointment packaged in a multi-use tube |
| **Device:** | Multi -use white tube with cap | Multi -use white tube with cap |
| **Method for individualizing dosage:** | 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 further evaluated the safety, tolerability and effectiveness of AZR-MD-001 ointment/semi-solid drug, surfactant free 0.1%, 0.5%, 1.0%, and 2.5% dosed twice weekly and once daily in the Cohort 1, Groups 1 through 4 of ongoing study AZ201801. Up to the highest dose and frequency of administration declared safe by the data review committee (DRC) from study AZ201801, Cohort 1, at the start of this study can be included in this study.

### 6.1.3 DOSING AND ADMINISTRATION

The study medication will be self-administered by the patient (or administered by a caregiver) at the study site after all procedures have been completed for the visit. At these visits, each patient will be asked to stay at the site for 30 minutes after study drug administration. The patient (or administered by a caregiver) at the study site will not dose the patient immediately following conventional therapeutic treatment(s) for MGD at Month 1. The patients will be instructed to re-start dosing the following day.

Patients (or a caregiver) will apply a dose of approximately 5 mg using a dosing aid supplied by Azura Ophthalmics. Patients will then use their washed index finger or an applicator 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 (see the Dosing Instruction Sheet for more detail).

During the double-masked treatment period, each patient (or caregiver) must apply 1 application of the vehicle or active drug either once daily or twice weekly in the evening to the tarsus of the lower lid of both eyes.

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.

## PREPARATION/HANDLING/STORAGE/ ACCOUNTABILITY

### 6.1.4 ACQUISITION AND ACCOUNTABILITY

Whilst subjects are dosed at the site, they will administer their study treatment under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study subject identification will be confirmed at the time of dosing by a member of the study site staff.

Subjects will be instructed on proper instillation and storage of study drug at the end of the baseline, day 14, month 1, month 1 + 48 hr, month 1.5, month 2 and month 3 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 baseline up to and including month 4 to assess dosing. Dosing compliance will be based off of the used and unused tube count. If the subject is less than 80% or

more than 125% compliant with dosing based on the expected number of used tubes, then the subject will be deemed non-compliant and a deviation should be recorded.

#### 6.1.5 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

The study packaging will be performed by PCI Pharma Services (PCI). 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.

#### 6.1.6 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 Azura Ophthalmics 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 refrigerate between 2 – 8°C until opened and protected from light. Maintenance of a temperature log (manual or automated) is required at the clinical sites.

#### 6.1.7 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 set aside for return to study investigator.

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

Site personnel conducting efficacy measures will be masked to the treatment assignment for the 4 month treatment period.

Screening numbers will be assigned sequentially by site. At the end of the baseline visit, qualifying patients will be given a sequential randomization number which corresponds to a specific medication kit number(s) and type in the randomization log. Designated site personnel will report a medication kit number to use for each patient corresponding to the randomization number and will be responsible for monitoring and documenting patient compliance with dosing at each visit. The individual dispensing drug and monitoring compliance will not be the same person who conducts efficacy measures for a given patient.

### 6.3 CONCOMITANT THERAPY

Patients must have discontinued and be willing to remain off all other ophthalmic preparations including artificial tears during the study (except those prescribed for use as part of the study).

At the month 1 visit the patients will receive conventional therapeutic treatment in both eyes (i.e., debridement in one randomly selected eye and debridement plus therapeutic expression of the meibomian glands in the other eye) and continue their assigned dosing regimen for three more months.

#### 6.3.1 RESCUE MEDICINE

In the event that rescue medication is required for worsening signs or symptoms of MGD, dry eye disease or CLD during the course of the study, patients will be provided an appropriate rescue regimen by the investigator/treating clinician, and may be exited from the study.

## 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 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.

## 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 the investigator.

Azura Ophthalmics may recommend the site withdraw a participant for the following reasons:

i. Patient Safety: New data/findings plus a DRC decision from ongoing study AZ201801 indicates it is unsafe to continue patients in that study at a dose and frequency being used in the current study;
ii. Manufacturing: Any problem identified with clinical supplies that may require stopping of dosing;
iii. Negligence: A general right to stop a study in the event of overt negligence by either party.

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

***Efficacy (CLD):*** The primary efficacy variables for CLD are change from baseline to day 14, month 1, month 1 + 48 hours, month 2, month 3, and month 4 in MGS, number of MGYLS, lid markers for CLD (see Table 1 in Siddireddy et al, 2018), and subjective vision ratings (VAS), CLDEQ-8 and comfortable wear time. A patient will be considered to be a meibum quality responder at a post-randomization visit if the MGS score in the study eye is > 3. The visit for the primary variable is month 1 for AZR-MD-001, month 2 for enhancement of conventional therapeutic treatment, and month 4 for prolongation of conventional therapeutic treatment. The primary analysis population is mITT. Statistical tests will be performed for each AZR-MD-001 group versus vehicle group, slope of change relative to an expected slope of 0 and ratio of pre and post conventional therapeutic treatment relative to an expected ratio of 1. Pairwise comparisons of the proportion of responders will be performed using the CMH method stratifying by average baseline MGD score. There will be no alpha adjustment for the multiple tests for the pairwise comparisons.

***Validating methods of measuring meibomian gland expression (MGE) (Vehicle group only):***

The efficacy variables are the ratio of change from baseline to month 1 and change from month 1 to month 2 in meibum gland secretion score (MGS) (lower lid: 0 to 45 scale; upper lid: 0 to 45 scale, or upper and lower lids combined) (e.g., (baseline – month 1)/(month 1 – month 2)) and number of Meibomian Glands Yielding Liquid Secretion (MGYLS) (lower lid: 0 to 15 scale; upper lid: 0 to 15 scale, or upper and lower lids combined). The primary analysis population is mITT. Statistical tests will be performed for the vehicle group. There will be no alpha adjustment for the multiple tests for the pairwise comparisons.

### 8.1.2 SECONDARY EFFICACY MEASURES

Secondary efficacy measures include the meibum gland secretion score (MGS), the number of Meibomian Glands Yielding Liquid Secretion (MGYLS), TBUT, CLD specific visual analogue scale (VAS), Contact Lens Dry Eye Questionnaire-8 (CLDEQ-8), Schirmer's test without anesthesia, tear evaporation rate, sodium fluorescein corneal staining (Oxford scale), and lissamine green conjunctival staining. Refer to Section 1 for a complete list and specific timings of additional efficacy measures.

## 8.2 SAFETY AND OTHER ASSESSMENTS

### 8.2.1 SAFETY MEASURES

The following safety measures will be examined:

- adverse events (ocular and nonocular)
- best-corrected visual acuity (BCVA)
- slit-lamp biomicroscopy
- intraocular pressure (IOP)
- ophthalmoscopy
- urine pregnancy test

## 8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Adverse events occurring during the study will be recorded on an adverse event form. 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 source 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 source page.

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.<br>• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.<br>• New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study.<br>• Signs, symptoms, or the clinical sequelae of a suspected interaction.<br>• 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).<br>• "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.<br>• 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.<br>• Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.<br>• Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).<br>• 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 source).
- 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 within 24 hours of the investigator's or site's knowledge of the event, 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. SAEs will be reported to Azura Ophthalmics, the Human Research Ethics Committee and any other relevant approving authorities.

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 Azura Ophthalmics.

UNSW 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.

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 source document, 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

Subjects with AEs will be followed-up 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 source documents.

Subjects should be followed up for 30 days 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 source 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 all site personnel to determine which treatment has been assigned and institute appropriate follow-up care.

The reason for unmasking the patient 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 UNSW 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 UNSW 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 UNSW 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 UNSW.

### 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 the UNSW.

## 9 STATISTICAL CONSIDERATIONS

### 9.1 SAMPLE SIZE DETERMINATION

The sample size is determined empirically.

## 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 who have values at randomization, and at least 1 post-randomization for MGE. 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 2 or later will be used to replace missing data at visits where data are not recorded.

## 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. 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 Cochran-Mantel-Haenszel (CMH) or the Wilcoxon rank-sum test for between-treatment comparisons and the sign-rank test for within-treatment comparisons.

***Efficacy (CLD):*** The primary efficacy variables for CLD are change from baseline to day 14, month 1, month 1 + 48 hours, month 2, month 3, and month 4 in MGS, number of MGYLS, lid markers for CLD (see Table 1 in Siddireddy et al, 2018), and subjective vision ratings (VAS), CLDEQ-8 and comfortable wear time. A patient will be considered to be a meibum quality responder at a post-randomization visit if the MGS score in the study eye is > 3. The visit for the primary variable is month 1 for AZR-MD-001, month 2 for enhancement of conventional therapeutic treatment, and month 4 for prolongation of conventional therapeutic treatment. The primary analysis population is mITT. Statistical tests will be performed for each AZR-MD-001 group versus vehicle group, slope of change relative to an expected slope of 0 and ratio of pre and post conventional therapeutic treatment relative to an expected ratio of 1. Pairwise comparisons of the proportion of responders will be performed using the CMH method stratifying by average baseline MGD score. There will be no alpha adjustment for the multiple tests for the pairwise comparisons.

***Validating methods of measuring meibomian gland expression (MGE) (Vehicle group only):***

The efficacy variables are the ratio of change from baseline to month 1 and change from month 1 to month 2 in meibum gland secretion score (MGS) (lower lid: 0 to 45 scale; upper lid: 0 to 45 scale, or upper and lower lids combined) (e.g., (baseline – month 1)/(month 1 – month 2)) and number of Meibomian Glands Yielding Liquid Secretion (MGYLS) (lower lid: 0 to 15 scale; upper lid: 0 to 15 scale, or upper and lower lids combined). The primary analysis population is mITT. Statistical tests will be performed for the vehicle group. There will be no alpha adjustment for the multiple tests for the pairwise comparisons.

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

The primary efficacy variables (see Section 8.1.1) will be analyzed at month 1 for AZR-MD-001, month 2 for enhancement of conventional therapeutic treatment, and month 4 for prolongation of conventional therapeutic treatment. Using an analysis of covariance [ANCOVA] model with baseline MGS score as a covariate 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.

### 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 as a covariate 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 and month 1
- Patients in the AZR-MD-001 vehicle group: changes from baseline to days 14 and month 1
- Eyes in the AZR-MD-001 ointment/semi-solid drug treatment group + debridement: changes from month 1 to month 1 + 48 hours, month 2, month 3, and month 4.
- Eyes in the AZR-MD-001 ointment/semi-solid drug treatment group + debridement plus gland expression: changes from month 1 to month 1 + 48 hours, month 2, month 3, and month 4.
- Eyes in the AZR-MD-001 vehicle group + debridement: changes from month 1 to month 1 + 48 hours, month 2, month 3, and month 4.
- Eyes in the AZR-MD-001 vehicle group + debridement plus gland expression: changes from month 1 to month 1 + 48 hours, month 2, month 3, and month 4.

Patients/eyes in the AZR-MD-001 vehicle group: difference in changes from baseline to day 14 and month 1 and changes from month 1 to month 1 + 48 hours, month 2, month 3, and month 4. Within each treatment group, shift tables for complete treatment response (yes/no) by eye (study eye to month 1 and both eyes thereafter) will be presented for patients in the mITT population for endpoint signifying a "clinical cure" (Proportion of patients with a MGS score > 3; Proportion of patients with a TBUT > 5 seconds at each visit; and Proportion of patients with a Schirmer's test ≥ 5 mm at each visit; :

- Patients in the AZR-MD-001 ointment/semi-solid drug treatment group: changes from baseline to days 14 and month 1
- Patients in the AZR-MD-001 vehicle group: changes from baseline to days 14 and month 1
- Eyes in the AZR-MD-001 ointment/semi-solid drug treatment group + debridement: changes from month 1 to month 1 + 48 hours, month 2, month 3, and month 4.
- Eyes in the AZR-MD-001 ointment/semi-solid drug treatment group + debridement plus gland expression: changes from month 1 to month 1 + 48 hours, month 2, month 3, and month 4.
- Eyes in the AZR-MD-001 vehicle group + debridement: changes from month 1 to month 1 + 48 hours, month 2, month 3, and month 4.
- Eyes in the AZR-MD-001 vehicle group + debridement plus gland expression: changes from month 1 to month 1 + 48 hours, month 2, month 3, and month 4.

The CMH test for general association, stratified by baseline MGS score will be used to compare treatments with respect to the proportion of patients achieving a "clinical cure" in the study eye/each eye. Pairwise comparisons will be performed for each AZR-MD-001 treatment groups versus vehicle. Two-sided confidence intervals (95%) will be provided for the differences between treatments. The confidence intervals will be constructed using the normal approximation to the binomial distribution.

#### 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.

#### 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

An interim analysis is planned for the study at month 1. A final analysis will occur at the completion of month 4. At the final analysis, statistical significance will be declared for 2-sided p-values $\leq 0.05$.

Given the exploratory nature of the study no adjustments for multiplicity will be applied across the primary or secondary endpoints.

#### 9.4.7 SUB-GROUP ANALYSES

Patients will be stratified by average baseline MGS score (i.e., both eyes should meet the inclusion/exclusion criteria).

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

1. Average MGS score $< 6$
2. Average MGS score $\geq 6$ 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

Additional exploratory statistical analysis may be performed at the UNSW's or Azura Ophthalmics discretion.

# 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 reconsent will be obtained.

## 10.5 SUBJECT CONFIDENTIALITY

Monitors, auditors, 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 UNSW Sydney. In addition, inspections may be conducted by regulatory authorities at their discretion.

## 11.2 MONITORING

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

## 11.3 DATA MANAGEMENT AND CODING

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 reason(s) for the termination or suspension will be provided. 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 Azura Ophthalmics, IRB and/or applicable regulatory agencies.

## 12.2 FUTURE USE OF STORED SPECIMENS AND DATA

### 12.2.1 HANDLING OF BIOLOGICAL SPECIMENS

Not applicable.

#### 12.2.1.1 TEAR SAMPLES

Not applicable.

## 12.3 RETENTION OF DOCUMENTATION

For countries falling within the scope of the ICH guidelines, all study related correspondence, patient records, consent forms, patient privacy documentation, records of the distribution and use of all investigational products, and copies of source 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 Azura Ophthalmics 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.

## 12.4 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 source 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.

## 12.5 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.

### 12.6 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 requests the SOPs and membership lists, the IRB should comply with the request.

### 12.7 PUBLICATION AND DATA SHARING POLICY

See Clinical Trials Research Agreement for Publication and Data sharing policy.

### 12.8 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.

### 12.9 ADDITIONAL CONSIDERATIONS

None

## 12.10 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 |
| DED | Dry Eye Disease |
| EC | Ethics Committee |
| 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 secretion score |
| 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 |

## 12.11 PROTOCOL AMENDMENT HISTORY

| Version | Date | Description of Change | Brief Rationale |
|---|---|---|---|
| 2.0 | 05-Aug-2019 | Delete 0.5% dose concentration of AZR-MD-001 planned to be evaluated in this study | The 1.0% AZR-MD-001 concentration has been selected for evaluation in this study |
| 3.0 | 12-Aug-2019 | Addition of lipid layer thickness measurement using the LipiView II and associated exclusion criteria | To include measurement of an additional tear film parameter that may demonstrate changes following treatment with AZR-MD-001 |
| 4.0 | 24-Sep-2019 | Addition of tear meniscus height measurement and tear collection | To include evaluation of additional tear film parameters that may demonstrate changes following treatment with AZR-MD-001 |
| 5.0 | 04-Dec-2019 | Addition of: (i) study ointment to be applied at night only; (ii) instillation of a commercially available artificial tear eye drop in each eye (Hylo-Forte®) 5 minutes prior to applying the study ointment; (iii) include the 0.5% dose of AZR-MD-001 to allow participants to be dispensed with the lower concentration of study IP by an unmasked investigator (where applicable); (iv) allow the study IP to be removed 15 mins after application using a cotton wipe moistened with saline. | To reduce the risk of ocular toxicity events and improve participant tolerability to the study ointment upon application, the proposed actions are to be initiated in a stepped approach. This will enable the method of ointment application to be optimized to meet the participants' needs. |
| 6.0 | 17-Feb-2020 | Deletion of the MGD group from this study. | As recruitment has not yet begun for the MGD group, this group will be removed from this study and a new research study protocol proposed. |
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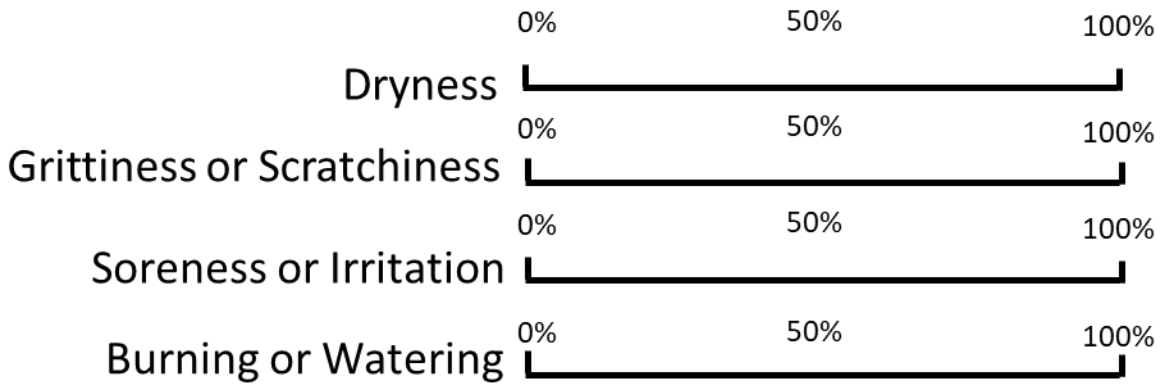
# 14 SUBJECTIVE STUDY SCALES

## 14.1 VISUAL ANALOG SCALE (VAS) SENSITIVE TO CLD

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.”


0%
50%
100%
Dryness
0%
50%
100%
Grittiness or Scratchiness
0%
50%
100%
Soreness or Irritation
0%
50%
100%
Burning or Watering

## 14.2 CONTACT LENS DRY EYE QUESTIONNAIRE-8 (CLDEQ-8)

1. Questions about **EYE DISCOMFORT**:

   a. During a typical day in the past 2 weeks, **how often** did your eyes feel discomfort while wearing your contact lenses?

   **0** Never
   **1** Rarely
   **2** Sometimes
   **3** Frequently
   **4** Constantly

   When your eyes felt discomfort with your contact lenses, **how intense was this feeling of discomfort…**

   b. At the end of your wearing time?

| Never have it | Not at All Intense | | | | Very Intense |
|---|---|---|---|---|---|
| **0** | **1** | **2** | **3** | **4** | **5** |

2. Questions about **EYE DRYNESS**:

   a. During a typical day in the past 2 weeks, **how often** did your eyes feel dry?

   **0** Never
   **1** Rarely
   **2** Sometimes
   **3** Frequently
   **4** Constantly

   When your eyes felt dry, **how intense was this feeling of dryness**…

   b. At the end of your wearing time?

| Never have it | Not at All Intense | | | | Very Intense |
|---|---|---|---|---|---|
| **0** | **1** | **2** | **3** | **4** | **5** |

3. Questions about **CHANGEABLE, BLURRY VISION:**

   a. During a typical day in the past 2 weeks, **how often** did your vision change between clear and blurry or foggy while wearing your contact lenses?

   **0** Never
   **1** Rarely
   **2** Sometimes
   **3** Frequently
   **4** Constantly

   When your vision was blurry, **how noticeable was the changeable, blurry, or foggy vision** …

   b. At the end of your wearing time?

| Never have it | Not at All Intense | | | | Very Intense |
|---|---|---|---|---|---|
| **0** | **1** | **2** | **3** | **4** | **5** |

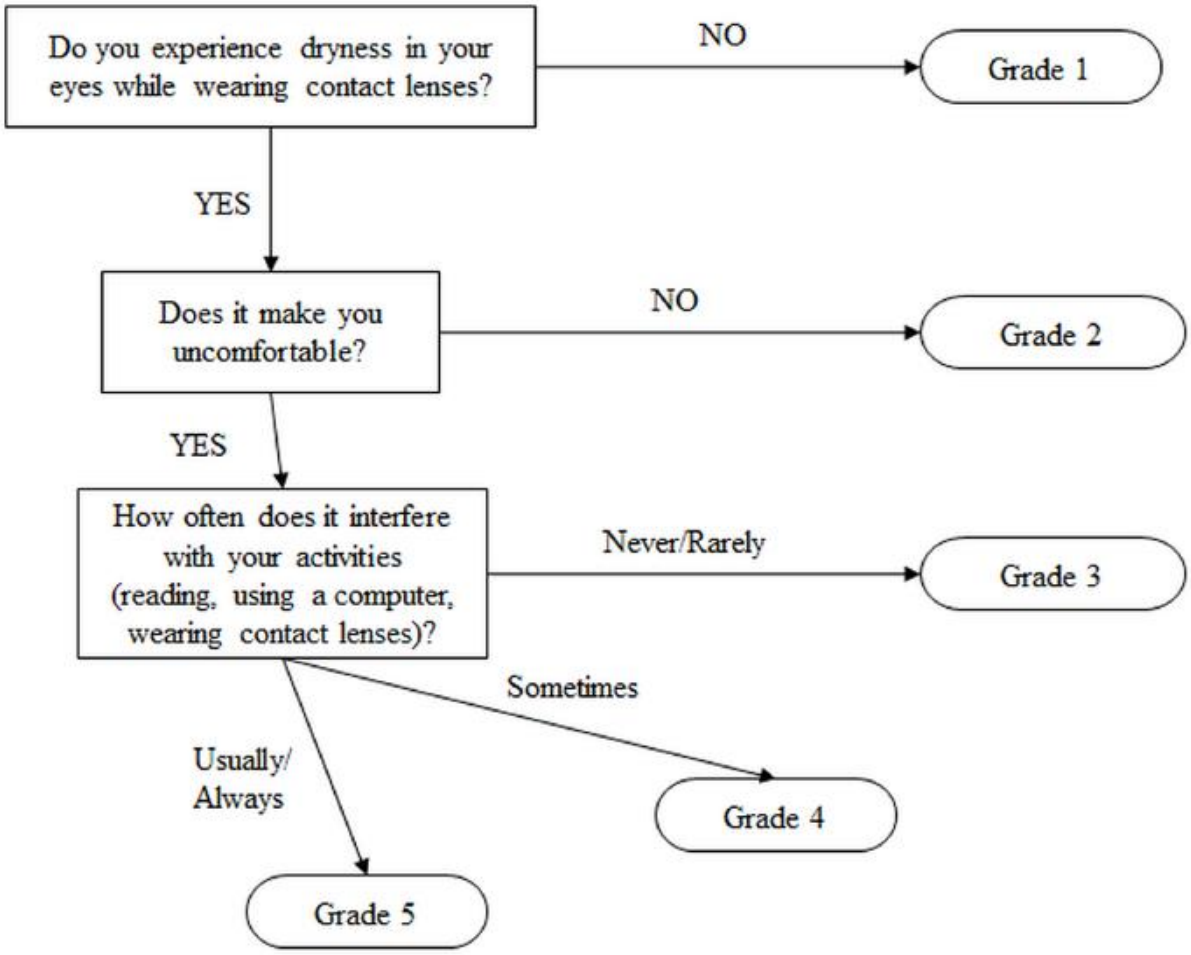
4. Question about **CLOSING YOUR EYES:** During a typical day in the past 2 weeks, **how often** did your **eyes bother you so much that you wanted to close them**?

   **0** Never
   **1** Rarely
   **2** Sometimes
   **3** Frequently
   **4** Constantly

5. Question about **REMOVING YOUR LENSES:** How often during the past 2 weeks, did your eyes *bother you so much* while wearing your contact lenses that you felt as if you needed to stop whatever you were doing and **take out your contact lenses**?

   **1** Never
   **2** Less than once a week
   **3** Weekly
   **4** Several times a week
   **5** Daily
   **6** Several times a day

## 14.3 BERKELEY DRY EYE FLOW CHART (DEFC)



# 15 APPROVAL(S)

| | |
|---|---|
| **Protocol Title:** | A Single-center, Vehicle-controlled, Study to Evaluate the Safety, Tolerability, and Pharmacodynamics of AZR-MD-001 as Adjunctive Therapy to Conventional Therapeutic Treatment for Meibomian Gland Dysfunction (MGD) or Contact Lens Discomfort (CLD) |
| **Protocol Number:** | SOVS2019-070 |
| **Final Date:** | 17Feb2020 |

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

Signed:_____ Date:_____

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