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)

Protocol Number:	AZ201801
National Clinical Trial (NCT) Identified Number:	TBD
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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
Section 1.1, Objectives Section 1.2., Expansion Cohort & Section 4.1	**Expansion Cohort**: To evaluate the safety, tolerability, and pharmacodynamics of 2 different concentrations of AZR-MD-001 ointment/semi-solid drug (0.5% and 1.0%) applied to the lower lid twice-weekly for up to 6 months compared to its placebo in patients with meibomian gland dysfunction (MGD) ~~and signs and symptoms of evaporative dry eye disease (DED)~~.	Updated to reflect feedback from FDA on MGD as an indication by deleting the reference to DED.
Section 1.1, Clinical Hypotheses ,Expansion Cohort	AZR-MD-001 ointment/semi-solid drug (0.5% or 1.0%) is more effective than placebo for treating MGD as measured by the **meibomian glands yielding liquid secretion score (MGYLS)**. Deleted MGS and replaced it with MGYLS.	The Interim Analysis from Cohort 1 of AZ201801 suggests that MGYLS has more power than MGS for detecting the benefit of AZR-MD-001.

Affected Section(s)	Summary of Revisions Made	Rationale
Section 1.2 5.5, & 9.1.2, Study Population Characteristics	Cohort 1: The total number of randomized patients for Cohort 1 will be approximately 60. Approximately 30 patients should have a baseline MGS score of < 6 and approximately 30 patients should have a baseline MGS score ≥6 and ≤ 12. Based upon data from the LipiFlow® development program a screen failure rate of ~ 40% is expected. Thus, ~84 patients will need to be screened to achieve ~60 patients randomized to treatment. Expansion Cohort: The total number of randomized patients, with a Total OSDI < 34, for the Expansion Cohort will be approximately 225. Approximately 112 patients should have a baseline MGS score of < 6 and approximately 112 patients should have a baseline MGS score ≥6 and ≤ 12. Based upon data from the LipiFlow® development program a screen failure rate of ~ 40% is expected. Thus, ~315 patients will need to be screened to achieve ~225 patients randomized to treatment with a Total OSDI < 34.	Clarified the section by separating Cohort 1 from the Expansion Cohort. Increased the sample size in the Expansion Cohort from 50 to 75 patients a group.
Section 1.2 & 5.1, Key Inclusion Criteria	Evidence of ~~Evaporative DED~~ MGD at the screening and baseline visits: 1. Score ≥6 on the Standard Patient Evaluation of Eye Dryness questionnaire (SPEED) 2. Ocular Surface Disease Index (OSDI) questionnaire score ≥13 and < 34 ~~(Cohort 1 only)~~	Clarified the section by removing Evaporative DED and replacing it with MGD. The study is targeting the signs and symptoms of MGD in the Expansion Cohort. The main inclusion criteria for Total OSDI was reset to match Cohort 1.

Affected Section(s)	Summary of Revisions Made	Rationale
Section 1.2 & 5.1, Key Inclusion Criteria	Women of childbearing potential must have a history of bilateral tubal ligation or use oral contraceptives, implants, injectables, transdermal patch, intrauterine device, or double barrier contraceptive for birth control during the study. If these methods of birth control do not apply, woman of childbearing potential must have a monogamous partner who has had a vasectomy at least 3 months before the screening visit. Complete abstinence for four weeks before exposure to study medication, throughout the study, and for at least four weeks after the last dose of study medication is acceptable for study inclusion. Added "double barrier contraceptive" and allowed for "Complete abstinence for four weeks before exposure to study medication, throughout the study, and for at least four weeks after the last dose of study medication is acceptable for study inclusion."	Added additional flexibility for adequate birth control measures. AZR-MD-001 represents extremely low risk as there is no evidence for measurable changes in systemic exposure following dosing in Cohort 1.
Section 1.2 & 5.2, Key Exclusion Criteria	Enrollment in a previous Stage of the current study **or other Azura study using AZR-MD-001**	Added bold text to assure patients with prior exposure to AZR-MD-001 are not enrolled into the study.
Section 1.2 & Table 3-1, Primary Efficacy Measures	Primary Efficacy Sign for MGD: • US: Change from Baseline to month 3 in meibomian~~um~~ glands **yielding liquid secretion** score (MG**YL**S) (0 to ~~45~~ **15** scale) • Regions requiring longer duration of follow-up (e.g., EU): Change from Baseline to month 6 in meibomian~~um~~ glands **yielding liquid secretion** score (MG**YL**S) (0 to 145 scale)	Updated primary sign for MGD to MGYLS in the Expansion Cohort.

Affected Section(s)	Summary of Revisions Made	Rationale
Section 1.2 & 8.1.5 Other Efficacy Measures	Other Efficacy Measures: • Change from Baseline to day 14, month 1.5, **month 3**, ~~and~~ month 4.5 **and month 6** in MGS (0 to 45 scale) • Change from Baseline to day 14, month 1.5, and ~~month 3~~ month 4.5 ~~and month 6~~ in the number of Meibomian Glands Yielding Liquid Secretion (MGYLS) (0 to 15 scale) Proportion of patients with a change from baseline in MGYLS score ≥ 5 at each visit	Updated Other Efficacy Measures to reflect MGYLS as a primary sign for MGD. Added responder analyses for MGYLS.
Section 1.2, General Statistical Methods, Primary Efficacy (MGD)	The primary efficacy sign for MGD is change from baseline in **MGYLS**.	Changed primary endpoint to MGYLS.
Section 1.2, Expansion Cohort: Sample Size Calculation:	Updated means and estimates of variance based upon the Cohort 1, final Interim Analysis.	Updated sample size to match Section 1.2, Study Population Characteristics.
Figure 1	The primary endpoints for the US will serve as an Interim Analyses for the Month 6 primary endpoints. The sample size may be adjusted for power or to address any concerns for alpha inflation.	Added note to figure so reviewers catch that the sample size can be adjusted after the Expansion Cohort Month 3 analyses to adjust power if necessary or if requested by global regulatory agencies. Updated Expansion Cohort sample size.
Table 1 Schedule of Visits and Procedures	Split Month 1.5 and 4.5 in the Schedule of Visits and Procedures. Also added “Month = 28 days” below the table.	Sites were getting confused and missing the Month 4.5 visit. Sites requested clarification of length of one month.

Affected Section(s)	Summary of Revisions Made	Rationale
Section 6.1.3	During the double-masked treatment period, each patient (or caregiver) must apply 1 application of the ~~vehicle (Cohort 1) or placebo (Expansion Cohort)~~ assigned treatment in the evening to the tarsus of the lower lid of both eyes.	Clarified the text.
Section 6.2.1	Whilst patients are dosed at site (**i.e., Cohort 1 all visits, and practice dose at the baseline visit only of the Expansion Cohort**), 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.	Clarified the text.
Section 6.2.1	The used ~~and unused~~ study drug tubes will be collected at each visit from baseline up to and including study exit **(along with any unused tubes)** to assess dosing and symptom assessment compliance. Added bold text.	Clarified the text.
Section 9.4.1 & 9.4.3	Updated primary endpoint for the Expansion Cohort to MGYLS. Proportion of patients with a **change from baseline** in MGYLS score of **≥5** Added bold text**.**	Updated to match primary endpoint and responder analyses from the full Cohort 1 Interim Analyses.
Section 9.4.6	The primary endpoints for the US will serve as an Interim Analyses for the Month 6 primary endpoints. The sample size may be adjusted for power or to address any concerns for alpha inflation. Added text at end.	Added test so reviewers catch that the sample size can be adjusted after the Expansion Cohort Month 3 analyses to adjust power if necessary or if requested by global regulatory agencies.

Affected Section(s)	Summary of Revisions Made	Rationale
Section 14.2	Changed the figure of the OSDI	Permission was granted by Allergan to use the OSDI in Phase 3. The attachment was updated to match the version Allergan sent to AZURA.

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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 Harmonization Good Clinical Practice (ICH GCP) and all applicable state, local and federal regulatory requirements.

- The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) for review and approval. Approval of both the protocol and the consent form will be obtained before any participant is enrolled.

- Maintain all information supplied by Azura Ophthalmics in confidence and, when this information is submitted to an Institutional Review Board (IRB), Independent Ethics Committee (IEC) or another group, it will be submitted with a designation that the material is confidential.

- I have read this protocol in its entirety and I agree to all aspects.

_____	_____	_____
Investigator Printed Name	Signature	Date

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Study Compound(s):	AZR-MD-001 (Selenium Disulfide)
Phase:	2a
Objectives:	**Cohort 1**: To evaluate the safety and tolerability of 3 different concentrations of AZR-MD-001 ointment/semi-solid drug (0.1%, 0.5% and 1.0%) applied to the lower lid either twice-weekly or once every evening for up to 3 months compared to its vehicle in patients with meibomian gland dysfunction (MGD) and signs and symptoms of evaporative Dry Eye Disease (DED). **Expansion Cohort**: To evaluate the safety, tolerability, and pharmacodynamics of 2 different concentrations of AZR-MD-001 ointment/semi-solid drug (0.5% and 1.0%) applied to the lower lid twice-weekly for up to 6 months compared to its placebo in patients with meibomian gland dysfunction (MGD).
Clinical Hypotheses:	**Cohort 1**: At least 1 concentration of AZR-MD-001 ointment/semi-solid drug (i.e., 0.1%, 0.5%, or 1.0%) has an acceptable safety and tolerability profile following twice-weekly, evening ocular administration for the study treatment duration. At least 1 concentration of AZR-MD-001 ointment/semi-solid drug (i.e. 0.1%, 0.5%, or 1.0%) has an acceptable safety and tolerability profile following once daily, evening ocular administration for the study treatment duration. At least 1 concentration of AZR-MD-001 ointment/semi-solid drug (i.e., 0.1%, 0.5%, or 1.0%) is more effective than vehicle for treating MGD as measured by the meibum gland secretion score (MGS), the number of Meibomian Glands Yielding Liquid Secretion (MGYLS), or the proportion of patients improving on both a gland score (e.g., MGS or MGYLS) and a patient reported outcome measure (e.g., OSDI). At least 1 concentration of AZR-MD-001 ointment/semi-solid drug (i.e., 0.1%, 0.5%, or 1.0%) is more effective than vehicle for treating Evaporative DED as measured by either a sign (e.g., TBUT) or symptom (e.g., eye dryness measured by VAS or OSDI).

Clinical Hypotheses: **Expansion Cohort**:

AZR-MD-001 ointment/semi-solid drug (0.5% or 1.0%) has an acceptable safety and tolerability profile following twice-weekly, evening peri-ocular administration for the study treatment duration.

AZR-MD-001 ointment/semi-solid drug (0.5% or 1.0%) is more effective than placebo for treating MGD as measured by the meibomian glands yielding liquid secretion score (MGYLS).

AZR-MD-001 ointment/semi-solid drug (0.5% or 1.0%) is more effective than placebo for treating symptoms associated with MGD as measured by Total Ocular Surface Disease Index (OSDI) score.

1.2 SCHEMA

Study Design: *Structure:* Multicenter, double-masked, vehicle-controlled, randomized, parallel group study carried out in 2 sequential cohorts - Cohort 1: sequential rising concentrations of AZR-MD-001 ointment/semi-solid drug (i.e., 0.1%, 0.5%, or 1.0%) and AZR-MD-001 vehicle dosed twice-weekly and/or once daily in the evening; Expansion Cohort: parallel doses of two concentrations of AZR-MD-001 ointment/semi-solid drug (i.e., 0.5% and 1.0%) and AZR-MD-001 placebo dosed twice-weekly in the evening.

Cohort 1:

For Cohort 1, 2 sequential groups of 10 patients each will be followed by 2 sequential groups of 20 patients each. All patients will be diagnosed with MGD and signs and symptoms of Evaporative DED and they will be randomly assigned in a 4:1 ratio to receive either a single concentration of AZR-MD-001 ointment/semi-solid drug (i.e., 0.1% for Group 1, 0.5% for Group 2, 1.0% for Group 3, and a 0.5% for Group 4) or AZR-MD-001 vehicle twice weekly for 1 month. The patients in either the active or vehicle groups will further be assigned in a 1:1 ratio to 1 of 2 treatment regiments at the baseline visit: 1) they will receive treatment twice weekly for their entire 3 month treatment period; or 2) they will receive treatment twice weekly for the first month of their treatment period and will then receive treatment once every evening for months 1 to 3 of their treatment period. At the day 14 visit for the 10th patient in groups 1 and 3 and at month 1.5 for group 2, an unmasked Data Review Committee (DRC) will review all the tolerability and safety data for the patients and recommend a starting dose for the next group of patients (i.e., the DRC can elect not to escalate the dose concentration and can instead repeat a dose that has already been tested). At the month 1 visit the investigator will determine, by patient, if the treatment was well tolerated. If the regimen was well tolerated, the patients will continue their assigned dosing regimen (twice weekly dosing) or escalate to once daily dosing, based on their treatment regimen assigned at the baseline visit. If the investigator does not feel it is safe to escalate dosing and it is safe to continue dosing with the current regimen for a particular patient, that patient will be instructed to continue on their current regimen irrespective of treatment assignment.

The DRC will be unmasked to Cohort 1 treatment assignment and will have the freedom to evaluate all data throughout the study. To protect the integrity of the study, members of the DRC will not disclose study information to members of the clinical study team who are overseeing the conduct of the study, study sites, personnel, or patients.

For Cohort 1, a screening visit will be followed by a qualification period where patients will dose with AZR-MD-001 placebo for 14 days. At the end of the qualification period patients who still exhibit signs of MGD and signs and symptoms of Evaporative DED will be enrolled into a 3-month treatment period. The study flow is shown in Figure 1a.

Expansion Cohort:

When the last patient enrolled in Cohort 1 Group 4 completes the month 3 visit, the DRC will evaluate all available safety and efficacy data before recommending initiation of the Expansion Cohort. Each concentration of AZR-MD-001 ointment/semi-solid drug and each frequency of administration will be evaluated for safety and tolerability in Cohort 1 before expansion of that same concentration and dose regimen in the Expansion Cohort. Two concentrations of AZR-MD-001 and a single dosing regimen will be selected for the Expansion Cohort (i.e., twice-weekly).

For the Expansion Cohort, patients with MGD will be randomly assigned in a 1:1:1 ratio to receive either a single concentration of AZR-MD-001 ointment/semi-solid drug (i.e., 0.5% o r 1.0%) or AZR-MD-001 placebo.

A screening visit will be followed by a baseline visit 14 days later (qualification period). At the end of the qualification period patients who still exhibit signs of MGD and who can comply with dosing instructions at the baseline visit will be enrolled into a 6-month treatment period. The study flow is shown in Figure 1b. For the Expansion Cohort, the site staff member performing efficacy and safety measurements will not be involved in drug dispensing or accountability and should remain masked to the treatment received by the patient.

Duration: The total duration of study is approximately 3.5 months (from screening to study completion for Cohort 1) and is approximately 6.5 months (from screening to study completion for the Expansion Cohort).

Study Treatment Groups:

Cohort 1:
AZR-MD-001 ointment/semi-solid drug (i.e., 0.1%, 0.5%, or 1.0%).

Expansion Cohort:
AZR-MD-001 ointment/semi-solid drug (i.e., 0.5% or 1.0%).

Active Period Control:

Cohort 1:
AZR-MD-001 Vehicle

Expansion Cohort:
AZR-MD-001 Placebo

Run-In Period/Sample Dosing:

Cohort 1:
AZR-MD-001 Placebo

Expansion Cohort:
"Vaseline" (AZR-MD-001 Placebo)

Dosage/Dose Regimen: For Cohort 1, study patients will receive a 2-week run-in on AZR-MD-001 placebo to be administered twice-weekly for a period of 2 weeks. For the Expansion Cohort, patients will dose (sample dose) with AZR-MD-001 placebo at the baseline visit to confirm their ability to follow dosing instructions. Upon meeting inclusion/exclusion criteria patients in Cohort 1 will be randomized to AZR-MD-001 ointment/semi-solid drug (i.e., 0.1% 0.5%, or 1.0%) or AZR-MD-001 vehicle administered twice-weekly for one month. If the regimen was well tolerated, the patients will continue their assigned dosing regimen (twice weekly dosing) or escalate to once daily dosing, based on their treatment regimen assigned at the baseline visit. If the investigator does not feel it is safe to escalate doing frequency, patients in Cohort 1 will be asked to continue their twice-weekly dosing regimen. Expansion Cohort patients will receive either AZR-MD-001 ointment/semi-solid drug (i.e., 0.5% or 1.0%) or AZR-MD-001 placebo twice-weekly for 6 months depending upon the dosing regimen recommended by the DRC.

Randomization/Stratification: Patients will be randomized to receive AZR-MD-001 ointment/semi-solid drug (i.e., 0.1%, 0.5% or 1.0%) or AZR-MD-001 vehicle in a 4:1 treatment allocation ratio for Cohort 1. For the Expansion Cohort, patients will be randomized to receive AZR-MD-001 ointment/semi-solid drug (i.e., 0.5% or 1.0%) or AZR-MD-001 placebo in a 1:1:1 treatment allocation ratio. For Cohort 1 the patients in either the active or vehicle groups will further be assigned in a 1:1 ratio to 1 of 2 treatment regiments at the baseline visit: 1) they will receive treatment twice weekly for their entire 3 month treatment period; or 2) they will receive treatment twice weekly for the first month of their treatment period and will then receive treatment once every evening for months 1 to 3 of their treatment period.

For both Cohorts, patients will be stratified by duration of MGD diagnosis (i.e., < 5 years or ≥ 5 years) and baseline MGS score (MGS score of < 6 or MGS score ≥ 6 and ≤ 12) for the qualified eye (i.e., the eye meeting the inclusion/exclusion criteria). If the patient has 2 qualified eyes, the stratification will be based on the eye with the lower numerical MGS score. If the eyes have the same MGS score, then the right eye will be selected as the study eye. For Cohort 1, Groups 3 and 4 enrollment should continue until at least ten patients have a MGS score of $<$ 6 and ten have an MGS score ≥ 6 and ≤ 12.

Visit Schedule:

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

Expansion Cohort: Up to 7 scheduled visits: screening, randomization, day 14, month 1.5, month 3, month 4.5 and month 6 (Exit). For patients who discontinue the study early, the month 6 visit procedures should be completed.

Study Population Characteristics

Number of Patients:

Cohort 1: The total number of randomized patients for Cohort 1 will be approximately 60. Approximately 30 patients should have a baseline MGS score of < 6 and approximately 30 patients should have a baseline MGS score ≥6 and ≤ 12. Based upon data from the LipiFlow® development program a screen failure rate of ~ 40% is expected. Thus, ~84 patients will need to be screened to achieve ~60 patients randomized to treatment.

Expansion Cohort: The total number of randomized patients, with a Total OSDI < 34, for the Expansion Cohort will be approximately 225. Approximately 112 patients should have a baseline MGS score of < 6 and approximately 112 patients should have a baseline MGS score ≥6 and ≤ 12. Based upon data from the LipiFlow® development program a screen failure rate of ~ 40% is expected. Thus, ~315 patients will need to be screened to achieve ~225 patients randomized to treatment with a Total OSDI < 34.

Condition/Disease: Meibomian Gland Dysfunction (MGD) with signs and symptoms of Evaporative DED

Key Inclusion Criteria:

- Male or female, 18 years of age or older at screening visit
- Capable of understanding and willing to provide written informed consent and likely to complete the entire course of study according to instructions
- Written authorization for use and release of health and research study information has been obtained
- Best-corrected visual acuity (BCVA) of 20/40 or better (Snellen equivalent), using the logarithm of the minimum angle of resolution (LogMAR) in each eye at the screening and baseline visits
- Evidence of meibomian gland obstruction (based on a meibomian gland secretion (MGS) score of ≤12 for 15 glands of the lower lid) in both eyes at the screening and baseline visits
- Reported dry eye signs and symptoms within the past 3 months
- Prior to starting screening visit procedures, patients are required to have discontinued:
    - Use of systemic antihistamines or isotretinoin for at least 1 month
    - Anti-inflammatory treatments for DED (e.g., cyclosporine

ophthalmic emulsion [Restasis® or Ikervis®] or lifitegrast ophthalmic solution [Xiidra®]) for at least 3 months
    - All other prescription medications used for dry eye or MGD (e.g., antibiotics, corticosteroids, and non-steroidal anti-inflammatory drugs) for at least 2 weeks
    - LipiFlow® or other lid-heating therapy, meibomian gland probing, or therapeutic gland expression in either eye within 6 months prior to the screening visit
    - All other MGD treatments (e.g., at-home warm compress therapy, eyelid hygiene, eyelid massage, and manual lid expression) for at least 2 weeks

  And
    - All other topical ophthalmic preparations (including artificial tear substitutes) other than the study drops: 72 hours prior to screening visit. If artificial tear substitutes were used within 72 hours of the screening visit the visit should be rescheduled
- Evidence of MGD at the screening and baseline visits:
    - Score ≥6 on the Standard Patient Evaluation of Eye Dryness questionnaire (SPEED)
    - Ocular Surface Disease Index (OSDI) questionnaire score ≥13 and < 34

  And
    - TBUT < 10 seconds in both eyes
- Demonstrated ability to follow dosing instructions at the baseline visit
- A negative pregnancy test result for all women of childbearing potential at the screening visit
- Women of childbearing potential must have a history of bilateral tubal ligation or use oral contraceptives, implants, injectables, transdermal patch, intrauterine device, or double barrier contraceptive for birth control during the study. If these methods of birth control do not apply, woman of childbearing potential must have a monogamous partner who has had a vasectomy at least 3 months before the screening visit. Complete abstinence for four weeks before exposure to study medication, throughout the study, and for at least four weeks after the last dose of study medication is acceptable for study inclusion.

Exclusion Criteria:

- Uncontrolled ocular disease (except for MGD and dry eye disease/keratoconjunctivitis sicca) or uncontrolled systemic disease
- Patient has glaucoma, ocular hypertension, or intraocular pressure (IOP) in either eye at screening ≥24 mm Hg as determined by Goldman applanation tonometry (or a COVID-19 compliant device as required by local governance) or has planned insertion/removal of glaucoma filtration shunts/devices during the study
- Corneal abnormality or disorder that impacts normal spreading of the tear film (keratoconus, pterygia, scarring) or corneal integrity
- BCVA worse than 20/40 in either eye at the screening or baseline visit
- Current use of punctal plugs, anticipated insertion during the study, or a history of punctal cautery in either eye at any time prior to the screening visit or anticipate such a procedure during the study
- Keratoconjunctivitis sicca secondary to destruction of conjunctival goblet cells as occurs with vitamin A deficiency or scarring, such as that with

cicatricial pemphigoid, alkali burns, Stevens-Johnson syndrome, trachoma, or irradiation
- Keratoconjunctivitis sicca secondary to aqueous deficient DED
- Active ocular infection (bacterial, viral, or fungal) at the screening or baseline visits
- Corneal, conjunctival, or eyelid inflammation (including allergic, vernal, or giant papillary conjunctivitis and mucous membrane pemphigoid) that in the judgment of the investigator may interfere with the study results or the ability of patients to complete the treatment period
- Recent (within the past 3 months of the screening visit) ocular surgery, trauma, herpes, or recurrent inflammation
- Contact lens use anticipated during the study
- Periocular application of makeup during the study (e.g., mascara or eyeliner) that the investigator feels could interfere with the signs and symptoms of either MGD or Evaporative DED or tattooing of the lids
- Use of any type of scleral lenses or sealed compartment ocular frames within 2 months of the screening visit, or planned use during the study
- Use prohibited medications (topical, topical ophthalmic, systemic and/or injectable) during the appropriate pre-study wash-out period and during the study
- Unwilling to abstain from the use of systemic medications known to cause dryness for the study duration that is not used on a stable dosing regimen for at least 30 days prior to the baseline visit
- Unwilling to abstain from the use of systemic or topical treatments for MGD or dry eye for the study duration (Including over-the-counter [OTC] artificial tears, ocular lubricants, or dietary supplements known to impact ocular surface health)
- Eyelid abnormalities that affect normal lid function in either eye other than those caused by meibomian gland dysfunction
- Diagnosis of hepatitis C infection, human immunodeficiency virus (HIV) infection, sarcoidosis, amyloidosis, active tuberculosis, or graft versus host disease
- History of anterior segment surgery or trauma that could affect corneal sensitivity (e.g., cataract surgery or any surgery involving a limbal or corneal incision) in either eye within the 12 months prior to the screening visit
- Planned anterior segment surgery (e.g., cataract surgery or any surgery involving a limbal or corneal incision) in either eye during the study period
- Meibography score at the screening visit of 4 (greater than 75% partial glands using the gestalt grading system)
- Corneal staining ≥ 3 (between 33 and 100 dots) using the Oxford Scheme
- Schirmer's tear test without anesthesia ≤ 5 mm in either eye at the baseline visit
- Known allergy or sensitivity to fluorescein, lissamine green, or the study medication or its components
- Use of medicated shampoos containing selenium (e.g., Selsun Blue, Exsel, Selsum, and Seleen) following the screening visit
- Patient is unlikely to follow study instructions or to complete all required study visits or has a condition or situation that in the investigator's opinion, may put the patient at significant risk, may confound the study results, or may interfere significantly with the patient's participation in the study

- Patient is an employee at the investigational site or is related to any member of the study staff
- Patient cannot tolerate multiple blood draws (Cohort 1 only)
- Pregnant, nursing, or females of childbearing potential and not utilizing adequate birth control measures
- Positive urine pregnancy test at the screening visit
- Participation in another clinical trial involving a therapeutic drug or device within the past 30 days
- Enrollment in a previous Stage of the current study or other Azura study using AZR-MD-001
- The patient has a screening laboratory result (e.g., hematology, serum chemistry, or urinalysis) that, in the opinion of the investigator, would make the patient unsuitable for study participation (Cohort 1 only)

Response Measures

Cohort 1:

Primary Efficacy for MGD:

- Change from Baseline to Month 3 in meibum gland secretion score (MGS) (0 to 45 scale)
- Change from Baseline to Month 3 in the number of Meibomian Glands Yielding Liquid Secretion (MGYLS) (0 to 15 scale)
- Proportion of patients with improvement on a gland score (i.e., MGS or MGYLS) and a patient reported outcome (e.g., total OSDI)

Primary Efficacy for Evaporative DED:

- Change from Baseline to Month 3 in Tear Break-up Time (TBUT)
- Change from Baseline to Month 3 in OSDI (considered an endpoint for MGD by FDA in this trial design)
- Change from Baseline to Month 3 in eye dryness measured using a visual analogue scale (VAS)
- Proportion of patients with a Total OSDI change from baseline > 4.5, the known minimally important clinical difference (MICD) for early to moderate disease, at Month 3

Other Efficacy Measures:
MGD:

- Change from Baseline to day 14, month 1 and month 1.5 in MGS (0 to 45 scale)
- MGS score (0 to 45 scale) at each visit
- Change from Baseline to day 14, month 1 and month 1.5 in the number of MGYLS (0 to 15 scale)
- MGYLS (0 to 15 scale) at each visit
- Number of expressible glands yielding clear meibum at day 14, month 1, month 1.5, and month 3
- Eyelid margin erythema/telangiectasias at day 14, month 1, month 1.5, and month 3
- Proportion of patients with a MGS score > 12 at each visit

Evaporative DED

- Change from Baseline to day 14, month 1 and month 1.5 in TBUT
- TBUT at each visit
- Change from Baseline to day 14, month 1 and month 1.5 in Total OSDI
- Total OSDI, OSDI sub-scales, and individual items from the OSDI across visits
- Change from Baseline to day 14, month 1 and month 1.5 in eye dryness measured using VAS
- Eye dryness measured using a visual analogue scale (VAS) at each visit
- Patient ocular symptoms and change from baseline (e.g., blurred vision, burning, eye pain, light sensitivity, itching, foreign body sensation) across visits
- Proportion of patients with a TBUT ≥ 10 seconds at each visit
- Corneal and conjunctival staining (0 to 5 scale) at each visit
- Tear collection (for lipid and other exploratory analyses) (selected sites)
- Proportion of patients with a SPEED < 6 at each visit
- Proportion of patients with a Total OSDI < 13 at each visit
- Proportion of patients with a Total OSDI change from baseline > 4.5, the known minimally important clinical difference (MICD) for early to moderate disease, at each visit

Exploratory Efficacy Measures:

- Change from Baseline to day 14, month 1, month 1.5, and month 3 in Oculus Keratograph 5® measures (selected sites)

Health Outcomes:

- Standard Patient Evaluation of Eye Dryness (SPEED)

Expansion Cohort:

Primary Efficacy Sign for MGD:

- US: Change from Baseline to month 3 in meibomian glands yielding liquid secretion score (MGYLS) (0 to 15 scale)
- Regions requiring longer duration of follow-up (e.g., EU): Change from Baseline to month 6 in meibomian glands yielding liquid secretion score (MGYLS) (0 to 15 scale)

Primary Efficacy Symptom for MGD:

- US: Change from Baseline to month 3 in Total OSDI
- Regions requiring longer duration of follow-up (e.g., EU): Change from Baseline to month 6 in Total OSDI

Other Efficacy Measures:

- Change from Baseline to day14, month 1.5, month 3, month 4.5 and month 6 in MGS (0 to 45 scale)
- MGS score (0 to 45 scale) at each visit
- Proportion of patients with a MGS score > 12 at each visit
- Change from Baseline to day 14, month 1.5, and month 4.5 in the number of Meibomian Glands Yielding Liquid Secretion (MGYLS) (0 to 15 scale)

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

Cohort 1 & Expansion Cohort:

Safety:

- Adverse events
- Vital signs
- Study medication tolerability as measured by the Ocular Comfort Questionnaire (Cohort 1 only)
- Urine pregnancy test
- Best-corrected visual acuity (BCVA; Logarithmic visual acuity chart)
- Biomicroscopy
- Ophthalmoscopy
- Intraocular pressure (IOP)
- Lab analysis of blood and urine (including hematology, chemistry, and urinalysis) (Cohort 1 only)

General Statistical Methods and Types of Analyses:

The safety population will include all treated patients. For safety variables, patients in the safety population will be analyzed by the treatment actually received. The modified intent-to-treat (mITT) population will be comprised of all patients randomized and, who have values at randomization, and at least 1 post-randomization value for MGS at a regularly scheduled visit (i.e., Day 14 or Month 1 (Cohort 1) or Month 1.5 (Expansion Cohort)). All patients in the mITT population will be analyzed by the treatment received. This population will be used for the primary and the secondary efficacy analyses.

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

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

Cohort 1:

Efficacy (MGD): The primary efficacy variables for MGD are change from baseline to month 3 in MGS, number of MGYLS, and the proportion of patients with numerical improvement on a gland score (i.e., MGS or MGYLS) and improvement greater than or equal to the MICD for a patient reported outcome (e.g., 4.5 for Total OSDI). 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 > 12, MGYLS score > 2, or MGYOLS score > 2. The visit for the primary variable is month 3 and the primary analysis population is mITT. Statistical tests will be performed for each AZR-MD-001 group versus vehicle group. Odds ratio along with 95% CI will be obtained by pairwise comparisons of the proportion of responders for each AZR-MD-001 group versus vehicle group using the Logistic Regression method stratifying by baseline MGS score for the qualified eye (i.e., < 6 or ≥ 6 and ≤ 12) and duration of disease (i.e., < 5 years or ≥ 5 years). There will be no alpha adjustment for the multiple tests for the pairwise comparisons.

Efficacy (Evaporative DED): The primary efficacy variables for evaporative DED are change from baseline to month 3 in Tear Break-up Time (TBUT), OSDI, eye dryness measured using a visual analogue scale (VAS), and proportion of patients with improvement greater than or equal to the MICD for a patient reported outcome (e.g., 4.5 for Total OSDI). The visit for the primary variable is month 3 and the primary analysis population is mITT. Statistical tests will be performed for each AZR-MD-001 group versus vehicle group. Pairwise comparisons of the proportion of responders will be performed using the CMH method stratifying by

duration of disease. There will be no alpha adjustment for the multiple tests for the pairwise comparisons.

A patient will be considered to be an evaporative DED responder at a post-randomization visit if TBUT > 10 seconds, a Schirmer's test ≥ 10 mm, a Total OSDI < 13, a SPEED Score < 6, or an Average VAS or Worst VAS score decreased by ≥ 5 is observed.

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.

Expansion Cohort:

Primary Efficacy (MGD):
The primary efficacy sign for MGD is change from baseline in MGYLS. The visit for the primary variable is month 3 for the US and month 6 for regions where the longer follow-up is required (such as in EU). The primary analysis population is mITT. Statistical testing will be performed for the AZR-MD-001 group versus placebo group.

The primary efficacy symptom for MGD is change from baseline in Total OSDI. The visit for the primary variable is month 3 for the US and month 6 for regions where the longer follow-up is required. The primary analysis population is mITT. Statistical testing will be performed for the AZR-MD-001 group versus placebo group.

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

Cohort 1:

Sample Size Calculation: The sample size is determined empirically.

Interim Analysis: Interim database locks will be performed when the 10th patient in Cohort 1, Group 3 exits the study (First Interim Analysis) and when the last patient enrolled in Cohort 1, Group 4 exits the study (Second Interim Analysis). Only data collected up to the last patient exiting the study from Cohort 1, Group 3 will be included in the first data analysis set. All ongoing patients in Cohort 1, Group 4 will remain masked until the second Interim Analysis.

A second interim analysis is planned after the final patient from Cohort 1 exits the study (Cohort 1, Group 4). Outcomes from this analysis will assist in the

confirmation of the study drug concentration and frequency to be used for the Expansion Cohort.

Expansion Cohort:

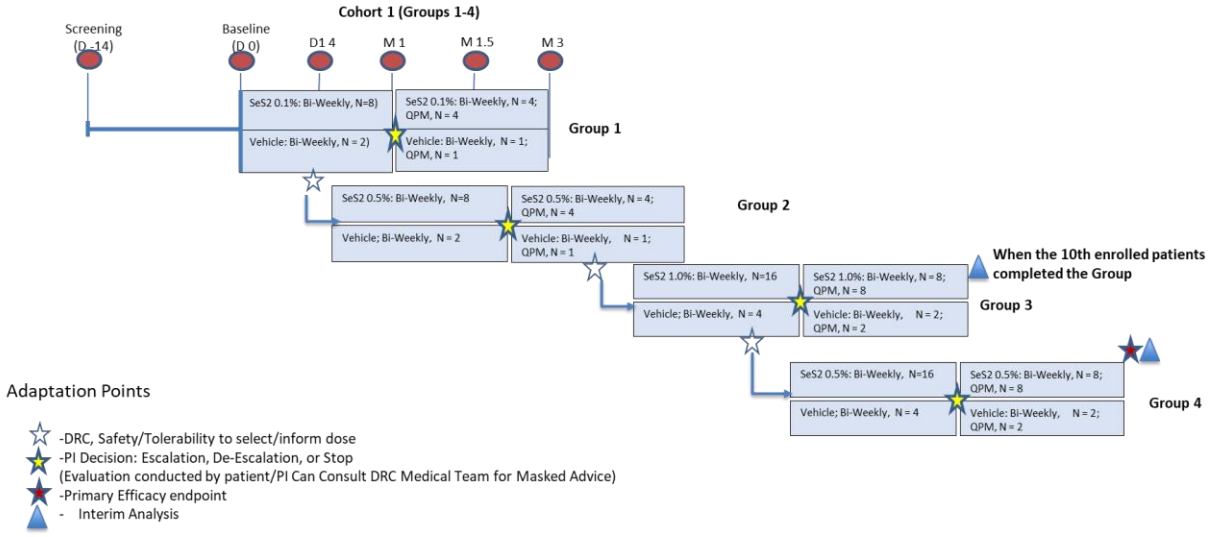
Sample Size Calculation: Estimates for sample size calculations are from the final Cohort 1 interim analysis from Azura Clinical Protocol AZ201801. The mean response of 0.77 and a standard deviation for MGYLS of 2.28 units was observed for control and a mean response of 2.77 units and a standard deviation for MGYLS of 3.35 units was observed for AZR-MD-001 0.5% . A sample size of 45 subjects per group will have 90% power to detect a difference of 2.0 units between the active treatment group and the placebo group using a two-sample t-test at a significance level of 0.05. The standard deviation for Total OSDI was 6.31 units for control and 8.34 units for the high dose. A sample size of 58 subjects per group will have 90% power to detect a difference of 4.52 units between the active treatment group and the control group using a two-sample t-test at a significance level of 0.05. To allow for additional site to site variability the sample size per group will be increased to approximately75 patients.

Multiplicity Consideration: To address the multiple primary endpoints defined in this study, the primary endpoints have been prioritized into a hierarchical structure. For example, in order to test the primary symptom endpoint of Total OSDI, the primary sign endpoint of MGYLS must be statistically significantly higher in the AZR-MD-001 treatment group compared to the vehicle treatment group using a two-sided significance level of 0.05. The final order of the endpoints will be defined in the Statistical Analysis Plan (SAP) prior to unmasking the study. Using this strategy, the family-wise Type I error rate will be maintained at the 0.05 significance level for the two primary endpoints.

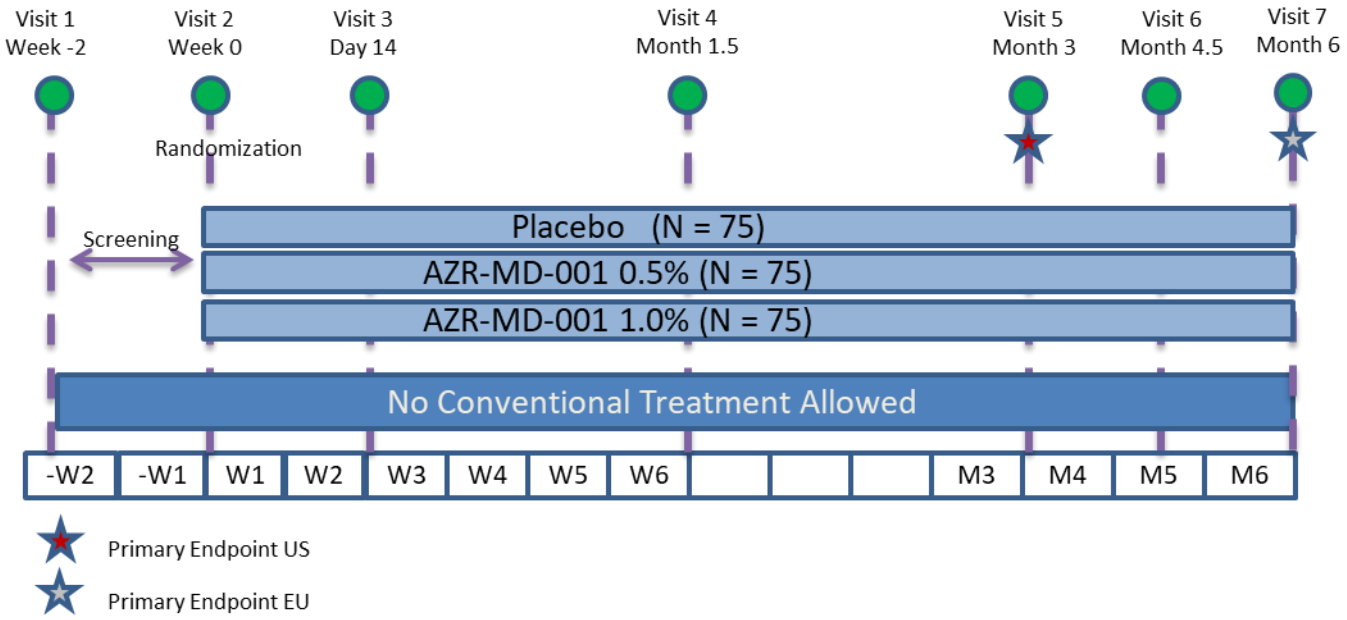
Interim Analysis: An interim analysis (Primary Endpoint for the U.S.) is planned after the final enrolled patient completes the month 3 visit. Only an independent biostatistician will be unblinded to the treatment patients actually received and only summary efficacy and safety tables will be provided. Outcomes from this analysis will assist in the confirmation of the study power calculations and potentially as part of a rolling submission to global regulatory agencies.

Figure 1 **Study Flow – Multicenter, double-masked, vehicle-controlled, randomized, parallel group study carried out in 2 sequentially overlapping cohorts**

a: Cohort 1:



b: Expansion Cohort:



The primary endpoints for the US will serve as an Interim Analyses for the Month 6 primary endpoints. The sample size may be adjusted for power or to address any concerns for alpha inflation.

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

Table 1 Schedule of Visits and Procedures

Study Period	**Qualification**		**Double-Masked Period**					
NOTE: The recommended order for the procedures to be followed appears in the Procedure Manual	Screening [a] (Day -14)	Baseline Day 0 Randomization	Day 14	Month 1 (Coh.1 only)	Month 1.5	Month 3 (Exit Coh.1)	Month 4.5 (Expan.)	Month 6 (Exit Expan.)
Visit Window	*± 2 Days*	N/A	*± 2 Days*	*± 7 Days*	*± 7 Days*	*± 2 Days*	*± 7 Days*	*± 2 Days*
Informed consent/authorization	X							
Contact IVRS/IWRS for patient number assignment (screening number)	X							
Demographics (including height and weight)	X							
Inclusion/exclusion criteria	X	X						
Medical and ophthalmic history	X	X						
Medication history	X							
Washout medications	X							
Vital signs (pulse rate, blood pressure)	X	X		X		X		X
Pregnancy test (urine) for female patients [b]	X					X		X
Patient Ocular Symptoms (VAS)	X	X	X	X	X	X	X	X
OSDI	X	X	X	X	X	X	X	X
SPEED	X	X	X	X	X	X	X	X
Best-corrected visual acuity (BCVA)	X[c]	X	X	X	X	X	X	X
Slit-lamp biomicroscopy (includes eyelid margin erythema/telangiectasias and do not touch the	X	X	X	X	X	X	X	X
Oculus Keratograph 5® procedures: interferometry, redness test, and/or lower lid meibography photograph (selected sites) [d]	X	X	X	X	X	X		
LipiView® interferometer (selected sites) [d]	X	X	X	X	X	X		
Tear Break Up Time (TBUT) [g]	X	X	X	X	X	X	X	X
Sodium fluorescein corneal staining, Oxford scale	X	X	X	X	X	X	X	X
Lissamine green conjunctival staining, Oxford scale	X	X	X	X	X	X	X	X

Study Period	**Qualification**		**Double-Masked Period**					
NOTE: The recommended order for the procedures to be followed appears in the Procedure Manual	Screening [a] (Day -14)	Baseline Day 0 Randomization	Day 14	Month 1 (Coh.1 only)	*Month 1.5*	Month 3 (Exit Coh.1)	Month 4.5 (Expan.)	Month 6 (Exit Expan.)
Visit Window	± 2 Days	N/A	*± 2 Days*	*± 7 Days*	*± 7 Days*	*± 2 Days*	*± 7 Days*	*± 2 Days*
Meibomian gland evaluation (MGE) [g]	X	X	X	X	X	X	X	X
Schirmer without anesthesia	X	X		X		X		X
Tear Collection for biomarker analysis (selected sites) [d]		X		X		X		
Intraocular pressure (IOP)	X					X		X
Ophthalmoscopy exam [e]	X					X		X
Meibography	X					X		X
Lab – Blood safety (chemistry , hematology) and urinalysis (Cohort 1 Only)	X					X		
Study medication Tolerability/Comfort Questionnaire (Cohort 1 only) [f]		X	X	X	X	X		
Adverse events/medications/procedures	X	X	X	X	X	X	X	X
Discontinue concomitant medication(s) impacting inclusion/exclusion	X							
Contact IVRS/IWRS for patient randomization number		X						
Medication dispensing/return	X (Cohort 1)	X		X	X	X	X	X
Physician Observation of Drug Application	X (Cohort 1)	X						

BCVA = Best Corrected Visual Acuity; Coh. = Cohort; Expan. = Expansion; OSDI = Ocular Surface Disease Index; SPEED = Standard Patient Evaluation of Eye Dryness; TBUT = tear break up time; VAS = Visual Analogue Scale; PM = Evening, Month = 28 days

a Screening diagnostic procedures are not required to be performed on the same day, and can be performed across multiple days from days -14 to -2. At screening, patients will be asked to report use of artificial tears and all other treatments for MGD and/or DED. Patients should wash out from all medication listed in the inclusion/exclusion criteria. The screening period includes a 2-week, run-in with AZR-MD-001 placebo for Cohort 1. Patients who are re-enrolled following an initial screen failure will receive a new screening number upon re-screen (i.e., sites should not reuse the old number).
b For females of childbearing potential.
c Manifest refraction performed at screening will be used at each visit to obtain BCVA.
d Performed as a sub-study by selected sites and patients and approved by study sponsor.
e Ophthalmoscopy examination will be dilated at screening and undilated for study exit unless dilation is necessary
f Instill dose of medication after completing safety/efficacy measures and ~5 minutes before medication tolerability assessment (see Procedure Manual for more detail).
g TBUT and MGE should be performed by the same individual for a given patient. For the Expansion Cohort, *the individual performing the measurement will not be involved in drug dispensing or accountability and should remain masked to the treatment received by the patient*.

2 INTRODUCTION

2.1 BACKGROUND

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

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

2.2 STUDY RATIONAL & KNOWN POTENTIAL BENEFITS

The recognition that terminal duct obstruction from hyperkeratinization of the ductal epithelium on meibomian glands is a core mechanism behind meibomian gland dysfunction (MGD) is consistent with clinical experience demonstrating that effective treatments for MGD require resolution of ductal obstruction and evacuation of glandular contents (Nichols et al, 2011; Lane et al, 2012; Blackie et al, 2015). Warm compresses and thermal/mechanical 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.

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

1) Improvement in the meibum gland score (MGS) (0 to 45 scale);
2) Increases in the number of meibomian glands yielding liquid secretion (MGYLS) (0 to 15 scale);
3) Increased Tear Break-up Time (TBUT); and
4) Improved Total OSDI, SPEED and eye dryness scores (measured using a visual analogue scale [VAS]) (Blackie et al, 2015).

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

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

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

Based upon positive efficacy and safety results from clinical study MGSS1 for the ocular application of selenium disulfide 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.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Selenium sulfide is used as an anti-fungal and anti-dandruff ingredient in commercially available shampoo (i.e., Selsun Blue, Exsel, 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.

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

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

Group n°	Treatment (concentration)	Dose Regimen (Right eye)	Number of animals		
			Series 1	Series 2	Series 3
4	AZR149 (0.5% - 5 µL)	Twice weekly (q3.5d ± 1d) ocular topical application from Day 1 to Day 7 onto the lower lid margin	--	3	--
3	AZR150 (1% - 5 µL)		--	3	--
1	AZR141 (2.5% - 25 µL)		3	--	--
2	AZR140 (Placebo - 25 µL)		3	--	--
8	AZR149 (0.5% - 5 µL)	Once daily ocular topical application from Day 1 to Day 7 onto the lower lid margin	--	6	--
7	AZR150 (1% - 5 µL)		--	3	--
5	AZR141 (2.5% - 25 µL)		6	--	--
6	AZR140 (Placebo - 25 µL)		6	--	--
9	AZR149 (0.5% - 5 µL)	Twice daily (7h ± 1h) ocular topical application from Day 1 to Day 7 onto the lower lid margin	--	6	--
10	AZR141 (2.5% - 5 µL)	Once daily ocular topical application from Day 1 to Day 7 onto the lower lid margin	--	--	3*
*Note 1: These 3 animals were already treated once daily with AZR149 0.5% during 7 days before joining the series 3 (without wash-out period).					

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

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

2.3.2 ASSESSMENT OF POTENTIAL RISKS AND BENIFITS

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

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

3 OBJECTIVES AND ENDPOINTS

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

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR
Cohort 1 and Expansion Cohort		
To evaluate the safety, tolerability, and pharmacodynamics of different concentrations of AZR-MD-001 ointment/semi- solid drug applied to the lower lid either twice-weekly or once every evening for up to 3 months (Cohort 1) or up to 6 months (Expansion Cohort). Systemic pharmacokinetics (PK) will only be measured in Cohort 1.	**Safety/Adverse Events**: • Incidence rates of each treatment-emergent adverse event summarized by primary system organ class and preferred term. • Tables for all treatment- emergent adverse events regardless of causality. • Tables for all treatment- emergent adverse events considered to be treatment- related. • Shift tables for safety variables (e.g., IOP, biomicroscopy, and ophthalmoscopy). **Signal of Efficacy (Cohort 1):** *Primary Efficacy for MGD:* • Change from Baseline to Month 3 in meibum gland secretion score (MGS) (0 to 45 scale) • Change from Baseline to Month 3 in the number of Meibomian Glands Yielding Liquid Secretion (MGYLS) (0 to 15 scale) • Proportion of patients with improvement on a gland score (i.e., MGS or MGYLS) and a patient reported outcome (e.g., total OSDI) *Primary Efficacy for Evaporative DED:* • Change from Baseline to Month 3 in Tear Break-up Time (TBUT) • Change from Baseline to Month 3 in OSDI • Change from Baseline to Month 3 in eye dryness measured using a visual analogue scale (VAS) • Proportion of patients with a Total OSDI change from baseline > 4.5, the known minimally important clinical difference (MICD) for early to moderate disease, at Month 3	The endpoints for safety and tolerability are all commonly used in ophthalmic drug trials. Consistently observed benefits for devices designed to treat glandular obstruction include: • Improvement in the meibum gland secretion score (MGS) (0 to 45 scale); • Increases in the number of meibomian glands yielding liquid secretion (MGYLS) (0 to 15 scale); • Increased Tear Break-up Time (TBUT); and • Improved Total OSDI, SPEED and eye dryness scores (measured using a visual analogue scale [VAS]) (Blackie et al, 2015). .

	Signal of Efficacy (Expansion Cohort): See Response Measures in the synopsis *Primary Efficacy Sign for MGD:* • US : Change from Baseline to month 3 in meibomian glands yielding liquid secretion score (MGYLS) (0 to 15 scale) • Regions requiring longer duration of follow-up (e.g., EU): Change from Baseline to month 6 in meibomian glands yielding liquid secretion score (MGYLS) (0 to 15 scale) *Primary Efficacy Symptom for MGD:* • US: Change from Baseline to month 3 in Total OSDI • Regions requiring longer duration of follow-up (e.g., EU): Change from Baseline to month 6 in Total OSDI	

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a multicenter, double-masked, vehicle-controlled, randomized, parallel group study carried out in 2 sequential cohorts: Cohort 1: sequential rising concentrations of AZR-MD-001 ointment/semi-solid drug (i.e., 0.1%, 0.5% or 1.0%) and AZR-MD-001 vehicle dosed twice-weekly and/or once daily in the evening; Expansion Cohort: parallel doses of two concentrations of AZR-MD-001 ointment/semi-solid drug (i.e., 0.5% or 1.0%) and AZR-MD-001 placebo dosed twice-weekly in the evening.

Cohort 1:

For Cohort 1, 2 sequential groups of 10 patients each will be followed by 2 sequential groups of 20 patients each. All patients will be diagnosed with MGD and signs and symptoms of Evaporative DED and they will be randomly assigned in a 4:1 ratio to receive either a single concentration of AZR-MD-001 ointment/semi-solid drug (i.e., 0.1% for Group 1, 0.5% for Group 2, 1.0% for Group 3, and a 0.5% for Group 4) or AZR-MD-001 vehicle twice weekly for 1 month. The patients in either the active or vehicle groups will further be assigned in a 1:1 ratio to 1 of 2 treatment regiments at the baseline visit: 1) they will receive treatment twice weekly for their entire 3 month treatment period; or 2) they will receive treatment twice weekly for the first month of their treatment period and will then receive treatment once every evening for months 1 to 3 of their treatment period. At the day 14 visit for the 10th patient in groups 1 and 3 and at month 1.5 for group 2, an unmasked Data Review Committee (DRC) will review all the tolerability and safety data for the patients and recommend a starting dose for the next group of patients (i.e., the DRC can elect not to escalate the dose concentration and can instead repeat a dose that has already been tested). At the month 1 visit the investigator will determine, by patient, if the treatment was well tolerated. If the regimen was well tolerated, the patients will continue their assigned dosing regimen (twice weekly dosing) or escalate to once daily dosing, based on their treatment regimen assigned at the baseline visit. If the investigator does not feel it is safe to escalate dosing and it is safe to continue dosing with the current regimen for a particular patient, that patient will be instructed to continue on their current regimen irrespective of treatment assignment.

The DRC will be unmasked to Cohort 1 treatment assignment and will have the freedom to evaluate all data throughout the study. To protect the integrity of the study, members of the DRC will not disclose study information to members of the clinical study team who are overseeing the conduct of the study, study sites, personnel, or patients.

For Cohort 1, a screening visit will be followed by a qualification period where patients will dose

with AZR-MD-001 placebo for 14 days. At the end of the baseline period patients who still exhibit signs of MGD and signs and symptoms of Evaporative DED will be enrolled into a 3-month treatment period. The study flow is shown in Figure 1a.

Expansion Cohort:

When the last patient enrolled in Cohort 1, Group 4 completes the month 3 visit, the DRC will evaluate all available safety and efficacy data before recommending initiation of the Expansion Cohort. Each concentration of AZR-MD-001 ointment/semi-solid drug and each frequency of administration will be evaluated for safety and tolerability in Cohort 1 before expansion of that same concentration and dose regimen in the Expansion Cohort. Two concentrations of AZR-MD-001 and a single dosing regimen will be selected for the Expansion Cohort (i.e., twice-weekly).

For the Expansion Cohort, patients with MGD will be randomly assigned in a 1:1:1 ratio to receive either a single concentration of AZR-MD-001 ointment/semi-solid drug (i.e., 0.5% or 1.0%) or AZR-MD-001 placebo.

A screening visit will be followed by a baseline visit 14 days later (qualification period). At the end of the qualification period patients who still exhibit signs of MGD and who can comply with dosing instructions at the baseline visit will be enrolled into a 6-month treatment period. The study flow is shown in Figure 1b.

The total duration of study is approximately 3.5 months (from screening to study completion) for Cohort 1 and is approximately 6.5 months (from screening to study completion) for the Expansion Cohort.

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 dosed up to a total daily dose of 1.0% has also been applied to the lid margin as a treatment for seborrheic blepharitis (Bahn, 1954, see the Investigator's Brochure for more detail).

Azura Ophthalmics is evaluating AZR-MD-001 ointment/semi-solid drug (selenium disulfide) as a potential treatment for MGD and associated evaporative DED. Selenium sulfide exists as a

mixture of selenium monosulfide and selenium disulfide. AZR-MD-001 uses the same API as commercially available marketed products (i.e., Selsun Blue, Exsel, Selsum, and Seleen). In these shampoos selenium disulfide is used as an anti-fungal and anti-dandruff ingredient. It is marketed at a 1% concentration in non-prescription products and at a 2.5% concentration in prescription products.

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

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

Based upon positive results from clinical study MGSS1 and good safety and tolerability across 5 clinical studies with doses of selenium disulfide up to 2.5% twice weekly or 0.5% BID, 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. Azura Ophthalmics believes that the use of topical ophthalmic selenium sulfide in over 300 patients corroborated by preclinical ocular tolerability results in female albino rabbits with exaggerated dosing up to 2.5% selenium disulfide, once daily supports the proposed adaptive Phase 2 study design.

4.3 DATA REVIEW COMMITTEE (DRC)

A DRC consisting of physicians and trained study personnel, in addition to ad hoc internal/external experts, will assess study treatment effects. The composition, qualifications and activities of the committee are described in the DRC Charter. The DRC will review available data to determine the appropriateness of continuing dosing and enrollment in Cohort 1. Based on review of data from all executed Cohort 1 groups, the DRC will recommend whether to proceed to the Expansion Cohort and the dose levels to be employed. The DRC may recommend at any time during Cohort 1 to de-escalate, delay, or to stop patient recruitment. The number of treatment groups, doses, and number of patients pergroup in the Expansion Cohort will be based on recommendations by the DRC following review of available Cohort 1 data. Details of the planned analyses will be provided in the DRC analysis plan. The DRC may also request ad-hoc review of masked or unmasked data at any time throughout the course of Cohort 1 to evaluate new findings or recommend changes to study progression.

4.4 END OF STUDY DEFINITION

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

5 STUDY POPULATION

The study will consist of patients with Meibomian Gland Dysfunction (MGD) with signs and symptoms of Evaporative DED.

5.1 INCLUSION CRITERIA

- Male or female, 18 years of age or older at screening visit
- Capable of understanding and willing to provide written informed consent and likely to complete the entire course of study according to instructions
- Written authorization for use and release of health and research study information has been obtained
- Best-corrected visual acuity (BCVA) of 20/40 or better (Snellen equivalent), using the logarithm of the minimum angle of resolution (LogMAR) in each eye at the screening and baseline visits
- Evidence of meibomian gland obstruction (based on a meibomian gland secretion (MGS) score of ≤12 for 15 glands of the lower lid) in both eyes at the screening and baseline visits
- Reported dry eye signs and symptoms within the past 3 months
- Prior to starting screening visit procedures, patients are required to have discontinued:
    - Use of systemic antihistamines or isotretinoin for at least 1 month
    - Anti-inflammatory treatments for DED (e.g., cyclosporine ophthalmic emulsion [Restasis® or Ikervis®] or lifitegrast ophthalmic solution [Xiidra®]) for at least 3 months
    - All other prescription medications used for dry eye or MGD (e.g., antibiotics, corticosteroids, and non-steroidal anti-inflammatory drugs) for at least 2 weeks
    - LipiFlow® or other lid-heating therapy, meibomian gland probing, or therapeutic gland expression in either eye within 6 months prior to the screening visit
    - All other MGD treatments (e.g., at-home warm compress therapy, eyelid hygiene, eyelid massage, and manual lid expression) for at least 2 weeks

    And
    - All other topical ophthalmic preparations (including artificial tear substitutes) other than the study drops: 72 hours prior to screening visit. If artificial tear substitutes were used within 72 hours of the screening visit the visit should be rescheduled
- Evidence of MGD at the screening and baseline visits:
    - Score ≥6 on the Standard Patient Evaluation of Eye Dryness questionnaire (SPEED)
    - Ocular Surface Disease Index (OSDI) questionnaire score ≥13 and < 34

    And
    - TBUT < 10 seconds in both eyes

- Demonstrated ability to follow dosing instructions at the baseline visit
- A negative pregnancy test result for all women of childbearing potential at the screening visit
- Women of childbearing potential must have a history of bilateral tubal ligation or use oral contraceptives, implants, injectables, transdermal patch, intrauterine device, or double barrier contraceptive for birth control during the study. If these methods of birth control do not apply, woman of childbearing potential must have a monogamous partner who has had a vasectomy at least 3 months before the screening visit. Complete abstinence for four weeks before exposure to study medication, throughout the study, and for at least four weeks after the last dose of study medication is acceptable for study inclusion.

5.2 EXCLUSION CRITERIA

- Uncontrolled ocular disease (except for MGD and dry eye disease/keratoconjunctivitis sicca) or uncontrolled systemic disease
- Patient has glaucoma, ocular hypertension, or intraocular pressure (IOP) in either eye at screening ≥24 mm Hg as determined by Goldman applanation tonometry (or a COVID-19 compliant device as required by local governance) or has planned insertion/removal of glaucoma filtration shunts/devices during the study
- Corneal abnormality or disorder that impacts normal spreading of the tear film (keratoconus, pterygia, scarring) or corneal integrity
- BCVA worse than 20/40 in either eye at the screening or baseline visit
- Current use of punctal plugs, anticipated insertion during the study, or a history of punctal cautery in either eye at any time prior to the screening visit or anticipate such a procedure during the study
- Keratoconjunctivitis sicca secondary to destruction of conjunctival goblet cells as occurs with vitamin A deficiency or scarring, such as that with cicatricial pemphigoid, alkali burns, Stevens-Johnson syndrome, trachoma, or irradiation
- Keratoconjunctivitis sicca secondary to aqueous deficient DED
- Active ocular infection (bacterial, viral, or fungal) at the screening or baseline visits
- Corneal, conjunctival, or eyelid inflammation (including allergic, vernal, or giant papillary conjunctivitis and mucous membrane pemphigoid) that in the judgment of the investigator may interfere with the study results or the ability of patients to complete the treatment period
- Recent (within the past 3 months of the screening visit) ocular surgery, trauma, herpes, or recurrent inflammation
- Contact lens use anticipated during the study
- Periocular application of makeup during the study (e.g., mascara or eyeliner) that the investigator feels could interfere with the signs and symptoms of either MGD or Evaporative DED or tattooing of the lids
- Use of any type of scleral lenses or sealed compartment ocular frames within 2 months of the screening visit, or planned use during the study
- Use prohibited medications (topical, topical ophthalmic, systemic and/or injectable)

during the appropriate pre-study wash-out period and during the study.

- Unwilling to abstain from the use of systemic medications known to cause dryness for the study duration that is not used on a stable dosing regimen for at least 30 days prior to the baseline visit.
- Unwilling to abstain from the use of systemic or topical treatments for MGD or dry eye for the study duration (Including over-the-counter [OTC] artificial tears, ocular lubricants, or dietary supplements known to impact ocular surface health)
- Eyelid abnormalities that affect normal lid function in either eye other than those caused by meibomian gland dysfunction
- Diagnosis of hepatitis C infection, human immunodeficiency virus (HIV) infection, sarcoidosis, amyloidosis, active tuberculosis, or graft versus host disease
- History of anterior segment surgery or trauma that could affect corneal sensitivity (e.g., cataract surgery or any surgery involving a limbal or corneal incision) in either eye within the 12 months prior to the screening visit
- Planned anterior segment surgery (e.g., cataract surgery or any surgery involving a limbal or corneal incision) in either eye during the study period
- Meibography score at the screening visit of 4 (greater than 75% partial glands using the gestalt grading system)
- Corneal staining ≥ 3 (between 33 and 100 dots) using the Oxford Scheme
- Schirmer's tear test without anesthesia ≤ 5 mm in either eye at the baseline visit
- Known allergy or sensitivity to fluorescein, lissamine green, or the study medication or its components
- Use of medicated shampoos containing selenium (e.g., Selsun Blue, Exsel, Selsum, and Seleen) following the screening visit
- Patient is unlikely to follow study instructions or to complete all required study visits or has a condition or situation that in the investigator's opinion, may put the patient at significant risk, may confound the study results, or may interfere significantly with the patient's participation in the study
- Patient is an employee at the investigational site or is related to any member of the study staff
- Patient cannot tolerate multiple blood draws (Cohort 1 only)
- Pregnant, nursing, or females of childbearing potential and not utilizing adequate birth control measures
- Positive urine pregnancy test at the screening visit
- Participation in another clinical trial involving a therapeutic drug or device within the past 30 days
- Enrollment in a previous Stage of the current study or other Azura study using AZR-MD-001
- The patient has a screening laboratory result (e.g., hematology, serum chemistry, or urinalysis) that, in the opinion of the investigator, would make the patient unsuitable for study participation (Cohort 1 only)

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 screening visit or during the study.
- Patients must have discontinued (2 weeks before screening) and be willing to remain off other MGD treatments (e.g., at-home warm compress therapy, eyelid hygiene, eyelid massage, and manual lid expression) during the study.
- Patients should not have punctal plugs or plan to have punctal plugs inserted during the study.
- Patients must have discontinued (1 month before screening) and be willing to remain off antihistamines or isotretinoin during the study.
- Patients must have discontinued (3 months before screening) and be willing to remain off Anti-inflammatory treatments for DED (e.g., cyclosporine ophthalmic emulsion [Restasis® 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 screening visit.
- Patients must have discontinued (2 weeks before screening) and be willing to remain off all other prescription medications used for dry eye or MGD (e.g., antibiotics, corticosteroids, and non-steroidal anti-inflammatory drugs) during the study.
- Patients must have discontinued all other topical ophthalmic preparations (including artificial tear substitutes) other than the study drops 72 hours prior to the screening visit. If artificial tear substitutes were used within 72 hours of the screening visit the visit should be rescheduled.
- Patients must avoid periocular application of makeup during the study (e.g., mascara or eyeliner) that the investigator feels could interfere with the signs and symptoms of either MGD or Evaporative DED or tattooing of the lids

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. Individuals who do not meet the criteria for participation in the trial in Cohort 1 but who may be eligible under the revised criteria for the Expansion cohort may be re-screened 1 additional time. Rescreened participants should be assigned a new screening number and the original number should not be reused.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Cohort 1: The total number of randomized patients for the study Cohort 1 will be approximately 60. Approximately 30 patients should have a baseline MGS score of < 6 and approximately 30 patients should have a baseline MGS score ≥6 and ≤ 12. Based upon data from the LipiFlow® development program a screen failure rate of ~ 40% is expected. Thus, ~84 patients will need to be screened to achieve ~60 patients randomized to treatment.

Expansion Cohort: The total number of randomized patients, with a Total OSDI < 34, for the Expansion Cohort will be approximately 225. Approximately 112 patients should have a baseline MGS score of < 6 and approximately 112 patients should have a baseline MGS score ≥6 and ≤ 12. Based upon data from the LipiFlow® development program a screen failure rate of ~ 40% is expected. Thus, ~315 patients will need to be screened to achieve ~225 patients randomized to treatment with a Total OSDI < 34.

Patients who have not been dosed with study drug can be reallocated from discontinued groups to increase the power in Cohort 1 groups that are continued at the discretion of the DRC.

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

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

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

All concentrations of AZR-MD-001 Ophthalmic Ointment contain the drug product, AZR-MD-001 (0.1%, 0.5%, or 1.0%), and suitable excipient. The only excipient in the formulation is Petrolatum white. The AZR-MD-001 placebo to be used during the 14 day run-in period between the Screening and Baseline visits for Cohort 1 and during the treatment period for the Expansion Cohort contains only Petrolatum white. The AZR-MD-001 placebo (labelled "Vaseline") to be used at the Baseline visit of the Expansion Cohort contains only Petrolatum white. The AZR-MD-001 vehicle to be used during the active treatment period between the Baseline and Month 3 visits for Cohort 1 contains only Petrolatum white and yellow iron oxide to match both the texture and colour of the active product. The formulations will be supplied in identical unit dose containers (see Table 6.1.1–1).

Table 6.1.1–1 Investigational Product and Packaging / Labelling Characteristics

	Investigational Product		
Product name:	AZR-MD-001 (Selenium disulfide API in ointment/semi-solid Petrolatum white)	Vehicle (Cohort 1 only)	Placebo (Cohort 1& Expansion)
Formulation description:	AZR-MD-001 is an orange opaque dispersion ointment with an odour faintly of hydrogen sulfide	Ointment will match AZR-MD-001's texture and approximate its orange colour	Ointment will match AZR-MD-001's texture
Dosage form:	Ophthalmic ointment/semi-solid drug	Ophthalmic ointment/semi-solid drug	Ophthalmic ointment/semi-solid drug
Unit dose strength(s)/Dosage level(s):	Active: 0.1%/5mg (Cohort 1) 0.5%/5mg (Cohort 1 & Expansion) 1.0%/5mg(Cohort 1 & Expansion) 2.5%/5mg (Not tested, but available)	Vehicle Yellow iron oxide (colour)	Placebo Petrolatum, white
Route of Administration	Topical	Topical	Topical
Dosing instructions:	Store between 2 – 8°C until opened. **Refrigerate**. Do not **freeze**. Discard 4 weeks (30 days) after opening. Protect from light	Store between 2 – 8°C until opened. **Refrigerate**. Do not **freeze**. Discard 4 weeks (30 days) after opening. Protect from light	Store between 2 – 8°C until opened. **Refrigerate**. Do not **freeze**. Discard 4 weeks (30 days) after opening. Protect from light
Physical description:	An orange opaque ointment packaged in a multi-use tube	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	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.	Each container/tube is placed in an individual package and appropriately labelled.

API = Active pharmaceutical ingredient

6.1.2 SELECTION OF DOSES IN THE STUDY

Azura Ophthalmics is further evaluating the safety, tolerability and effectiveness of AZR-MD-001 ointment/semi-solid drug, surfactant free, in topical ophthalmic concentrations between 0.1% and 2.5% based upon positive results from clinical study MGSS1 using a 2.5% selenium disulfide concentration, published clinical studies (see the Investigators' Brochure for more detail) demonstrating the safe and effective treatment of seborrheic blepharitis with selenium sulfide exposures up to 0.5% twice-daily, pre-clinical safety data with exaggerated dosing up to 2.5% with the clinical formulation and the maximum concentration fulfils the criteria for a low risk Schedule 2 (Pharmacy medicine) classification as specified in the Australian Poisons Standard October 2017 (Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP), No. 18) (see Table 6.1.2-1).

Table 6.1.2-1: Australian Poisons Standard for Selenium

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

Azura Ophthalmics believes that the use of AZR-MD-001 ointment/semi-solid drug with selenium disulfide in a concentration range between 0.1% to 2.5% is likely to safely and effectively treat MGD with or without associated evaporative dry eye disease.

6.1.3 DOSING AND ADMINISTRATION

For Cohort 1, 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 run-in and post-randomization visits. At these visits, each patient will be asked to stay at the site for 30 minutes after study drug administration. No other dosing will be done in office as the product will be dosed in the evening only.

For the Expansion Cohort, the study medication will be self-administered by the patient at the study site after all procedures have been completed for the baseline visit only using "Vaseline". At this visit, each patient will be asked to stay at the site for 30 minutes after study drug administration. No other dosing will be done in office as the product will be dosed in the evening only.

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 (Cohort 1 and Expansion Cohort) or an applicator (Cohort 1 only) 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 assigned treatment 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 30 days and should return used and unused tubes at the next study visit to the study site.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Whilst patients are dosed at site (i.e., Cohort 1 all visits, and practice dose at the baseline visit only of the Expansion Cohort), 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.

Patients will be instructed on proper instillation and storage of study drug at the end of each visit, and will be given written instructions and may also watch an instructional video at the baseline visit. The used study drug tubes will be collected at each visit from baseline up to and including study exit (along with any unused tubes) to assess dosing and symptom assessment compliance. 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.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

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

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

6.2.3 PRODUCT STORAGE AND STABILITY

The study medication must be stored in a secure area at site, 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 account of the study medication received from the supplier. This includes the amount of study medication dispensed to patients, amount of study medication returned to the investigator by the patients, and the amount returned or disposed upon the completion of the study. A detailed inventory must be completed for the study medication.

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

6.2.4 PREPARATION

Patients should let the study tube equilibrate at room temperature below 25°C for up to 15 minutes before dosing. Patients will use the study medication directly from the dose container in accordance with the protocol and should return the dose container to refrigeration between 2 – 8°C following successful dosing. For the next day of dosing, this process should be repeated. This in use pattern should continue for 30 days at which time the dose container should be used for a final day of dosing and then discarded.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

During the Cohort 1 run-in period, the patients will all be supplied with AZR-MD-001 placebo. Patients will be informed that they will receive only placebo during the 2-week run-in period. Patients (or a caregiver) will apply approximately 5 mg using a dosing aid supplied by Azura Ophthalmics. Patients will use their washed index finger or an applicator (Cohort 1 only) 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.

During the Expansion Cohort qualification period, the patients will all be supplied with AZR-MD-001 placebo (“Vaseline”) at the baseline visit (single dose). During the active treatment period, patients (or a caregiver) will apply approximately 5 mg using a dosing aid supplied by Azura Ophthalmics. Patients will use their washed index finger to apply the drug to the tarsus of the lower lid of both eyes in the evening just before bedtime. The patient will then blink several times to transfer a portion of the drug from the lower eyelid to the upper eyelid.

To minimize the risk for noncompliance with the dosing instructions patients enrolled into the

clinical study will be given dosing instructions, will be observed by site personnel applying study placebo at the baseline visit, and will have access to instructional dosing videos. Only patients demonstrating compliance with the provided dosing instructions can be enrolled into the clinical study.

Following the run-in period in Cohort 1, the patient, investigator, site personnel, and the sponsor study team will be masked to the treatment assignment for the 3 month treatment period. All study medication will be provided in identical tubes and cartons to maintain masking of the study. The AZR-MD-001 vehicle was designed to have the same appearance as the active drug.

Following the qualification period in the Expansion Cohort, the patient, staff members performing all safety and efficacy assessments, site personnel (with the exception of designated personnel who are responsible for drug accountability) and the sponsor study team will be masked to the treatment assignment for the 6 month treatment period. All study medication will be provided in identical tubes and cartons to maintain masking of the study. Due to the difference in colour between the active and placebo treatments, which are in opaque tubes, designated personnel who are responsible for drug accountability will not perform any safety or efficacy assessments and will not discuss assigned treatment(s) with staff members who are performing safety or efficacy assessments.

For Cohort 1, patients will be randomized to receive AZR-MD-001 ointment/semi-solid drug (i.e., 0.1%, 0.5% or 1.0%) or AZR-MD-001 vehicle in a 4:1 treatment allocation ratio. For the Expansion Cohort, patients will be randomized to receive AZR-MD-001 ointment/semi-solid drug (i.e., 0.5% or 1.0%) or AZR-MD-001 placebo in a 1:1:1 ratio on day 0.

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

The automated IWRS system will provide the site with the specific medication kit number(s) to use for each qualified patient at the baseline visit. At the baseline/randomization visit, patients meeting all inclusion/exclusion criteria, will be placed in one of the strata for either Cohort 1 or the Expansion Cohort. A randomization number will be assigned to each patient corresponding to the treatment arm they are assigned to. The numbers will be assigned sequentially in order of enrollment within the patient's stratum. The IWRS system will report a medication kit number to use for each patient corresponding to the randomization number.

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

6.4 CONCOMITANT THERAPY

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

6.4.1 RESCUE MEDICINE

In the event that rescue medication is required for worsening signs or symptoms of MGD and/or dry eye disease 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.

Dosing Hylo-Forte® (or an equivalent product) approximately 5 minutes before study ointment has been reported to enhance either the safety or tolerability of AZR-MD-001.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

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

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

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

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

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

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

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

7.3 LOST TO FOLLOW-UP

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

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 COHORT 1: PRIMARY EFFICACY MEASURES

Primary efficacy measures are divided into endpoints for MGD and endpoints for evaporative dry eye (EDE). The primary efficacy measures for MGD are change from baseline to Month 3 in meibum gland secretion score (MGS) (0 to 45 scale), change from baseline to Month 3 in the number of Meibomian Glands Yielding Liquid Secretion (MGYLS) (0 to 15 scale), and the

proportion of patients improving on both a gland score (e.g., MGS or MGYLS) and a patient reported outcome measure (e.g., OSDI). 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 > 12, MGYLS score > 2, or MGYOLS score > 2. The primary efficacy measures for EDE are change from baseline to Month 3 in Tear Break-up Time (TBUT), change from Baseline to Month 3 in OSDI measures, change from baseline to Month 3 in eye dryness measured using a visual analogue scale (VAS), and proportion of patients with a Total OSDI change from baseline > 4.5, the known minimally important clinical difference (MICD) for early to moderate disease, at Month 3. A patient will be considered to be an evaporative DED responder at a post-randomization visit if TBUT > 10 seconds, a Schirmer's test ≥ 10 mm, a Total OSDI < 13, or a SPEED Score < 6, or an Average VAS or Worst VAS score decreased by ≥ 5 is observed.

8.1.2 COHORT 1: SECONDARY EFFICACY MEASURES

Secondary efficacy measures include the meibum gland secretion score (MGS), the number of Meibomian Glands Yielding Liquid Secretion (MGYLS), TBUT, OSDI measures, visual analogue scale (VAS), Schirmer's test without anesthesia, conjunctival redness score, 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.

8.1.3 COHORT 1: DATA REVIEW COMMITTEE (DRC)

Safety oversight will be under the direction of a DRC composed of individuals with the appropriate expertise (see Section 4.3). Members of the DRC should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DRC should meet at least monthly to assess safety and efficacy data on each arm of the study. The data of the first Cohort will be reviewed by the DRC prior to proceeding to the next dose level. The DRC will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DRC. At this time, each data element that the DRC needs to assess will be clearly defined. The DRC will provide its input to Azura Ophthalmics, the IEC and regulatory authorities as necessary.

Interim safety and preliminary efficacy evaluations will be performed and reviewed by the DRC when the first 10 patients in Cohort 1, Group 3 completes the Month 3 visit (First Interim Analysis) and when the last patient enrolled in Cohort 1, Group 4 completes the Month 3 visit (Second Interim Analysis). There is no plan to stop the study for efficacy on the basis of the interim analyses. However, termination due to futility may occur. Statistical significance will be declared at the time of the interim analysis.

8.1.4 EXPANSION COHORT: PRIMARY EFFICACY MEASURES

The primary efficacy sign for MGD is change from baseline in MGYLS. The visit for the primary variable is month 3 for the US and month 6 for regions (e.g. EU) where the longer follow-up is required. The primary analysis population is mITT. Statistical testing will be performed for the AZR-MD-001 group versus placebo group.

The primary efficacy symptom for MGD is change from baseline in Total OSDI. The visit for the primary variable is month 3 for the US and month 6 for regions (e.g. EU) where the longer follow-up is required. The primary analysis population is mITT. Statistical testing will be performed for the AZR-MD-001 group versus placebo group.

8.1.5 EXPANSION COHORT: SECONDARY EFFICACY MEASURES

Refer to Section 1 for a complete list and specific timings of additional efficacy measures.

Secondary efficacy measures include:

- Change from Baseline to day 14, month 1.5, month 3, month 4.5 and month 6 in MGS (0 to 45 scale)
- MGS score (0 to 45 scale) at each visit
- Proportion of patients with a MGS score > 12 at each visit
- Change from Baseline to day14, month 1.5, and month 4.5 in the number of Meibomian Glands Yielding Liquid Secretion (MGYLS) (0 to 15 scale)
- MGYLS (0 to 15 scale) at each visit
- Proportion of patients with a change from baseline in MGYLS score ≥ 5 at each visit
- Change from Baseline to day14, month 1.5, month 3, month 4.5 and month 6 in TBUT
- TBUT at each visit
- Proportion of patients with a TBUT score > 5 at each visit
- Change from Baseline to day14, month 1.5, month 3, month 4.5 and month 6 in Standard Patient Evaluation of Eye Dryness (SPEED)
- SPEED at each visit
- Proportion of patients with a SPEED < 6 at each visit
- Change from Baseline to day14, month 1.5, month 3, month 4.5 and month 6 in average visual analogue scale (VAS)

- Average VAS at each visit
- Change from Baseline to day14, month 1.5, month 3, month 4.5 and month 6 in worst VAS
- Worst VAS at each visit
- Change from Baseline to day 14, month 1.5 and month 4.5 in Total OSDI
- Total OSDI, OSDI sub-scales, and individual items from the OSDI across visits
- Proportion of patients with a Total OSDI change from baseline > 4.5, the known minimally important clinical difference (MICD) for early to moderate disease, at month 3 and month 6
- Proportion of patients with a Total OSDI < 13 at each visit
- Number of expressible glands yielding clear meibum at day14, month 1.5, month 3, month 4.5 and month 6
- Eyelid margin erythema/telangiectasias at day14, month 1.5, month 3, month 4.5 and month 6
- Corneal and conjunctival staining (0 to 5 scale) at each visit

8.1.6 EXPANSION COHORT: DATA REVIEW COMMITTEE (DRC)

There is no DRC for the Expansion Cohort.

8.2 SAFETY AND OTHER ASSESSMENTS

8.2.1 SAFETY MEASURES

The following safety measures will be examined:

- adverse events (ocular and nonocular)
- study medication tolerability as measured by the Ocular Comfort Questionnaire (Cohort 1 only)
- best-corrected visual acuity (BCVA)
- slit-lamp biomicroscopy
- intraocular pressure (IOP)
- ophthalmoscopy

- photographic conjunctival hyperemia assessment
- vital signs (pulse rate, blood pressure)
- laboratory tests (chemistry, hematology, urinalysis (excluding creatinine analysis)) (Cohort 1 only)
- urine pregnancy test

For Cohort 1, laboratory test results will be forwarded from the local laboratory to the study site and to Azura Ophthalmics or its designee. The laboratory results from screening should be reviewed prior to randomization. Laboratory tests at screening may be repeated once at the discretion of the investigator and pending discussion with Azura Ophthalmics Medical Monitor, to confirm exclusionary status. Study treatment will be performed only if the investigator deems the laboratory results to be acceptable. The most current specimen results will be reviewed prior to randomization. The investigator will review all laboratory results for the clinical significance of any abnormalities. Evaluation and management of abnormal laboratory results should be conducted according to local site practice. Clinically significant abnormalities are to be recorded on an adverse event electronic case report form (eCRF) page.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

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

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

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

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

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

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

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

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

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

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

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

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

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

8.3.2.1 REPORTING OF SERIOUS ADVERSE EVENTS

Any SAE must be reported by the investigator if it occurs during the clinical study or within 30 days of receiving the study drug, whether or not the SAE is considered to be related to the investigational product. An SAE report consists of the SAE form, the AE form, medical history and the concomitant medication form. A copy of these forms must be faxed within 24 hours for the attention of the product safety scientist at:

Syneos Health Safety and Pharmacovigilance fax/email details:
Attention: Safety & Pharmacovigilance
Local Toll-Free Fax (Australia): 1800 256 952
Local Toll-Free Fax (New Zealand): 0800 456 231
Alternate (Global) Fax: +1 877 464 7787
Email: SafetyReporting@SyneosHealth.com

For medical emergencies contact:
Dr Kiran Haridas (Medical Monitor) phone : +91-9945385388
Dr. Jyoti Puri (back- up Medical Monitor), phone: +91 7303111499

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

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

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

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

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

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

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

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

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

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

8.3.3.3 ACTION TAKEN

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

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

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

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

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

8.3.4.1 DOCUMENTATION AND REPORTING OF ADVERSE EVENTS

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

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

8.3.5 REPORTING EVENTS TO PARTICIPANTS

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

The treatment assignment for the patient can be determined by designated site personnel accessing the IWRS system via password protected access. The reason for breaking the code must be recorded in the patient's source documents.

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

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

8.3.6 EVENTS OF SPECIAL INTEREST

8.3.6.1 UNEXPECTED ADVERSE REACTION DEFINITION

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

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

8.3.7 REPORTING OF PREGNANCY

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

9 STATISTICAL CONSIDERATIONS

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

9.1 SAMPLE SIZE DETERMINATION

9.1.1 COHORT 1

The sample size is determined empirically.

9.1.2 EXPANSION COHORT

Estimates for sample size calculations are from the final Cohort 1 interim analysis from Azura Clinical Protocol AZ201801. The mean response of 0.77 and a standard deviation for MGYLS of 2.28 units was observed for control and a mean response of 2.77 units and a standard deviation for MGYLS of 3.35 units was observed for AZR-MD-001 0.5%. A sample size of 45 subjects per group will have 90% power to detect a difference of 2.0 units between the active treatment group and the placebo group using a two-sample t-test at a significance level of 0.05. The standard deviation for Total OSDI was 6.31 units for control and 8.34 units for the high dose. A sample size of 58 subjects per group will have 90% power to detect a difference of 4.52 units between the active treatment group and the control group using a two-sample t-test at a significance level of 0.05. To allow for additional site to site variability the sample size per group will be increased to approximately75 patients.

Multiplicity Consideration: To address the multiple primary endpoints defined in this study, the primary endpoints have been prioritized into a hierarchical structure. For example, in order to test the primary symptom endpoint of Total OSDI, the primary sign endpoint of MGYLS must be statistically significantly higher in the AZR-MD-001 treatment group compared to the vehicle treatment group using a two-sided significance level of 0.05 for a given concentration. The final order of the endpoints will be defined in the Statistical Analysis Plan (SAP) prior to unmasking the study. Using this strategy, the family-wise Type I error rate will be maintained at the 0.05 significance level for the two primary endpoints.

Interim Analysis (Primary efficacy endpoint for the US): An interim analysis is planned after the final enrolled patient completes the month 3 visit. Only an independent biostatistician will be unblinded to the treatment patients actually received and only summary efficacy and safety tables will be provided. Outcomes from this analysis will assist in the confirmation of the study power calculations and potentially as part of a rolling submission to global regulatory agencies.

9.2 POPULATIONS FOR ANALYSES

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

The method of Last Observation Carried Forward (LOCF) will be used for efficacy on the mITT population. In these analyses, non-missing values recorded at visit 3 or later will be used to replace missing data at visits where data are not recorded.

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

9.3 PROTOCOL DEVIATIONS

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

These practices are consistent with ICH GCP:

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

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

9.4 STATISITICAL ANALYSES

9.4.1 GENERAL APPROACH

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

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

Cohort 1: Efficacy (MGD):

The primary efficacy variables for MGD are change from baseline to month 3 in MGS, number of MGYLS, and the proportion of patients improving on both a gland score (e.g., MGS or MGYLS) and a patient reported outcome measure (e.g., OSDI). 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 > 12, MGYLS score > 2, or MGYOLS score > 2. The visit for the primary variable is month 3 and the primary analysis population is mITT. Statistical tests will be performed for each AZR-MD- 001 group versus vehicle group. Odds ratio along with 95% CI will be obtained by pairwise comparisons of the proportion of responders for each AZR-MD- 001 group versus vehicle group using the Logistic Regression method stratifying by baseline MGS score for the qualified eye (i.e., < 6 or ≥ 6 and ≤ 12) and duration of disease (i.e., < 5 years or ≥ 5 years). There will be no alpha adjustment for the multiple tests for the pairwise comparisons.

Cohort 1: Efficacy (Evaporative DED):

The primary efficacy variables for evaporative DED are change from baseline to month 3 in Tear Break-up Time (TBUT), OSDI, eye dryness measured using a visual analogue scale (VAS), and proportion of patients with a Total OSDI change from baseline > 4.5, the known minimally important clinical difference (MICD) for early to moderate disease, at Month 3. A patient will be considered to be an evaporative DED responder at a post-randomization visit if TBUT > 10 seconds, a Schirmer's test ≥ 10 mm, a Total OSDI < 13, a SPEED Score < 6, or an Average VAS or Worst VAS score decreased by ≥ 5 is observed.

Separate analyses will be performed for each definition of a responder. The visit for the primary variable is month 3 and the primary analysis population is mITT. Statistical tests will be performed for each AZR-MD-001 group versus vehicle group. Odds ratio along with 95% CI will be obtained by pairwise comparisons of the proportion of responders for each AZR-MD- 001 group versus vehicle group using the Logistic Regression method stratifying by baseline MGS score for the qualified eye (i.e., < 6 or ≥ 6 and ≤ 12) and duration of disease (i.e., < 5 years or ≥ 5 years). There will be no alpha adjustment for the multiple tests for the pairwise comparisons.

Expansion Cohort: Efficacy (MGD):

Co-primary endpoints of change from baseline in signs (MGYLS) and symptoms (Total OSDI) will be employed:

- For the US, the primary efficacy sign for MGD is change from baseline to month 3 in MGYLS. For regions (e.g. EU) requiring 6 months of efficacy data, the primary efficacy variables for MGD is change from baseline to month 6 in MGYLS.

- For the US, the primary efficacy symptoms for MGD is change from baseline to month 3 in Total OSDI. For regions (e.g. EU) requiring 6 months of efficacy data, the primary efficacy variables for MGD is change from baseline to month 6 in Total OSDI.

To address the multiple primary endpoints defined in the Expansion Cohort, the primary endpoints have been prioritized into a hierarchical structure. For example, in order to test the primary symptom endpoint of Total OSDI, the primary sign endpoint of MGYLS must be statistically significantly higher in the AZR-MD-001 treatment group compared to the placebo treatment group for the same concentration (i.e., 0.5% or 1.0%) using a two-sided significance level of 0.05. The final order of the endpoints will be defined in the Statistical Analysis Plan (SAP) prior to unmasking the study. Using this strategy, the family-wise Type I error rate will be maintained at the 0.05 significance level for the two primary endpoints for each concentration.

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

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary efficacy variables (see Section 8.1) will be analyzed at month 3 using an analysis of covariance [ANCOVA] model with baseline MGS score and duration of disease as covariates and treatment (AZR-MD-001 ointment/semi-solid drug or vehicle/placebo) as factors in the model. Pairwise comparisons will be performed for each AZR-MD-001 ointment/semi-solid drug treatment group versus vehicle/placebo using t-tests of the least square means from this model. Two-sided confidence intervals (95%) will be provided for the differences between treatments. To support regions (e.g. EU) requiring 6 months of efficacy data in the Expansion Cohort, the same model will be applied at 6 months.

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

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The secondary efficacy variables (see Section 8.1) will be analyzed using an analysis of covariance [ANCOVA] model with baseline MGS score and duration of disease as covariates and treatment (AZR-MD-001 ointment/semi-solid drug or vehicle/placebo) as factors in the model. Pairwise comparisons will be performed for each AZR-MD-001 ointment/semi-solid drug treatment group versus vehicle/placebo using t-tests of the least square means from this model. Two-sided confidence intervals (95%) will be provided for the differences between treatments. To support

regions (e.g. EU) requiring 6 months of efficacy data in the Expansion Cohort, the same model will be applied at 6 months.

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

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

Expansion Cohort:

- Patients in the AZR-MD-001 ointment/semi-solid drug treatment group: changes from baseline to days 14, month 1.5, month 3, month 4.5 and month 6
- Patients in the AZR-MD-001 placebo group: changes from baseline to days 14, month 1.5, month 3, month 4.5 and month 6

Within each treatment group, shift tables for complete treatment response (yes/no) in the study eye will be presented for patients in the mITT population for endpoint signifying a "clinical cure" (Proportion of patients with a MGS score > 12; Proportion of patients with a change from baseline in MGYLS score of ≥5; Proportion of patients with a MGYLOS score of >2; Proportion of patients with a TBUT > 10 seconds at each visit; Proportion of patients with a Schirmer's test ≥ 10 mm at each visit; Proportion of patients with a Total OSDI < 13 at each visit; and Proportion of patients with a SPEED Score < 6; Proportion of patients with an Average VAS or Worst VAS score decreased by ≥ 5 at each visit.

Cohort 1:

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

Expansion Cohort:

- Patients in the AZR-MD-001 ointment/semi-solid drug treatment group: changes from baseline to days 14, month 1.5, month 3, month 4.5 and month 6
- Patients in the AZR-MD-001 placebo group: changes from baseline to days 14, month 1.5, month 3, month 4.5 and month 6

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

9.4.4 SAFETY ANALYSES

Safety measures will be analyzed using the safety population. Medical Dictionary for Regulatory Activities (MedDRA) nomenclature will be used to code adverse events. Treatment-emergent adverse events will be summarized. The adverse events will be classified into ocular and nonocular types and will be summarized separately. Detailed methods for the analyses of adverse events and other safety variables will be described in the analysis plan.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

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

9.4.6 PLANNED INTERIM ANALYSES

Two official interim analyses are planned for Cohort 1 of the study. The first interim analysis is planned for after the 10th patient in Cohort 1, Group 3 exits the study. Only data collected up to the last patient exiting the study from Cohort 1, Group 3 will be included in the first interim analysis. All ongoing patients in Cohort 1 will remain masked until the second interim analysis.

A second interim analysis is planned after the final patient from Cohort 1 exits the study (Cohort 1, Group 4). Outcomes from this analysis will assist in the confirmation of the study drug concentration and frequency to be used for the Expansion Cohort.

One interim analyses is planned for the Expansion Cohort of the study. The interim analysis is planned for after the last enrolled patient completes the month 3 visit. Only data collected up to the month 3 visit will be included in the interim analysis. The primary endpoints for the US will serve as an Interim Analyses for the Month 6 primary endpoints. The sample size may be adjusted for power or to address any concerns for alpha inflation.

A final database lock will occur at the completion of the Expansion Cohort and the safety, tolerability, and efficacy data from Cohort 1 and the Expansion Cohort will be analyzed separately and in a combined fashion. At the final analysis, statistical significance will be declared for 2-sided p-values ≤ 0.05.

Given the exploratory nature of Cohort 1 no adjustments for multiplicity will be applied across the primary or secondary endpoints in this cohort. Multiplicity will be controlled across the primary endpoints in the Expansion Cohort as described in Section 9.4.1.

9.4.7 SUB-GROUP ANALYSES

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

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

1. MGD diagnosis < 5 years and MGS score for the qualified eye < 6
2. MGD diagnosis < 5 years and MGS score for the qualified eye ≥ 6 and ≤ 12
3. MGD diagnosis ≥ 5 years and MGS score for the qualified eye < 6
4. MGD diagnosis ≥ 5 years and MGS score for the qualified eye ≥ 6 and ≤ 12.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

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

9.4.9 EXPLORATORY ANALYSES

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

10 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1 INDEPENDENT ETHICS COMMITTEE

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the participants, 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 patients 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. Participants 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. Participants 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 patients will be informed about this new information and reconsent will be obtained.

10.5 SUBJECT CONFIDENTIALITY

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

11 QUALITY ASSURANCE

11.1 AUDIT AND INSPECTION

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

11.2 MONITORING

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

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

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

11.3 DATA MANAGEMENT AND CODING

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

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

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

12 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

12.1 STUDY DISCONTINUATION AND CLOSURE

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

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

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

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

12.2 FUTURE USE OF STORED SPECIMENS AND DATA

12.2.1 HANDLING OF BIOLOGICAL SPECIMENS

All samples will be returned to Azura Ophthalmics or Azura Ophthalmics designee at the completion of the study. Azura Ophthalmics shall have full ownership rights to any biological specimens/samples derived from the study.

12.2.1.1 COHORT 1: BLOOD AND URINE SAMPLES FOR SAFETY ANALYSIS

Samples of blood (nonfasting) and urine will be evaluated for blood chemistry (Albumin, Blood urea nitrogen, Glucose, Alkaline phosphatase, Calcium, Potassium, Alanine aminotransferase, Chloride, Sodium, Aspartate aminotransferase, Creatinine, Total bilirubin, Total protein, Whole blood selenium), hematology (Hematocrit, Differential count, Red blood cells, Hemoglobin, Basophils, White blood cells, Mean corpuscular hemoglobin, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Platelet count, Mean corpuscular hemoglobin concentration, Mean

corpuscular volume and coagulation (Prothrombin time, International normalized ratio, Partial thromboplastin time) at a local clinical laboratory with certification from a recognized accreditation agency. Urinalysis (Blood, Glucose, Protein, Ketones) will be performed at site using a dipstick test. Details of sample collection are found in the procedure manual.

12.2.1.2 TEAR SAMPLES

Details of sample collection and handling are found in the procedure manual.

All samples will be stored at the clinical site until shipment to the bioanalytical laboratory.

12.3 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor**	**DRC Chair**
Stephanie L Watson, M.D.	Dr Kiran Haridas MD MBA.	Patty Delaney
Sydney Cornea Clinic,	Syneos Health	Azura Ophthalmics
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12.4 RETENTION OF DOCUMENTATION

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

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

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

Azura Ophthalmics requires that it be notified in writing if the investigator wishes to relinquish

ownership of the data so that mutually agreed-upon arrangements can be made for transfer of ownership to a suitably qualified, responsible person.

12.5 SOURCE DOCUMENTS

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

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

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

12.6 STUDY SUMMARY

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

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

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

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

2. The day at least 3 years after the date of the termination or completion of the clinical study

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

12.8 PUBLICATION AND DATA SHARING POLICY

Azura Ophthalmics as the sponsor, has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and Azura Ophthalmics personnel. Authorship will be established prior to the writing of the manuscript.

As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Azura Ophthalmics.

12.9 CONFLICT OF INTEREST POLICY

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

12.10 ADDITIONAL CONSIDERATIONS

None.

12.11 ABBREVIATIONS

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

12.12 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
Amendment 1, Version 2.0	6/May/18	Added a top dose of 1.0%, allowed 14 days in use, included AZR-MD- 001 placebo for the run-in period, and allowed for the use of an instructional dosing video.	New data on stability, tolerability and toxicology with the clinical formulation has been collected. The Investigator's Brochure, Protocol, ICF, and dosing instructions are all being updated to reflect this new information.
Amendment 2, Version 3.0	14/Jan/19	Added a top dose of 2.5%, added Cohort 1, Group 4, designed all groups in Cohort 1 to have a similar design to Cohort , Group 1, allowed 30 days in use, included an interim analysis, clarified that no creatinine analysis is part of the Urinalysis test, TBUT and MGE to be performed by the same investigator for a given patient, screen fail patients who are re-enrolled will receive a new screening number (not reusing the old number), and added endpoints for MGD and Evaporative DED.	Clinical data collected in Cohort 1, Groups 1 & 2 on 0.1% and 0.5% support the safety profile of AZR-MD-001. To enable a greater range for safety testing 2.5% AZR-MD-001 was added to the protocol. The remaining changes incorporate existing memos to the trial master file and informal feedback from regulatory agencies on potential trial endpoints.
Amendment 3, Version 4.0	27/Jan/20	Added a second interim analysis after the final patient from Cohort 1 exits the study (Cohort 1, Group 4).	Outcomes from this analysis will assist in the confirmation of the study drug concentration and frequency to be used for the Expansion Cohort.
Amendment 4, Version 5.0	4/Sep/20	For the Expansion Cohort: Defined the dose groups and dosing frequency, removed the cap on the OSDI for study entry, prospectively defined the primary endpoint(s), changed the control to AZR-MD-001 placebo, removed the run-in on AZR-MD-001 placebo, allowed for a month 3 interim analysis in the Expansion Cohort, extended the study to 6 months and added a month 4.5 visit.	Outcomes from the Expansion Cohort will serve as the first confirmatory study of the safety and efficacy of AZR-MD-001.

Amendment 5, Version 6.0	19/Mar/21	Updated based upon outcomes from the final Cohort 1 analyses that impact power calculations and suggest less variability in symptom endpoints for a baseline Total OSDI < 34.	Outcomes from the Expansion Cohort will serve as the first confirmatory study of the safety and efficacy of AZR-MD-001.

13 REFERENCES

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14 SUBJECTIVE STUDY SCALES

14.1 VISUAL ANALOG SCALE (VAS)

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

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

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

14.2 OCULAR SURFACE DISEASE INDEX (OSDI)

The OSDI questionnaire consists of 12 questions regarding ocular symptoms, environmental triggers, and vision-related functioning in patients with DED. The patient will be asked to rate each symptom using a 5-point scale (0 to 4), where 0 = none of the time; 1 = some of the time; 2 = half of the time; 3 = most of the time; and 4 = all of the time. Seven questions related to visual functioning allow a response of "N/A" (not applicable). The total OSDI will be calculated by EDC from the raw scores of each of the 12 questions based on the formula: ([sum of scores for all questions answered[a]] X 100)/([total number of questions answered[a]] X 4).

[a] Questions answered with N/A will be excluded in the calculation of total OSDI.

OCULAR·SURFACE·DISEASE·INDEX·©¶

(Australia·English·version·of·the·OSDI)¶

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Please·answer·the·following·questions,·marking·a·tick·in·the·box·that·best·represents·your·answer.¶

Have·you·experienced·any·of·the·following·**during·the·past·week:¶**

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

¶

Have·problems·with·your·eyes·limited·you·in·performing·any·of·the·following·**during·the·past·week:¶**

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

¶

Have·your·eyes·felt·uncomfortable·in·any·of·the·following·situations·**during·the·past·week:¶**

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

¶

¶

14.3 STANDARD PATIENT EVALUATION OF EYE DRYNESS (SPEED)

SPEED™ QUESTIONNAIRE

Name: _____ **Date:** ____/____/____ **Sex:** M F (Circle) **DOB:** ____/____/____

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

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

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

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

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

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

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

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

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

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

Cornea. 2013 Sep;32(9):1204-10

13-ADV-123 A

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

14.4 STUDY MEDICATION TOLERABILITY/COMFORT QUESTIONAIRE

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

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

Drug Felt	0% Uncomfortable	100% Comfortable
Drug Felt	0% Not Soothing	100% Soothing
Drug Felt	0% Not Moistening/Lubricating	100% Moistening/Lubricating
Drug Enhanced	0% Did not Enhance Clear Vision	100% Clear Vision
Drug Caused	0% No Stickiness	100% Stickiness
Drug Caused	0% No Blur	100% Blur
Drug Caused	0% No Burning/Stinging	100% Burning/Stinging
Drug Caused	0% No Discomfort	100% Discomfort

15 SPONSOR APPROVAL(S)

Protocol Title:	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)
Protocol Number:	AZ201801
Final Date:	19 March 2021

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

Signed:_____ Date:_____

Charles Bosworth Ph.D.
Chief Medical Officer
Azura Ophthalmics