A Single-centre, Vehicle-controlled Study to Evaluate Methods to Enhance the Safety and Tolerability of AZR-MD-001 for Meibomian Gland Dysfunction (MGD).

Short Title:	Methods to enhance AZR-MD-001 for Meibomian Gland Dysfunction (MGD)
Protocol Number:	SOVS2020-080
National Clinical Trial (NCT) Identified Number:	TBD
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Funded by:	Azura Ophthalmics, Level 9, 31 Queens Street Melbourne, VIC 300 Australia
Version and Version Number:	Final, 2.0
Date: 14Apr2020	

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
1.2 and 5.2	Added exclusion criteria “Known carrier of infectious disease”	As per UNSW HREC’s recommendation

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STATEMENT OF COMPLIANCE

INVESTIGATOR:

STUDY LOCATION:

I agree to:

- Implement and conduct this study diligently and in strict compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP) and all applicable state, local and federal regulatory requirements.

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

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

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

Investigator Printed Name	Signature	Date

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Study Compound(s):	AZR-MD-001 (Selenium Disulfide)
Phase:	2
Objectives:	To determine the safety and tolerability of AZR-MD-001 1.0% following evening only dosing for Meibomian Gland Dysfunction (MGD). To determine if dosing Hylo-Forte® approximately 5 minutes before study ointment will enhance either the safety or tolerability of AZR-MD-001 1.0% following evening only dosing.
Clinical Hypotheses:	AZR-MD-001 1.0% ointment/semi-solid drug has an acceptable safety and tolerability profile following twice-weekly evening ocular administration for the duration of the study. Dosing Hylo-Forte® approximately 5 minutes before study ointment will enhance the safety or tolerability of AZR-MD-001 1.0% following evening only dosing.

1.2 SCHEMA

Study Design:	*Structure:* Single-center, single-masked (the individual(s) performing efficacy and safety measures will be masked to treatment assignment for the patient(s) they are assessing), vehicle-controlled, randomized study. For all dose groups a screening visit will be followed by a baseline visit 14 days later (qualification period). At the end of the qualification period patients who still exhibit signs of MGD and who can comply with dosing instructions at the baseline visit will be enrolled into a 3-month treatment period. At the baseline (Day 0) visit , patients will be randomly assigned in a 2:2:1:1 ratio to receive either AZR-MD-001 1.0% ointment/semi-solid drug or AZR-MD-001 1.0% ointment/semi-solid drug plus Hylo-Forte® or AZR-MD-001 vehicle or AZR-MD-001 vehicle plus Hylo-Forte® for twice-weekly evening administration for 3 months. The study flow is shown in Figure 1. *Duration:* The total duration of study is approximately 3.5 months (from screening to study completion). *Study Treatment Groups:* AZR-MD-001 ointment/semi-solid drug (1.0%) and AZR-MD-001 ointment/semi-solid drug (1.0%) plus Hylo-Forte®. *Controls:* AZR-MD-001 vehicle and AZR-MD-001 vehicle plus Hylo-Forte®. *Baseline Visit*: “Vaseline” (AZR-MD-001 Vehicle)

Dosage/Dose Regimen: All study treatments are to be self-administered by the patient twice-weekly in the evening. Where applicable, Hylo-Forte® will be dosed approximately 5 minutes before study ointment.

Randomization/Stratification: At Day 0, patients will be randomly assigned in a 2:2:1:1 ratio to receive either AZR-MD-001 1.0% ointment/semi-solid drug or AZR-MD-001 1.0% ointment/semi-solid drug plus Hylo-Forte® or AZR-MD-001 vehicle or AZR-MD-001 vehicle plus Hylo-Forte® for twice-weekly evening administration for 3 months.

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

Visit Schedule: Six scheduled visits: screening (-2 weeks), baseline (day 0), 2 weeks, 4 weeks, 6 weeks and 3 months. For patients who discontinue the study early, the month 3 visit procedures should be completed.

Study Population Characteristics

Number of Patients: Approximately thirty (30) patients with MGD will be randomized to the study. Based upon data from the LipiFlow® development program a screen failure rate of ~ 40% is expected for new patients. Thus, ~up to 42 patients will need to be screened to achieve ~up to 30 patients randomized to treatment.

Condition/Disease: Meibomian Gland Dysfunction (MGD)

Key Inclusion Criteria:

- Male or female, 18 years of age or older at screening visit
- Capable of understanding and willing to provide written informed consent and likely to complete the entire course of study according to instructions
- Written authorization for use and release of health and research study information has been obtained
- Best-corrected visual acuity (BCVA) of 20/40 or better (Snellen equivalent), using the logarithm of the minimum angle of resolution (LogMAR) in each eye at the screening visit
- 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 visit
- Reported dry eye signs and symptoms within the past 3 months: Ocular Surface Disease Index (OSDI) score ≥ 13; TBUT < 10 seconds in both eyes
- Demonstrated ability to follow dosing instructions at the baseline visit
- Prior to the screening visit patients are required to discontinue:
    - Use of systemic antihistamines or isotretinoin for at least 1 month

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

- Women of childbearing potential must have a history of bilateral tubal ligation or use oral contraceptives, implants, injectables, transdermal patch, or intrauterine device for birth control during the study. Abstinence is considered a reliable method of birth control. If these methods of birth control do not apply, women of childbearing potential must have a monogamous partner who has had a vasectomy at least 3 months before the screening visit or who is of the same gender.

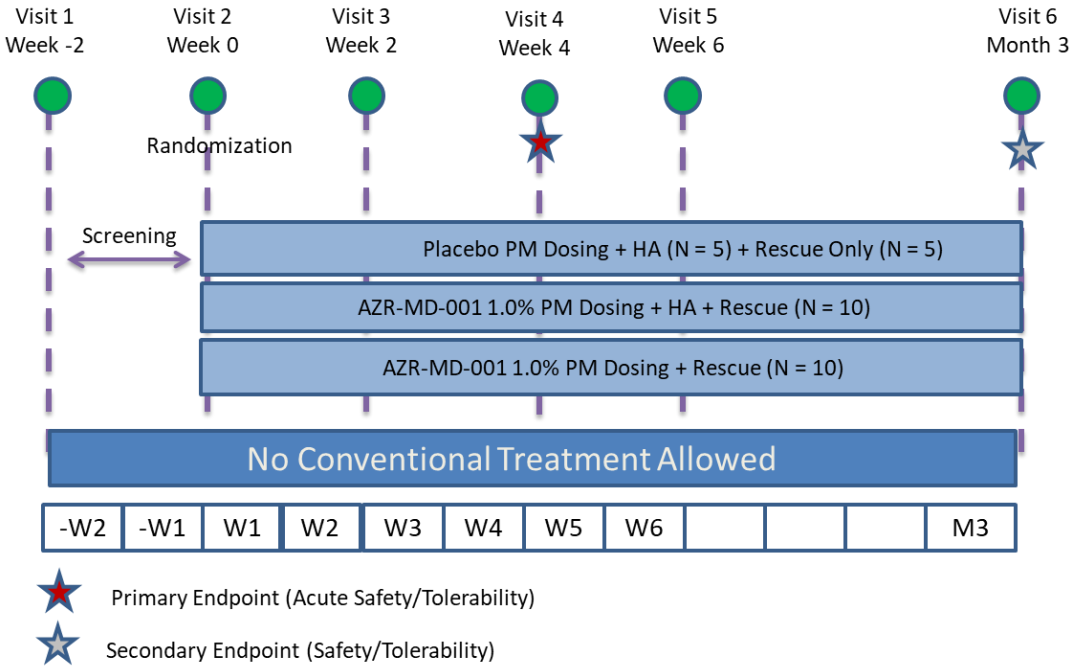
Exclusion Criteria:

- Uncontrolled ocular disease (except for MGD) or uncontrolled systemic disease
- Patient has glaucoma or ocular hypertension as demonstrated by an intraocular pressure (IOP) in either eye at screening of ≥24 mm Hg determined by Goldman applanation tonometry or has planned insertion/removal of glaucoma filtration shunts/devices during the study
- Corneal abnormality or disorder that impacts normal spreading of the tear film (keratoconus, pterygia, scarring) or corneal integrity
- BCVA worse than 20/40 in either eye at the screening visit
- Current use of punctal plugs, anticipated insertion during the study, or a history of punctal cautery in either eye at any time prior to the baseline visit or anticipate such a procedure during the study
- Keratoconjunctivitis sicca secondary to destruction of conjunctival goblet cells as occurs with vitamin A deficiency or scarring, such as that with cicatricial pemphigoid, alkali burns, Stevens-Johnson syndrome, trachoma, or irradiation
- Keratoconjunctivitis sicca secondary to aqueous deficient DED
- Active ocular infection (bacterial, viral, or fungal) at the screening visit
- Corneal, conjunctival, or eyelid inflammation (including allergic, vernal, or giant papillary conjunctivitis and mucous membrane pemphigoid) that

	in the judgment of the investigator may interfere with the study results or the ability of subjects to complete the treatment period • Recent (within the past 3 months of the baseline visit) ocular surgery, trauma, herpes, or recurrent inflammation • Contact lens use anticipated during the study • Periocular application of makeup during the study or tattooing of the lids • Use of any type of scleral lenses or sealed compartment ocular frames within 2 months of the 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 screening 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 [e.g., Omega 3 supplements] except those prescribed for use as part of the study) • Eyelid abnormalities that affect normal lid function in either eye other than those caused by meibomian gland dysfunction • Diagnosis of hepatitis C infection, human immunodeficiency virus (HIV) infection, sarcoidosis, amyloidosis, active tuberculosis, or graft versus host disease • Known carrier of infectious 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 • Known allergy or sensitivity to fluorescein, lissamine green, or the study medication or its components • Use of medicated shampoos containing selenium (e.g., Selsun Blue, Exsel, Selsum, and Seleen) following the screening visit • Patient is unlikely to follow study instructions or to complete all required study visits or has a condition or situation that in the investigator's opinion, may put the patient at significant risk, may confound the study results, or may interfere significantly with the patient's participation in the study • Patient is an employee at the investigational site or is related to any member of the study staff • Pregnant, nursing, or females of childbearing potential and not utilizing adequate birth control measures, or planning pregnancy • Participation in another clinical trial involving a therapeutic drug or device within the past 30 days (except for AZR-MD-001) • Epilepsy or history of migraines exacerbated by flashing, strobe-like lights

	• 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 seconds in either eye at the screening visit
Response Measures	*Evidence for safety and tolerability of AZR-MD-001 1.0%:* • Adverse events • Study medication tolerability as measured by the Ocular Comfort Questionnaire • Best-corrected visual acuity (BCVA) • Biomicroscopy • Ophthalmoscopy
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. *Safety*: 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. 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. *Sample Size Calculation*: The sample size is determined empirically.

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



1.3 SCHEDULE OF ACTIVITIES (SOA)

Table 1 Schedule of Visits and Procedures

	Screening/-2 weeks	Day 0	2, 4 and 6 weeks	Month 3 (Exit)
Visit Window	N/A	*± 3 Days*	*± 7 Days*	*± 7 Days*
Informed consent/authorization	X			
Demographics	X			
Inclusion/exclusion criteria	X			
Medical and ophthalmic history	X			
Medication history	X			
Washout medications	X			
Best-corrected visual acuity (BCVA)	X	X	X	X
Subjective questionnaires including visual analogue scales (VAS) and ocular surface disease index (OSDI)	X	X	X	X
Tear evaporation rate	X	X	X	X
Non-Invasive Tear Break Up Time (TearScope)	X	X	X	X
Lipid layer thickness (LipiView II)	X	X	X	X
Tear meniscus height (Oculus Keratograph 5M)	X	X	X	X
Tear Break Up Time (TBUT)	X	X	X	X
Sodium fluorescein corneal staining, Oxford scale	X	X	X	X
Sodium fluorescein staining (Eyelid margin and mucocutaneous junction evaluation)	X	X	X	X
Meibomian gland evaluation	X	X	X	X
Slit-lamp biomicroscopy (includes eyelid margin) [a]	X	X	X	X
Lissamine green conjunctival staining, Oxford scale	X		X	X
Lissamine green staining (Eyelid margin and mucocutaneous junction evaluation)	X	X	X	X
Schirmer without Anesthesia	X	X	X	X
Intraocular pressure (IOP)	X			X
Ophthalmoscopy exam	X			X
Meibography	X			X
Adverse events/medications/tolerability	X	X	X	X
Medication dispensing/return	X	X	X	X
Physician Observation of Drug Application Methods		X		

[a] a photograph of each eye will be obtained at least once for each patient, and photographs and video recording of any interesting/unusual findings may also be made for documentation and/or follow-up purposes

2 INTRODUCTION

2.1 BACKGROUND MGD

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

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

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

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

and forms a barrier to protect the eye from microbial agents and organic matter (e.g., dust and pollen) (Green-Church et al, 2011).

2.2 STUDY RATIONALE & KNOWN POTENTIAL BENEFITS

While there are no approved pharmacological treatments for terminal duct obstruction from hyperkeratinization associated with MGD, compounds that reduce disulfide bonds (S-S) have shown promise. Akyol-Salman and colleagues (2010) used N-acetyl-cysteine (NAC) in 20 patients with MGD and demonstrated a statistically significant improvement in TBUT and symptoms (e.g., itching) by 1 month (Akyol-Salman et al, 2010; Akyol-Salman et al, 2012). Selenium sulfide as a 0.5% ointment has also been applied to the lid margin as a treatment for seborrheic blepharitis (see Table 2).

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

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

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

Clinical study MGSS1 was a prospective, interventional, non-randomized, contra-lateral eye controlled pilot study of selenium sulfide shampoo (2.5%) in 18 MGD patients. Patients were treated under additional safety measures, twice-weekly for 34 weeks and then had a single treatment on day 44. Selenium sulfide shampoo (2.5%) was safe and well tolerated with controlled dosing. One patient (FHT,002) developed conjunctivitis and superficial punctate keratitis and one patient (MCG,006) developed superficial punctate keratitis. The adverse events could be attributed to the surfactant in the shampoo (Sodium Lauryl Sulphate). Both patient's symptoms

resolved upon cessation of treatment. Significant improvements in TBUT (p = 0.0008), meibum quality (p = 0.002), and patency (p=0.02) for the drug treated eye over the contra-lateral eye were observed by day 22.

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

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

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

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

preferred nighttime application over daytime application in the clinic as they experienced better study drug tolerability. Investigators also noted that tolerability was improved for some patients with pre-dosing of an artificial tear.

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

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Selenium sulfide:

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

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

Ocular toxicity studies with selenium sulfide have been completed in rabbits. Selenium sulfide was administered to the conjunctival sac of rabbits to compare the toxicity of 0.5% selenium disulfide ophthalmic ointment to that of 2.5% selenium sulfide shampoo (Rosenthal and Adler, 1962). Administration of the 0.5% selenium disulfide ophthalmic ointment was not associated with any ocular toxicity while 2.5% selenium sulfide shampoo was associated with chemosis, redness, corneal clouding, edema, and “total staining” in all eyes within 2 hours of administration. It is unclear if 2.5% selenium sulfide or if another ingredient of the shampoo is bothersome to the ocular surface. Ocular irritation, conjunctivitis, and epithelial keratitis have been reported in humans dosed with selenium sulfide as a 0.5% ophthalmic ointment and Sodium Lauryl Sulphate applied to the lid margin (Bahn, 1954). In clinical study MGSS1, selenium sulfide shampoo (2.5%) was safe and well tolerated with controlled dosing. One patient (FHT,002) developed conjunctivitis and superficial punctate keratitis and one patient (MCG,006) developed superficial punctate keratitis. Both patient’s symptoms resolved upon cessation of drug treatment. The observed ocular signs could be attributed to the surfactant, Sodium Lauryl Sulphate, in the shampoo.

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

2.3.2 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The predominate conventional treatments for obstructive MGD are relatively invasive, time consuming and uncomfortable for patients. There are currently no approved pharmacologic treatments for MGD. Thus, there is a medical need for pharmacologic treatments for MGD. resulting in an improved safety profile.

Given that the tolerability findings associated with AZR-MD-001 1.0% in protocols SOVS-2019-070 and AZ201801 appear to be improved by both nighttime drug application and artificial tear use, it is desirable to determine the safety and tolerability of AZR-MD-001 1.0% following evening administration only, and whether dosing Hylo-Forte® approximately 5 minutes before study ointment will enhance either the safety or tolerability of AZR-MD-001 1.0% following evening dosing.

3 OBJECTIVES AND ENDPOINTS

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

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
To evaluate the safety and tolerability of AZR-MD-001 1.0% ointment/semi-solid drug applied to the lower lid twice-weekly following evening only dosing for up to 3 months in MGD. To evaluate whether dosing Hylo-Forte® approximately 5 minutes before study ointment will enhance either the safety or tolerability of AZR-MD-001 1.0% following evening only dosing.	**Safety/Adverse Events**: • Incidence rates of each treatment-emergent adverse events. • 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).	The endpoints for safety and tolerability are all commonly used in ophthalmic drug and device trials.

4 STUDY DESIGN

4.1 OVERALL DESIGN

Single-center, single-masked (the individual(s) performing efficacy and safety measures will be masked to treatment assignment for the patient(s) they are assessing), vehicle-controlled, randomized, parallel group study. For all dose groups a screening visit will be followed by a baseline visit 14 days later (qualification period). At the end of the qualification period patients who still exhibit signs of MGD and who can comply with dosing instructions at the baseline visit will be enrolled into a 3-month treatment period.. At the baseline (Day 0) visit, patients will be randomly assigned in a 2:2:1:1 ratio to receive either AZR-MD-001 1.0% ointment/semi-solid drug or AZR-MD-001 1.0% ointment/semi-solid drug plus Hylo-Forte® or AZR-MD-001 vehicle or AZR-MD-001 vehicle plus Hylo-Forte® for twice-weekly evening administration for 3 months. Where applicable, Hylo-Forte® will be dosed approximately 5 minutes before study ointment. The study flow is shown in Figure 1.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

While there are no approved pharmacological treatments for terminal duct obstruction from hyperkeratinization associated with MGD, compounds that reduce disulfide bonds (S-S) have shown promise. Akyol-Salman and colleagues (2010) used N-acetyl-cysteine (NAC) in 20 patients with MGD and demonstrated a statistically significant improvement in TBUT and symptoms (e.g., itching) by 1 month (Akyol-Salman et al, 2010; Akyol-Salman et al, 2012). Selenium sulfide as a 0.5% ointment has also been applied to the lid margin as a treatment for seborrheic blepharitis (see Table 2).

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

Clinical study MGSS1 was a prospective, interventional, non-randomized, contra-lateral eye controlled pilot study of selenium sulfide shampoo (2.5%) in 18 MGD patients. Patients were treated under additional safety measures, twice-weekly for 34 weeks and then had a single treatment on day 44. Selenium sulfide shampoo (2.5%) was safe and well tolerated with controlled dosing. One patient (FHT,002) developed conjunctivitis and superficial punctate keratitis and one

patient (MCG,006) developed superficial punctate keratitis. The adverse events could be attributed to the surfactant in the shampoo (Sodium Lauryl Sulphate). Both patient's symptoms resolved upon cessation of drug treatment. Significant improvements in TBUT ($p = 0.0008$), meibum quality ($p = 0.002$), and patency ($p=0.02$) for the drug treated eye over the contra-lateral eye were observed by day 22.

Clinical study AZ201801, Amendment 3 is an ongoing multicenter, double-masked, vehicle-controlled, randomized, parallel group study carried out in 2 sequentially overlapping cohorts (Cohort 1: sequential rising concentrations of AZR-MD-001 ointment/semi-solid drug (i.e., Cohort 1, Group 1-0.1%, Cohort 1, Group 2-0.5%, Cohort 1, Group 3-1.0%, and Group 4-0.1%, 0.5%, 1.0%, or 2.5%) and AZR-MD-001 vehicle dosed twice-weekly and/or once daily in the evening; Expansion Cohort: parallel doses of up to two concentrations of AZR-MD-001 ointment/semi-solid drug (i.e., two of four available concentrations: 0.1%, 0.5%, 1.0%, or 2.5%) and AZR-MD-001 vehicle dosed either twice-weekly or once daily in the evening. For Cohort 1 patients will be randomized in a 4:1 ratio (AZR-MD-001: Vehicle) and in the Expansion Cohort patients will be randomized in a 1:1:1 ratio (see Section 2.2 for more detail on the study).

Clinical study SOVS2019-070 is an ongoing single-center, double-masked, vehicle-controlled, randomized study to evaluate the efficacy, safety and tolerability of AZR-MD-001 1.0% in participants with contact lens discomfort (CLD). During this study, some tolerability issues were observed, with three participants experiencing adverse events which led to discontinuation from the study. All findings were consistent with prior reported adverse events for AZR-MD-001 and selenium sulfide and were reversable upon discontinuation of treatment.

Based upon these findings, patient's antidotal reports of improved tolerability with nighttime application, and the successful use of artificial tears before dosing to improve tolerability, it is desirable to investigate different methods to improve the safety and tolerability of AZR-MD-001 1.0% in patients with MGD, who are the target population for this treatment.

4.3 END OF STUDY DEFINITION

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

5 STUDY POPULATION

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

5.1 INCLUSION CRITERIA

- Male or female, 18 years of age or older at screening visit
- Capable of understanding and willing to provide written informed consent and likely to complete the entire course of study according to instructions
- Written authorization for use and release of health and research study information has been obtained
- Best-corrected visual acuity (BCVA) of 20/40 or better (Snellen equivalent), using the logarithm of the minimum angle of resolution (LogMAR) in each eye at the screening visit
- Evidence of meibomian gland obstruction (based on a meibomian gland secretion (MGS) score of ≤12 for 15 glands of the lower lid) in both eyes at the baseline visit
- Reported dry eye signs and symptoms within the past 3 months: Ocular Surface Disease Index (OSDI) score ≥ 13; TBUT < 10 seconds in both eyes
- Demonstrated ability to follow dosing instructions at the baseline visit
- Prior to the screening visit patients are required to discontinue:
    - Use of systemic antihistamines or isotretinoin for at least 1 month
    - Anti-inflammatory treatments for DED (e.g., cyclosporine ophthalmic emulsion [Restasis® or Ikervis®] or lifitegrast ophthalmic solution [Xiidra®]) for at least 3 months
    - All other prescription medications used for dry eye or MGD (e.g., antibiotics, corticosteroids, and non-steroidal anti-inflammatory drugs) for at least 2 weeks
    - LipiFlow® or other lid-heating therapy, meibomian gland probing, or therapeutic gland expression in either eye within 6 months prior to the 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

    - Women of childbearing potential must have a history of bilateral tubal ligation or use oral contraceptives, implants, injectables, transdermal patch, or intrauterine

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

5.2 EXCLUSION CRITERIA

- Uncontrolled ocular disease (except for MGD) or uncontrolled systemic disease
- Patient has glaucoma or ocular hypertension as demonstrated by an intraocular pressure (IOP) in either eye at screening of ≥24 mm Hg determined by Goldman applanation tonometry or has planned insertion/removal of glaucoma filtration shunts/devices during the study
- Corneal abnormality or disorder that impacts normal spreading of the tear film (keratoconus, pterygia, scarring) or corneal integrity
- BCVA worse than 20/40 in either eye at the screening visit
- Current use of punctal plugs, anticipated insertion during the study, or a history of punctal cautery in either eye at any time prior to the baseline visit or anticipate such a procedure during the study
- Keratoconjunctivitis sicca secondary to destruction of conjunctival goblet cells as occurs with vitamin A deficiency or scarring, such as that with cicatricial pemphigoid, alkali burns, Stevens-Johnson syndrome, trachoma, or irradiation
- Keratoconjunctivitis sicca secondary to aqueous deficient DED
- Active ocular infection (bacterial, viral, or fungal) at the screening visit
- Corneal, conjunctival, or eyelid inflammation (including allergic, vernal, or giant papillary conjunctivitis and mucous membrane pemphigoid) that in the judgment of the investigator may interfere with the study results or the ability of subjects to complete the treatment period
- Recent (within the past 3 months of the baseline visit) ocular surgery, trauma, herpes, or recurrent inflammation
- Contact lens use anticipated during the study
- Periocular application of makeup during the study or tattooing of the lids
- Use of any type of scleral lenses or sealed compartment ocular frames within 2 months of the 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 screening 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 [e.g., Omega 3 supplements] except those prescribed for use as part of the study)
- Eyelid abnormalities that affect normal lid function in either eye other than those caused by meibomian gland dysfunction
- Diagnosis of hepatitis C infection, human immunodeficiency virus (HIV) infection, sarcoidosis, amyloidosis, active tuberculosis, or graft versus host disease
- Known carrier of infectious 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
- Known allergy or sensitivity to fluorescein, lissamine green, or the study medication or its components
- Use of medicated shampoos containing selenium (e.g., Selsun Blue, Exsel, Selsum, and Seleen) following the screening visit
- Patient is unlikely to follow study instructions or to complete all required study visits or has a condition or situation that in the investigator's opinion, may put the patient at significant risk, may confound the study results, or may interfere significantly with the patient's participation in the study
- Patient is an employee at the investigational site or is related to any member of the study staff
- Pregnant, nursing, or females of childbearing potential and not utilizing adequate birth control measures, or planning pregnancy
- Participation in another clinical trial involving a therapeutic drug or device within the past 30 days (except for AZR-MD-001)
- Epilepsy or history of migraines exacerbated by flashing, strobe-like lights

- 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 seconds in either eye at the screening visit

5.3 LIFESTYLE CONSIDERATIONS

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

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

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

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

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

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of normal variability in safety measures may be rescreened one additional time. Rescreened participants should be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Approximately thirty (30) patients with MGD will be randomized to the study. Based upon data from the LipiFlow® development program a screen failure rate of ~ 40% is expected for new patients. Thus, ~up to 42 patients will need to be screened to achieve ~up to 30 patients randomized to treatment.

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

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

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

AZR-MD-001 Ophthalmic Ointment contains the drug product, AZR-MD-001 (1.0%), and suitable excipient. The only excipient in the formulation is White Soft Paraffin (Petrolatum white). The AZR-MD-001 vehicle and product labelled “Vaseline” for use at the baseline visit contain only Petrolatum white. The formulations will be supplied in 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 sterile ophthalmic ointment (Selenium disulfide API in suspension)	Vehicle	"Vaseline"
Formulation description:	AZR-MD-001 is an orange opaque dispersion ointment with an odor faintly of hydrogen sulfide	Placebo ointment will match AZR-MD-001's texture	Placebo 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):	1.0%10mg	Placebo Petrolatum, white	Placebo Petrolatum, white
Route of Administration	Topical	Topical	Topical
Dosing instructions:	Store between 2 – 8°C until opened. **Refrigerate**. Do not **freeze**. Stop use 4 weeks (30 days) after opening. Protect from light	Store between 2 – 8°C until opened. **Refrigerate**. Do not **freeze**. Stop use 4 weeks (30 days) after opening. Protect from light.	Store between 2 – 8°C until opened. **Refrigerate**. Do not **freeze**. Stop use 4 weeks (30 days) after opening. Protect from light.
Physical description:	An orange opaque ointment packaged in a multi-use tube	A white opaque ointment packaged in a multi-use tube	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

AZR-MD-001 1.0% ointment/semi-solid drug has been selected for evaluation in this study.

6.1.3 DOSING AND ADMINISTRATION

The study medication will be self-administered by the patient (or administered by a caregiver) at home in the evening.

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

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

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

PREPARATION/HANDLING/STORAGE/ ACCOUNTABILITY

6.1.4 ACQUISITION AND ACCOUNTABILITY

Subjects will be instructed on proper instillation and storage of study drug at the end of the baseline (day 0), 2 weeks, 4 weeks and 6 weeks visits, will be given written instructions and may also watch an instructional video. The used and unused study drug tubes will be collected at each visit from baseline up to and including month 3 to assess dosing. Dosing compliance will be based off of the used and unused tube count. If the subject is less than 80% or more than 125% compliant with dosing based on the expected number of used tubes, then the subject will be deemed non-compliant and a deviation should be recorded.

6.1.5 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

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

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

6.1.6 PRODUCT STORAGE AND STABILITY

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

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

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

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

6.1.7 PREPARATION

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

6.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Site personnel conducting efficacy and safety measures will be masked to the treatment assignment for the 3 month treatment period.

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

Additionally, site personnel will observe patients applying ointment from a tube labelled "Vaseline" at the baseline visit, and will have access to instructional dosing videos.

6.3 CONCOMITANT THERAPY

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

6.3.1 RESCUE MEDICINE

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

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

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

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

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

If a patient discontinues participation in the study early, every attempt must be made to complete the exit procedures.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

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

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

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

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

7.3 LOST TO FOLLOW-UP

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

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

- The site will attempt to contact the participant and reschedule the missed visit within the specified visit window (see Table 1.3) and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

- Before a patient is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record or study file.

- Should the patient continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 SAFETY AND OTHER ASSESSMENTS

8.1.1 SAFETY MEASURES

The following safety measures will be examined:

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

8.2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

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

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

8.2.1 DEFINITION OF ADVERSE EVENTS (AE)

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

source under specific efficacy assessments. Anticipated fluctuations of pre-existing conditions, including the disease under study that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

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

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

Events meeting AE definition include:
• Any abnormal safety assessments (e.g., vital signs), 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.

8.2.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

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

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

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

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

suggest any significant hazard, contraindication, side effect, or precaution that may be associated with the use of the investigational product.

8.2.2.1 REPORTING OF SERIOUS ADVERSE EVENTS

Any SAE must be reported by the investigator if it occurs during the clinical study within 24 hours of the investigator's or site's knowledge of the event, whether or not the SAE is considered to be related to the investigational product. An SAE report consists of the SAE form, the AE form medical history and the concomitant medication form. SAEs will be reported to Azura Ophthalmics, the Human Research Ethics Committee and any other relevant approving authorities.

The site investigator will handle the SAE and ensure appropriate review and onward reporting to the Sponsor, with oversight of reporting to the ethics committees and competent authority as per local regulatory requirements:

For medical emergencies contact the medical monitor: Peter McCluskey

Phone: 02 9382 7300

E-Mail: peter.mccluskey@sydney.edu.au

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

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

UNSW will promptly notify all relevant investigators and the regulatory authorities of findings that could adversely affect the safety of subjects, impact on the conduct of the study or alter the independent ethics committee (IEC)/institutional review board (IRB) approval/favorable opinion of the study.

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

8.2.3 CLASSIFICATION OF AN ADVERSE EVENT

8.2.3.1 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

8.2.3.2 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.

8.2.3.3 ACTION TAKEN

The investigator will describe the action taken in the appropriate source document, as follows:

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

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

Subjects with AEs will be followed-up until the event is resolved or until, in the opinion of the investigator, the event is stabilized or determined to be chronic. Details of AE resolution must be documented in the source documents.

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

8.2.4.1 DOCUMENTATION AND REPORTING OF ADVERSE EVENTS

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

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

8.2.5 REPORTING EVENTS TO PARTICIPANTS

When necessary for the safety and proper treatment of the patient, the investigator can unmask the patient's treatment assignment to all site personnel to determine which treatment has been assigned and institute appropriate follow-up care.

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

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

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

8.2.6 EVENTS OF SPECIAL INTEREST

8.2.6.1 UNEXPECTED ADVERSE REACTION DEFINITION

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

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

8.2.7 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 Opththalmics.

9 STATISTICAL CONSIDERATIONS

9.1 SAMPLE SIZE DETERMINATION

The sample size is determined empirically.

9.2 POPULATIONS FOR ANALYSES

The safety population will include all treated patients. For safety variables, patients in the safety population will be analyzed by the treatment actually received. The modified intent-to-treat (mITT) population will be comprised of all patients randomized and who have values at

randomization, and at least 1 post-randomization for MGE. All patients in the mITT population will be analyzed by the treatment received. This population will be used for the primary and the secondary efficacy analyses.

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

9.3 PROTOCOL DEVIATIONS

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

These practices are consistent with ICH GCP:

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

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

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

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

9.4.2 ANALYSIS OF THE PRIMARY SAFETY ENDPOINT(S)

Safety measures will be analyzed using the safety population. Medical Dictionary for Regulatory Activities (MedDRA) nomenclature will be used to code adverse events. Treatment-emergent adverse events will be summarized. The adverse events will be classified into ocular and nonocular types and will be summarized separately.

9.4.3 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.

9.4.4 PLANNED INTERIM ANALYSES

No interim analysis is planned for this study.

9.4.5 SUB-GROUP ANALYSES

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

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

1. Average MGS score < 6
2. Average MGS score ≥ 6 and ≤ 12

9.4.6 TABULATION OF INDIVIDUAL PARTICIPANT DATA

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

9.4.7 EXPLORATORY ANALYSES

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

10 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1 INDEPENDENT ETHICS COMMITTEE

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

10.2 REGULATORY AUTHORITIES

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

10.3 ETHICAL CONDUCT OF THE STUDY

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

10.4 INFORMED CONSENT PROCESS

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

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

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

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

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

10.5 SUBJECT CONFIDENTIALITY

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

11 QUALITY ASSURANCE

11.1 AUDIT AND INSPECTION

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

11.2 MONITORING

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

11.3 DATA MANAGEMENT AND CODING

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

12 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

12.1 STUDY DISCONTINUATION AND CLOSURE

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

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

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

- Determination of futility

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

12.2 FUTURE USE OF STORED SPECIMENS AND DATA

12.2.1 HANDLING OF BIOLOGICAL SPECIMENS

Not applicable.

12.2.1.1 TEAR SAMPLES

Not applicable.

12.3 RETENTION OF DOCUMENTATION

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

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

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

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

12.4 SOURCE DOCUMENTS

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

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

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

12.5 STUDY SUMMARY

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

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

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

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

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

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

12.7 PUBLICATION AND DATA SHARING POLICY

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

12.8 CONFLICT OF INTEREST POLICY

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

12.9 ADDITIONAL CONSIDERATIONS

None

12.10 ABBREVIATIONS

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

12.11 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
2.0	14Apr2020	Addition of exclusion criteria "Known carrier of infectious disease"	As per UNSW HREC's recommendation

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14 APPROVAL(S)

Protocol Title:	**A Single-center, Vehicle-controlled, Study to Evaluate Methods to Enhance the Safety and Tolerability of AZR-MD-001 for Meibomian Gland Dysfunction (MGD)**
Protocol Number:	SOVS2020-080
Final Date:	14Apr2020

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

Signed:_____ Date:_____

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