Statistical Analysis Plan for Three Month Primary Analysis

Sponsor Name: Azura Ophthalmics

Protocol Number: AZ201801 Expansion Cohort

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 Version and Date: Amendment 5, version 6.0 – 19 March 2021
and All Country-Specific Addenda

Cohort: Expansion Cohort

Syneos Health Project Code: 1010854

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REVISION HISTORY

Version #	Date (DD-Mmm-YYYY)	Revision Summary
Final v1.0	22-Apr-2022	Initial Release Version of Expansion Cohort SAP

I confirm that I have reviewed this document and agree with the content.

Approvals	
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LIST OF ABBREVIATIONS

Abbreviation	Description
ANCOVA	analysis of covariance
ATC	anatomical therapeutic chemical
BCVA	best-corrected visual acuity
CMH	cochran-mantel-haenszel
CRF	case report form
DED	dry eye disease
eCRF	electronic case report forms
ET	early termination
IOP	intraocular pressure
ITT	intent-to-treat
IWRS	interactive web response system
LogMAR	logarithm of the minimal angle of resolution
LOCF	last observation carried forward
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MGD	meibomian gland dysfunction
MGS	meibomian gland score
MGYLS	meibomian glands yielding liquid secretion
MGYOLS	meibomian glands yielding optimal liquid secretion
MI	multiple imputation
mITT	modified intent-to-treat
OSDI	Ocular Surface Disease Index
PP	Per-Protocol
PP6	Per-Protocol Analysis Set, Month 6
PT	Preferred Term
SAE	serious adverse events
SAP	Statistical Analysis Plan

Abbreviation	Description
SOC	System Organ Class
SPEED	Standard Patient Evaluation of Eye Dryness questionnaire
TBUT	tear break-up time
TEAE	treatment-emergent adverse event
WHODRUG	World Health Organization Drug Dictionary
VAS	visual analogue scale

1. PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings and summary tables which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives described under Azura Ophthalmics Protocol AZ201801 titled "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)", Version Amendment 5, 6.0 dated 19 March 2021 and all country-specific addenda. This SAP supports the analyses for health authorities that will accept the Month 3 timepoint for the primary efficacy endpoint.

In accordance with the US FDA pre-IND meeting minutes (Question 19), this SAP is *only* for the Expansion Cohort; a separate AZ201801 SAP covers Cohort 1. No analyses of the combined cohorts are planned.

1.1. Responsibilities

Syneos Health will perform the statistical analyses and are responsible for the production and quality control of all tables and listings consistent with a Phase 3 confirmatory study.

1.2. Timings of Analyses

The primary analysis for the AZ201801 Expansion Cohort will occur after the final enrolled patient completes the Month 3 visit. All patients will be followed for safety for an additional 3 months. The analysis of data collected during this additional safety follow-up, including supplemental safety analyses and exploratory efficacy analyses, is covered by this SAP.

Prior to the 3 month database freeze and subsequent unmasking of specific study team members, the data for the primary efficacy endpoints (changes from baseline to Month 3 in meibomian glands yielding liquid secretion [MGYLS] and Ocular Surface Disease Index [OSDI] total score) will be evaluated in a masked fashion, in order to re-open enrollment to additional patients if the variability is higher than expected, as described in Section 2.3.

If additional patients are enrolled, the 3-month database freeze, unmasking of specific study team members, and analyses will be conducted after the last of those additional patients completes the Month 3 visit.

The unmasking of specific study team members following the Month 3 database freeze is documented in the AZ201801 Expansion Cohort Unmasked Data Access Plan, which details how a specific group of individuals will be unmasked in order to perform the Month 3 analyses, while the study execution team will remain masked to treatments until all patients have

completed Month 6. All data collected through Month 3 will be cleaned prior to freezing the database. All data collected through Month 6 will be cleaned prior to database lock and unmasking of the rest of the study team.

The primary safety analysis will be performed after all patients have either completed the Month 3 visit or discontinued from the study. An additional 3-month safety follow-up (including Month 4.5 and Month 6 visits) will be conducted, and supplemental safety results will be produced after the completion of the Month 6 visits (study completion). Exploratory efficacy analyses, utilizing efficacy data collected during the safety follow-up period, will also be performed after the completion of the Month 6 visits.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective is to evaluate the safety and efficacy of 2 different concentrations of AZR-MD-001 ointment/semi-solid drug applied to the lower lid twice-weekly for up to 6 months, as compared to placebo, in patients with MGD.

2.2. Brief Description

The study is a multi-center, double-masked, placebo-controlled, randomized, parallel group study carried out in 2 sequential cohorts. The Expansion Cohort includes parallel doses of 2 concentrations of AZR-MD-001 ointment/semi-solid drug (0.5% and 1.0%) and placebo, dosed twice-weekly in the evening. Patients are to be followed for 6 months. Primary efficacy analyses will be performed based on the 3-month data, and exploratory efficacy analyses will be performed on data collected during the subsequent 3-month safety follow-up.

Inclusion and exclusion criteria are provided in AZ201801 Protocol Sections 5.1 and Section 5.2.

Key inclusion criteria require patients have meibomian gland secretion (MGS) scores of ≤12 in both eyes at the Screening and Baseline visits; reported dry eye signs and symptoms within the past 3 months; Standard Patient Evaluation of Eye Dryness questionnaire (SPEED) score ≥6; OSDI questionnaire total score ≥13 and <34; and tear break-up time (TBUT) <10 seconds in both eyes.

Exclusion criteria include best corrected visual acuity (BCVA) worse than 20/40 in either eye; anticipated contact lens use; Schirmer's tear test without anesthesia ≤5 mm in either eye at the baseline visit; or corneal staining ≥3 (between 33 and 100 dots) using the Oxford Scheme.

2.3. Determination of Sample Size

2.3.1. Initial Determination of Sample Size

Estimates for Expansion Cohort sample size calculations are from the integrated analysis of AZ201801 Cohort 1, AZ202001, SOVS2019-070, and SOVS2020-080, limited to the mITT Analyzable population (refer to the integrated Clinical Study Report). The means and standard deviations of the changes from baseline at Month 3, after applying last observation carried forward (LOCF) imputation, are utilized (Table 1).

Table 1 Integrated Analyses Change from Baseline to Month 3

	AZR-MD-001 0.5% Mean (SD)	**AZR-MD-001 1.0% Mean (SD)**	**Placebo Mean (SD)**
MGYLS	2.77 (3.35)	3.79 (4.11)	0.77 (2.28)
OSDI	-8.36 (9.06)	-5.33 (8.39)	-0.81 (6.31)

Abbreviations: MGYLS = meibomian glands yielding liquid secretion; OSDI = Ocular Surface Disease Index; SD = standard deviation.

The study was designed to have 95% power to detect treatment differences between AZR-MD-001 0.5% and placebo, and between AZR-MD-001 1.0% and placebo, which requires 72 patients per treatment arm. To allow for additional site-to-site variability, the sample size per group was increased to 75 randomized patients per arm.

The total number of randomized patients for the Expansion Cohort will be approximately 225 (75× 3). 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.

2.3.2. Sample Size Re-Estimation

As described in Section 1.2, additional patients may be enrolled if the observed variability within the Expansion Cohort is higher than anticipated, after the evaluation of the MGYLS and OSDI total score changes from baseline to Month 3 using LOCF imputation. The standard deviation of the pooled treatment groups will be calculated in a masked fashion for both MGYLS and OSDI total score and compared to the pooled standard deviations of 3.63 (MGYLS) and 8.71 (OSDI) from the integrated study. No unmasking will be performed as part of this re-estimation.

The power calculations from the integrated studies will be re-derived based on pooled standard deviations (resulting in 0.918 for the MGYLS comparison of AZR-MD-001 0.5% to placebo, and >0.999 for the other comparisons), for the sole purpose of providing a basis for comparison to the power re-calculations based on the pooled standard deviations from the Expansion Cohort.

Patients may be added up to the specified numbers, to maintain the current power of the study, if possible. For example:

- If the pooled standard deviation is 3.64-3.85 for MGYLS or 8.72-9.64 for OSDI total score, up to 30 additional patients may be randomized (10 per treatment arm).
- If the pooled standard deviation is 3.86-4.07 for MGYLS or 9.65-10.20 for OSDI total score, up to 60 additional patients may be randomized (20 per treatment arm).
- If the pooled standard deviation is 4.08-4.29 for MGYLS or 10.21-10.74 for OSDI total score, up to 90 additional patients may be randomized (30 per treatment arm).

The specific sample sizes needed will be recalculated using the initial mean changes from baseline from the integrated studies, in conjunction with the pooled standard deviations from the Expansion Cohort, using the following pseudocode:

```
proc power;
  twosamplemeans test=diff dist=normal groupmeans=(2.77 0.77)
  stddev=xxx sides=2 power=.918 npergroup=.;
  run;
proc power;
  twosamplemeans test=diff dist=normal groupmeans=(3.79 0.77)
  stddev=xxx sides=2 power=.999 npergroup=.;
  run;
proc power;
  twosamplemeans test=diff dist=normal groupmeans=(-8.36 -0.81)
  stddev=xxx   sides=2 power=.999 npergroup=.;
  run;
proc power;
  twosamplemeans test=diff dist=normal groupmeans=(-5.33 -0.81)
  stddev=xxx sides=2 power=.999 npergroup=.;
  run;
```

If additional patients are added, the database freeze and unmasking of specific team members will be postponed until after those patients complete their Month 3 visit.

2.4. Treatment Assignment and Masking

At the Baseline visit, patients meeting all study criteria will be stratified by disease duration (<5 or 5+ years) and baseline MGS score in the study eye (<6 or 6-≤12). Patients will be randomized in a 1:1:1 ratio, within each of the 4 strata, to AZR-MD-001 0.5%, AZR-MD-001 1.0%, or placebo. The interactive web response system (IWRS) system will provide both a patient randomization number and study kit number to use for that patient.

Patients will be dispensed Vaseline (in a separate kit from study kit, and identified by a Vaseline kit number), and will administer it while onsite during the Baseline visit. Patients demonstrating the ability to correctly apply the ointment will be randomized and subsequently dispensed the

study kit (AZR-MD-001 0.5%, AZR-MD-001 1.0%, or placebo), to be administered twice weekly at home. All study kit medication will be provided in identical tubes and cartons to maintain masking of the study. The placebo packaging was designed to have the same appearance as the AZR-MD-001 treatment.

Upon database freeze, a designated team (as described in the AZ201801 Expansion Cohort Unmasked Data Access Plan) will be unmasked in order to conduct the Month 3 analyses, and those team members will not participate in study execution after unmasking. The remainder of the study personnel will be unmasked after all patients have completed Month 6, and the database has been locked.

2.5. Administration of Study Medication

Vaseline will be administered while at the study site, during the Baseline visit.

Subsequently, patients (or a caregiver) will apply a dose of approximately 5 mg for each application of the randomized study treatment, applied twice weekly in the evenings as described in AZ201801 Protocol Section 6.1.3.

Multi-dose tubes of the masked study medication are each to be used for only 30 days for both eyes. The number of used tubes, unused returned tubes, and unreturned tubes will be recorded at subsequent visits.

2.6. Study Procedures and Flowchart

Table 2 provides the schedule of activities.

Table 2 Schedule of Activities

Study Period	Qualification		Double-Masked Period				
	Three Month Efficacy Evaluation					Safety Follow-Up	
	Screening [a] (Day -14)	Baseline Day 0 Randomization	Day 14	Month 1.5	Month 3	Month 4.5	Month 6
Visit Window	± 2 Days	N/A	± 2 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
Pregnancy test (urine) for female patients [b]	X						
Patient Ocular Symptoms (VAS)	X	X	X	X	X	X	X
OSDI	X	X	X	X	X	X	X
SPEED	X	X	X	X	X	X	X
BCVA	X[C]	X	X	X	X	X	X
Slit-lamp biomicroscopy (includes eyelid margin erythema/telangiectasias)	X	X	X	X	X	X	X
TBUT[d]	X	X	X	X	X	X	X
Sodium fluorescein corneal staining, Oxford scale	X	X	X	X	X	X	X
Lissamine green conjunctival staining, Oxford scale	X	X	X	X	X	X	X

Study Period	Qualification		Double-Masked Period				
	Three Month Efficacy Evaluation					Safety Follow-Up	
	Screening [a] (Day -14)	Baseline Day 0 Randomization	Day 14	Month 1.5	Month 3	Month 4.5	Month 6
Visit Window	**± 2 Days**	**N/A**	**± 2 Days**	**± 7 Days**	**± 2 Days**	**± 7 Days**	**± 2 Days**
MGE[d]	X	X	X	X	X	X	X
Schirmer without anesthesia	X	X			X		X
IOP	X				X		X
Ophthalmoscopy exam [e]	X				X		X
Meibography	X				X		X
Adverse events/medications/procedures	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		X	X	X	X
Physician Observation of Drug Application		X					

Abbreviations: BCVA = best-corrected visual acuity; DED = dry eye disease; IOP = intraocular pressure; MGD = meibomian gland dysfunction; MGE = meibomian gland evaluation; OSDI = ocular surface disease index; SPEED = standard patient evaluation of eye dryness; TBUT = tear break-up time; VAS = visual analogue scale.

[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. Patients who are re-enrolled following an initial screen failure will receive a new screening number.

[b] For females of childbearing potential.

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

[d] TBUT and MGE should be performed by the same individual for a given patient. 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.

[e] Ophthalmoscopy examination will be dilated at screening and undilated for study exit unless dilation is necessary.

3. ENDPOINTS

3.1. Efficacy Endpoints

3.1.1. Primary Efficacy Endpoints

Primary efficacy measures are divided into endpoints for primary efficacy signs and primary efficacy symptoms for MGD.

- The primary efficacy sign for MGD is the Change from Baseline at Month 3 in MGYLS (0 to 15 scale; higher scores are better).
- The primary efficacy symptom for MGD is the Change from Baseline at Month 3 in OSDI total score (0 to 100 scale; lower scores are better).

3.1.2. Secondary Efficacy Endpoints

The key secondary efficacy endpoints include:

- MGYLS
  - Proportion of patients with a change from baseline in MGYLS score ≥5 at Day 14, Month 1.5, and Month 3
- OSDI
  - Proportion of patients with OSDI total score < 13 at Day 14, Month 1.5, and Month 3.
- SPEED
  - Change from Baseline at Day 14, Month 1.5, and Month 3 in SPEED.
- Eye Dryness Visual Analogue Scale (VAS)
  - Change from Baseline at Day 14, Month 1.5, and Month 3 for Eye Dryness VAS.

The secondary efficacy endpoints include:

- MGS (0 to 45 scale; higher scores are better)
  - Change from Baseline at Day 14, Month 1.5, and Month 3 in MGS.
  - Proportion of patients with MGS score >12 at Day 14, Month 1.5, and Month 3.
- MGYLS
  - Change from Baseline at Day 14 and Month 1.5 in MGYLS
- OSDI
  - Change from Baseline at Day 14 and Month 1.5 in OSDI total score.

3.1.3. Exploratory Efficacy Endpoints

3.1.3.1. Exploratory Efficacy Endpoints Evaluated At Month 3

- MGYLS
  - Proportion of patients with MGYLS >2 at Day 14, Month 1.5, and Month 3.
- Meibomian Glands Yielding Optimal Liquid Secretion (MGYOLS, e.g., number of expressible glands yielding clear meibum)
  - Change from Baseline at Day 14, Month 1.5, and Month 3 in MGYOLS.
  - Proportion of patients with MGYOLS score >2 at Day 14, Month 1.5, and Month 3.
- OSDI total score and subscales
  - Proportion of patients with OSDI total score Decrease from Baseline >4.5 at Month 3 (4.5 is the minimally important clinical difference for early to moderate disease).
  - Change from Baseline at Day 14, Month 1.5, and Month 3 in OSDI subscales
- SPEED
  - Proportion of patients with SPEED <6 at Day 14, Month 1.5, and Month 3
- TBUT
  - Change from Baseline at Day 14, Month 1.5, and Month 3 in TBUT.
  - Proportion of patients with TBUT score >5 at Day 14, Month 1.5, and Month 3.
  - Proportion of patients with TBUT score >10 at Day 14, Month 1.5, and Month 3.
- Schirmer's Test without Anesthesia
  - Change from Baseline at Day 14, Month 1.5, and Month 3 in Schirmer's test.
  - Proportion of patients with Schirmer's test result ≥10mm at Day 14, Month 1.5, and Month 3.
- VAS
  - Change from Baseline at Day 14, Month 1.5, and Month 3 in individual VAS results (besides eye dryness), Average VAS, and Worst VAS, separately.
  - Proportion of patients with score decreased by ≥5, separately for Average VAS and Worst VAS, at Day 14, Month 1.5, and Month 3.
- Other
  - Eyelid margin erythema/telangiectasias at Day 14, Month 1.5, and Month 3.
  - Corneal and conjunctival staining (0 to 5 scale) at Day 14, Month 1.5, and Month 3.

3.1.3.2. Exploratory Efficacy Endpoints Evaluated After Completion of Safety Follow-up Period

- MGYLS
  - Change from Baseline at Month 4.5 and Month 6 in MGYLS.
  - Proportion of patients with a change from baseline in MGYLS score ≥5 at Month 4.5 and Month 6.
  - Proportion of patients with MGYLS > 2 at Month 4.5 and Month 6.

- OSDI total score and subscales
  - Change from Baseline at Month 4.5 and Month 6 in OSDI total score
  - Proportion of patients with OSDI total score < 13 at Month 4.5 and Month 6
  - Proportion of patients with OSDI total score Decrease from Baseline >4.5 at Month 6.
  - Change from Baseline at Month 4.5 and Month 6 in OSDI subscales.
- SPEED
  - Change from Baseline at Month 4.5 and Month 6 in SPEED
  - Proportion of patients with SPEED <6 at Month 4.5 and Month 6
- VAS
  - Change from Baseline at Month 4.5 and Month 6 in individual VAS results, Average VAS, and Worst VAS, separately.
  - Proportion of patients with score decreased by ≥5, separately for Average VAS and Worst VAS, at Month 4.5 and Month 6.
- MGS
  - Change from Baseline at Month 4.5 and Month 6 in MGS.
  - Proportion of patients with MGS score >12 at Month 4.5 and Month 6.
- MGYOLS
  - Change from Baseline at Month 4.5 and Month 6 in MGYOLS.
  - Proportion of patients with MGYOLS score >2 at Month 4.5 and Month 6.
- TBUT
  - Change from Baseline at Month 4.5 and Month 6 in TBUT.
  - Proportion of patients with TBUT score >5 at Month 4.5 and Month 6.
  - Proportion of patients with TBUT score >10 at Month 4.5 and Month 6.
- Schirmer's Test without Anesthesia
  - Change from Baseline at Month 4.5 and Month 6 in Schirmer's test.
  - Proportion of patients with Schirmer's test result ≥ 10mm at Month 4.5 and Month 6.
- Other
  - Eyelid margin erythema/telangiectasias at Month 4.5 and Month 6.
  - Corneal and conjunctival staining (0 to 5 scale) at Month 4.5 and Month 6.

3.2. Safety Endpoints

Safety endpoints will be evaluated through Month 3, and supplemental safety analyses (including information collected through Month 6) will be evaluated at the end of the safety follow-up period. Safety endpoints include:

- Adverse events
- Vital signs
- BCVA (Logarithmic visual acuity chart)
- Biomicroscopy (Slit Lamp)

- Ophthalmoscopy
- Intraocular pressure (IOP)
- Conjunctival hyperemia (redness)

4. ANALYSIS SETS

4.1. Intent-to-Treat Analysis Set

The Intent-to-Treat (ITT) Set will include all patients who were randomized. Patients will be analyzed according to treatment as randomized. The ITT Set will be used for analyses of efficacy data.

4.2. Modified Intent-to-Treat Analysis Set

The Modified Intent-to-Treat (mITT) Set will be comprised of all randomized patients who meet inclusion/exclusion criteria, have MGS values at randomization, have baseline OSDI <34, and received 1 or more applications of randomized study treatment. All patients in the mITT Set will be analyzed by the treatment as randomized. This population will be used for primary efficacy analyses.

4.3. Per-Protocol Analysis Set, Month 3

The Per-Protocol (PP) Set will be comprised of all mITT patients who do not have a Grade 4 or Grade 5 protocol deviation impacting Baseline through Month 3 (as per Section 7). Deviations which end before the Baseline visit date or begin after the Month 3 visit will not impact inclusion in the PP Set. All patients in the PP Set will be analyzed by the treatment as randomized. The PP Set will be used for primary efficacy analyses.

4.4. Per-Protocol Analysis Set, Month 6 (PP6)

The Per-Protocol Analysis Set, Month 6 (PP6) will be comprised of all mITT patients who do not have a Grade 4 or Grade 5 protocol deviation impacting Baseline through Month 6 (as per Section 7). Deviations which end before the Baseline visit date will not impact inclusion in the PP6 Set. All patients in the PP6 Set will be analyzed by the treatment as randomized. The PP6 Set will be used for exploratory efficacy analyses.

4.5. Pre-Randomization Vaseline Application Set

The pre-randomization Vaseline Application Set will include all patients who were applied Vaseline during the Baseline visit, prior to randomization. This set will be used for summaries of any adverse events due to Vaseline application at the Baseline visit.

Vaseline administration is documented by a positive response to the question, '*Did the patient apply the ointment over the full lower eyelid length (nasal to temporal)?*' on the Physician Observation of Drug Application electronic case report form (eCRF), or, for negative responses to that question, a non-zero response to the subsequent question, '*If not, to what percentage of the lower lid margin was the ointment applied?*'.

4.6. Safety Set

The Safety Set will include all patients who were administered at least one dose of randomized study medication. Patients will be analyzed according to treatment received. The Safety Set will be used for all analyses of safety data.

5. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

5.1. General Methods

All analyses and summaries will be produced using SAS® version 9.4 (or higher). Data will be summarized descriptively by treatment group.

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 covariance (ANCOVA) techniques. Categorical variables will be summarized by sample size (N), frequency count, and percent, and will be analyzed using Cochran-Mantel-Haenszel (CMH) to evaluate the difference between treatments, controlling for disease duration category and baseline MGS score category. If CMH comparisons are not estimable, Pearson's chi-square test or Fisher's exact test (if the expected cell count is <5 in 25% or more of the cells) will be used.

For analysis purposes, assessments at **unscheduled** visits will be mapped to the nearest scheduled visit (e.g., analysis visit), using the following approach, as summarized in Table 3. All unscheduled visits prior to the Baseline visit date, or in patients who have not had a Baseline visit, will be mapped to the Screening visit.

For assessments scheduled for every study visit: Study visits are scheduled to occur at 14, 42, 84, 126, and 168 days after the Baseline visit for the Day 14, Month 1.5, Month 3, Month 4.5, and Month 6 visits respectively. Therefore, the numbers of days between those visits, not counting the actual visit days, are 13, 27, 41, 41, and 41. Dividing those periods in half and rounding down, the windows around visits should extend to 6, 13, 20, 20, and 20 days after the scheduled visit day. The next window should start the day after the prior window ends, resulting in the following windows:

- Baseline visit date through Baseline visit date + 6: mapped to Baseline visit.
- Baseline visit date + 7 through Baseline visit date + 26: mapped to Day 14 visit.

- Baseline visit date + 27 through Baseline visit date + 61: mapped to Month 1.5 visit.
- Baseline visit date + 62 through Baseline visit date + 103: mapped to Month 3 visit.
- Baseline visit date + 104 through Baseline visit date + 145: mapped to Month 4.5 visit.
- Baseline visit date + 146 or later: mapped to Month 6 visit.

For assessments not scheduled at every study visit: The same approach will be used, omitting the visits without planned assessments from the algorithm. For example, vital signs and Schirmer's assessment are planned for Baseline, Month 3, and Month 6 visits. The numbers of days between those visits are 83 in both cases, resulting in the first 41 days of the period being assigned to the earlier visit. Therefore:

- Baseline visit date through the Baseline visit date + 41 would be assigned to the Baseline visit;
- Baseline visit date + 42 through Baseline visit date + 125 would be assigned to the Month 3 visit, and
- Baseline visit date + 126 or later to the Month 3 visit.

In cases where an assessment is not scheduled to be performed at the Baseline visit, but is scheduled only at the Screening visit, Month 3, and Month 6, (such as IOP, meibography, or ophthalmology), visits prior to and including the Baseline visit will be windowed to the Screening visit, and visits between the Baseline and Month 3 visits will be windowed to Month 3. Visits between Month 3 and Month 6 will be split as described above.

Assessments conducted at the time of **early termination** (defined as assessments performed on the date of early termination or recorded on the same date as an End of Study visit is entered in the subject visit case report form [CRF] page) will also be mapped to the nearest planned visit, as described for unscheduled visits.

Table 3 Mapping of Unscheduled and Early Termination Visits

<table>
<tr><th rowspan="2">Visit</th><th rowspan="2">Date with Regards to Baseline Visit</th><th rowspan="2">Study Day</th><th colspan="3">Analysis Visit Mapping</th></tr>
<tr><th>Assessments Performed Each Visit</th><th>Assessments Performed at Screening, Baseline, Month 3, and Month 6</th><th>Assessments Performed at Screening, Month 3, and Month 6</th></tr>
<tr><td>Screening</td><td>Baseline -14 d</td><td>-14</td><td>Screening</td><td>Screening</td><td rowspan="2">Screening</td></tr>
<tr><td>Baseline</td><td>Baseline</td><td>1</td><td rowspan="3">Baseline</td><td rowspan="5">Baseline</td></tr>
<tr><td></td><td>…</td><td>…</td><td rowspan="4">Month 3</td></tr>
<tr><td></td><td>Baseline + 6 d</td><td>7</td></tr>
<tr><td></td><td>Baseline + 7 d</td><td>8</td><td rowspan="3">Day 14</td></tr>
<tr><td></td><td>…</td><td>…</td></tr>
<tr><td>Day 14</td><td>Baseline + 14 d</td><td>15</td></tr>
</table>

Visit	Date with Regards to Baseline Visit	Study Day	Analysis Visit Mapping		
			Assessments Performed Each Visit	Assessments Performed at Screening, Baseline, Month 3, and Month 6	Assessments Performed at Screening, Month 3, and Month 6
	…	…			
	Baseline + 26 d	27			
	Baseline + 27 d	28	Month 1.5		
	…	…			
	Baseline + 41 d	42			
Month 1.5	**Baseline + 42 d**	43			
	…	…			
	Baseline+61 d	62			
	Baseline+62 d	63	Month 3		
	…	…			
Month 3	**Baseline + 84 d**	85			
	…	…			
	Baseline+103 d	104			
	Baseline+104 d	105	Month 4.5		
	…	…			
	Baseline+125 d	126			
Month 4.5	**Baseline+126 d**	127			
	…	…			
	Baseline+145 d	146			
	Baseline+146 d	147	Month 6		
	…	…			
Month 6	**Baseline + 168 d**	169			
	…	…			
	End of Study				

Abbreviations: d = day(s).

Note: Ellipses indicate all dates between the prior and subsequent lines.

If multiple assessments are mapped to the same analysis visit (such as the scheduled visit and 1+ unscheduled visits), the following approach will be used:

- If only 1 non-missing result is present, that result will be used for summaries and analyses.
- If >1 non-missing result is present, the result collected later (chronologically) will be used for summaries and analyses.

All relevant patient data will be included in the listings. All information entered into the database will be included in patient data listings, including data not used for analysis purposes. Data will be listed by the nominal time point collected (whether a scheduled visit or unscheduled visit). Listings will display treatment as randomized. In the event that actual treatment differs from treatment as randomized, a footnote will be added to listings as appropriate, to provide specific information.

Summary statistics will be presented to the degree of precision provided in Table 4.

Table 4 Reporting Precision

Statistics	Degree of Precision
Mean, Median, Quartiles, Confidence intervals	One more decimal place than the raw data
Standard deviation (SD), Standard error (SE)	Two more decimal places than the raw data
Minimum, Maximum	The same number of decimal places as the raw data
p-value	Rounded to 4 decimal places and formatted as 0.xxxx; values smaller than 0.0001 as '<0.0001'
Percent	One decimal place

All fractional numeric values will be presented with a zero to the left of the decimal point (for example, 0.12-0.30, not .12-.30).

5.2. Key Definitions

5.2.1. Date of First Dose of Study Treatment

The date of first dose of study treatment will be the date of the Baseline visit, at which the randomized study treatment is dispensed. Patients are to be instructed to apply the first dose at home that evening. Patients who do not have confirmation of study treatment administration (defined as non-zero number of doses taken, on a study drug compliance eCRF at the Month 1.5 visit) will not have a date of first dose defined. If a patient takes zero doses before the Month 1.5 visit but does take subsequent doses, the date of first dose will reflect the date of dispensation of the first study treatment applied.

5.2.2. Baseline Values

The baseline assessment will be the last available measurement taken on or before the date of first dose of study treatment, including any assessments at unscheduled visits. Measurements taken on the date of first dose of study treatment will be considered to be taken prior to first dose. Baseline values are typically collected at the Baseline visit.

5.2.3. Study Day

Study day is calculated as (date - first dose date of study medication +1) for dates on or after first dose, and (date - first dose date) for dates before the first dose date. Therefore, the first dose date is Study Day 1, and the day immediately prior is Study Day -1. The first dose date of study medication will be based on the application of Vaseline while onsite during the Baseline visit. The first application of randomized study medication is expected to be applied that evening.

5.2.4. Change from Baseline to Post Study Medication Visits

Change from Baseline is (value - baseline value) and is calculated for subjects with both non-missing baseline values and non-missing post-baseline values.

5.2.5. Tear Break-up Time

The TBUT for a patient is calculated as average of 3 separate measurements for each eye separately.

5.2.6. Ocular Surface Disease Index Total Score and Subscale Scores

The OSDI questionnaire, provided in Appendix 2, 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 the time. There are 7 questions related to visual functioning that allow a response of "N/A" (not applicable).

The OSDI total score (on a scale of 0 to 100) is be calculated from the raw scores of each of the 12 questions based on the formula: ([sum of scores for all questions answered]×100)/([total number of questions answered]×4), where questions answered with N/A are considered unanswered and excluded from the calculation Higher scores represent greater disability.

Subscale scores are calculated similarly, where the Ocular Symptoms subscale includes the 5 questions on light sensitivity, gritty feeling, painful/sore eyes, blurred vision, and poor vision; the Vision Related Function subscale includes the 4 questions on problems reading, driving at night, working with a computer, or watching TV; and the Environmental Triggers subscale includes questions about windy conditions, low humidity, and air conditioning.

5.2.7. Visual Analogue Scale

Individual visual analogue scales will be completed for 7 different symptoms, as provided in Appendix 1. Lower values indicate better results:

- burning/stinging
- itching

- foreign body sensation
- eye discomfort
- eye dryness
- photophobia
- pain

The mean of the completed VAS scores will be calculated to produce the Average VAS score.

The Worst VAS will be defined as the individual VAS with the highest (worst) score at baseline. If two or more VAS results are tied for the highest score at baseline, the average of those two (or more) will be used as the Worst VAS. Changes from baseline at subsequent visits will then be calculated based on the average of those scores at subsequent visits.

5.2.8. Standard Patient Evaluation of Eye Dryness

The SPEED score will be calculated based on occurrence, frequency, and severity of the 4 symptoms of dryness, grittiness or scratchiness, soreness or irritation, burning or watering, and eye fatigue as shown in Appendix 3. Frequency is evaluated on a 4-point scale (0=never to 3=constant) and severity on a 5-point scale (0=no problem to 4=intolerable) for each symptom. The total SPEED score is derived as the sum of the frequency and severity scores across all 4 symptoms, with a range of possible values of 0 to 28, where higher scores indicate increasing severity.

5.2.9. Best Corrected Visual Acquity Logarithm of the Minimal Angle of Resolution

Logarithm of the Minimal Angle of Resolution (LogMAR) will be calculated from the total letter score as LogMAR = 1.7-0.02×(total letter score), for each eye.

5.3. Missing Data

Missing efficacy data will be handled as follows:

- The primary efficacy analyses and most other efficacy analyses will utilize multiple imputation.
- Sensitivity analyses will be performed on the primary using the LOCF approach, where non-missing post-baseline values are carried forward to subsequent visits.

Prior to performing imputation or analyses, results from unscheduled visits and early termination (ET) visits (defined as per Section 5.1) will be mapped to the closest scheduled visit (Day 14, Month 1.5, Month 3, Month 4.5, or Month 6). In other words, a patient with an ET visit at Day 40 would have its those results mapped to the Month 1.5 visit.

Actual item results will be imputed, and any subscale scores, total scores, changes from baseline, responder status, etc. will be derived from the imputed values where necessary.

For safety analyses, where incomplete dates are present, medications will be categorized as concomitant, and adverse events as treatment-emergent, unless sufficient information is present to definitely determine that the medication usage completed, or event resolved, prior to the first dose of study medication.

5.3.1. Multiple Imputation

Missing data will be imputed via multiple imputation (MI) using a Markov Chain Monte Carlo (MCMC) approach. This approach is suitable for non-monotone missingness (missed visits followed by completed visits), incorporates all available observed data as the basis for imputing values, and utilizes the same method to handle all missing data (i.e., not differentiating by cause of missingness). Studies have shown that MI is statistically superior to more traditional methods of imputation (e.g., LOCF; e.g., DeSouza et al., 2009; Tang et al., 2005).

5.3.1.1. Multiple Imputation for Primary Analysis

Multiple imputation will be performed separately for each assessment; in other words, MGYLS values will not be used to impute OSDI values. The same seed number (utilized in SAS® PROC MI) of 135790 will be used throughout. For each MI, 20 imputations will be created, analyses performed on each imputed dataset separately, and results combined using PROC MIANALYZE. The appropriate minimum and maximum values will be used for each variable, and results rounded to the same precision as collected values. Multiple imputation will be limited to patients in the analysis population being used, and will include values that are eligible for use in summaries and analyses as described in Section 5.1 (e.g., unscheduled and early termination visits will be mapped to scheduled visits, and visits with >1 non-missing values mapped to that visit will utilize the later result), through the Month 3 visit. Screening visit values will not be incorporated into the multiple imputation.

The following variables will be included in the multiple imputation model, as numeric variables:

- Treatment group (split into three dichotomous variables)
- Randomization criteria (disease duration category and baseline MGS score category)
- Age
- Sex
- Analysis value (MGYLS or OSDI total score) for each scheduled visit

The following pseudocode will be used:

```
proc mi data=xxx seed=135790 nimpute=20 out=yyy
            minimum = 0 0 0 18 0 0 0  0  0  0  0
```

```
            maximum = 1 1 1 99 1 1 1  xx xx xx xx
            round =   1 1 1 1  1 1 1  1  1  1  1  ;
      var Dur5yr MGSless6 male age trt0_5 trt1_0 trtpbo
            Day1 Day14 Day45 Day90;
      mcmc chain=multiple displayinit;
      run;

<proc genmod, etc.>

Proc mianalyze data=xxx (drop=effect);
      by trt01pn;
      modeleffects LSM;
      stderr;
      run;
```

5.3.1.2. Multiple Imputation for Exploratory Analyses

A second multiple imputation will be performed similarly for each assessment, utilizing the data through Month 6, for exploratory efficacy analyses performed after the completion of the safety follow-up period. For each of the initial 20 imputations created through Month 3, an additional 20 imputations will be created to impute Month 4.5 and Month 6. Subsequent analyses of the 20×20=400 imputations will be performed separately for each imputation, then results combined using PROC MIANALYZE.

The following pseudocode will be used, in addition to the prior pseudocode:

```
proc mi data=yyy (rename=(_imputation_=Imp1)) seed=1357902 nimpute=20 out=zzz
            minimum = 0 0 0 18 0 0 0  0  0  0  0  0  0
            maximum = 1 1 1 99 1 1 1  xx xx xx xx xx xx
            round =   1 1 1 1  1 1 1  1  1  1  1  1  1 ;

      by Imp1;

      var Dur5yr MGSless6 male age trt0_5 trt1_0 trtpbo
            Day1 Day14 Day45 Day90 Day135 Day180;

      mcmc chain=multiple displayinit;
      run;
```

5.3.2. Last Observation Carried Forward

The LOCF approach will be used to impute primary efficacy data for sensitivity analyses, where specified. Post-baseline values may be carried forward (i.e., scheduled visits at Day 14 or later, any post-baseline unscheduled or early termination visits that occur on or after Day 14), but values prior to first application of randomized study treatment will not be used for imputation. Further details are provided in Section 8.1.2.

6. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

6.1. Patient Disposition and Withdrawals

Patient disposition and follow-up will be summarized by treatment group and overall, reflecting completion or withdrawal through Month 3. This disposition summary will be based on the ITT Set, and will tabulate inclusion in analysis sets, completion status, and reason for withdrawal. Numbers of screen failures will also be presented.

Reason for screen failures and reason for withdrawal before treatment assignment/randomization will be listed separately from completion and withdrawal information for patients enrolled in the study.

After the completion of the safety follow-up period, an additional summary of disposition through Month 6 will be created as part of the supplemental safety analyses.

6.2. Demographic and Other Baseline Characteristics

Demographic data and baseline disease characteristics will be summarized by treatment, using the Safety and ITT analysis sets. Demographic data will include age, sex, childbearing potential (if applicable), race, and ethnicity. Baseline characteristics will include height, weight, duration of meibomian gland disease (i.e., <5 years or ≥5 years), study eye (left or right), and baseline MGS score in the study eye (<6 or 6-12).

6.3. Medical History

Non-ophthalmic history will be recorded by body system, medical condition, or surgery, and start and end dates. Ophthalmic history will be recorded by specific location (e.g., left lower eyelid or right eye); ocular disease, condition, or procedure; start and end dates; and whether medication is currently being taken for that condition. All medical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA®), using System Organ Class (SOC) and Preferred Term (PT).

Ophthalmic and non-ophthalmic medical history will be summarized separately by treatment, SOC, and PT, using the Safety Set. The number and percent of patients with ophthalmic and non-ophthalmic history will also be presented.

Non-Ophthalmic and ophthalmic medical history will be listed separately.

7. PROTOCOL DEVIATIONS

All protocol deviations will be identified, categorized, and graded by the investigator and an interdisciplinary team. An additional review by a multi-disciplinary team, for adherence to the grading, will be completed prior to database freeze, and unmasking of specific study personnel. Please refer to Protocol Deviation Definitions – Three Month Analysis for additional details regarding protocol deviation definitions and classifications.

Deviations will be graded as one of the following:

- Grade 1: No impact on data quality or patient safety
- Grade 2: Minor impact on data quality
- Grade 3: Minor impact on patient safety
- Grade 4: Major impact on data quality or patient safety
- Grade 5: Death

All patients with Grade 4 or Grade 5 deviations affecting Baseline through Month 3 will be excluded from the PP analysis set. All patients with Grade 4 or Grade 5 deviations affecting Baseline through Month 6 will be excluded from the PP6 analysis set.

Grade 2, 3, 4, and 5 protocol deviations through Month 3 will be summarized by deviation type, grade, and treatment, as well as listed by patient. As part of the supplemental safety analyses, Grade 2, 3, 4, and 5 protocol deviations through Month 6 will be similarly summarized and listed.

8. EFFICACY

Efficacy analyses will be performed on the ITT Set. The primary analyses will be repeated on the mITT Set (if different from the ITT Set) and PP Set. If the primary analyses are notably different between the ITT and mITT sets, additional analyses of the other efficacy endpoints may be performed on the mITT Set.

In addition to those analyses, which are performed at the 3-month time point, additional exploratory analyses will be performed at the 6 month time point, using data collected during the 3 month safety follow-up period. These analyses will also be performed on the ITT Set, with MGYLS and OSDI total score analyses repeated on the mITT and PP6 sets. P-values for analyses of data collected during the 3-month safety follow-up period (e.g., Month 4.5 and Month 6) are provided for descriptive purposes only.

Endpoints will be summarized descriptively, for all scheduled assessment time points. Actual values and changes from baseline will be summarized descriptively for all time points at which the endpoint is collected.

Dichotomous endpoints will be analyzed using a CMH test to compare each AZR-MD-001 treatment arm to placebo, controlling for disease duration category and baseline MGS score category. If CMH comparisons are not estimable, Pearson's chi-square or Fisher's Exact will be used, as described in Section 8.2 and Section 8.3.

8.1. Primary Efficacy Endpoints and Analysis

These endpoints will be analyzed using the ITT, mITT, and PP sets, with the primary analysis being performed on the ITT Set. Multiple imputation will be applied, unless otherwise indicated. Responder criteria based on eye-specific measurements (MGYLS, etc.) are calculated for the study eye only. These analyses will include all data collected through Month 3.

8.1.1. Primary Efficacy Endpoints

The primary efficacy variables are:

- change from baseline to Month 3 in MGYLS
- change from baseline to Month 3 in OSDI total score

The primary efficacy endpoints will be evaluated using the following hierarchical approach. For each endpoint, the subsequent endpoint will not be evaluated unless the prior endpoint is significant at α=0.05. Therefore, this hierarchical approach controls for the family-wise Type I error and does not require adjustment for multiplicity, as per Dmitrienko and D'Agostino, 2013.

a) Change from baseline to Month 3 in MGYLS, comparing AZR-MD-001 0.5% to placebo.
b) Change from baseline to Month 3 in OSDI total score, comparing AZR-MD-001 0.5% to placebo.
c) Change from baseline to Month 3 in MGYLS, comparing AZR-MD-001 1.0% to placebo.
d) Change from baseline to Month 3 in OSDI total score, comparing AZR-MD-001 1.0% to placebo.

Multiple imputation will be applied, as described in Section 5.3. Analyses will be performed as follows.

Change from baseline in MGYLS will be analyzed at Month 3 using an ANCOVA model with (continuous) baseline MGYLS score as a covariate and treatment (AZR-MD-001 ointment/semi-

solid drug or placebo), duration of disease category (i.e., <5 or ≥5 years), and baseline MGS score category (< 6 or ≥6 and ≤12) as factors in the model. This ANCOVA model will also be performed for each AZR-MD-001 ointment/semi-solid drug dosing level versus placebo. The least square means for the differences between treatments will be presented along with two-sided (95%) confidence intervals.

The following pseudocode will be used:

```
PROC GENMOD data=xxx;
      BY visit;
      CLASS treatment (ref = 'AZR-MD-001 PLACEBO') duration baseMGS;
      MODEL chg =treatment base duration baseMGS;
      LSMEANS treatment;
      run;
```

Change from baseline in OSDI total score will be analyzed at Month 3 using the same methodology as the change from baseline in MGYLS, using an ANCOVA model with (continuous) baseline OSDI total score as a covariate and treatment, duration of disease category, and baseline MGS score category as factors in the model.

8.1.2. Sensitivity Analyses of Primary Efficacy Endpoints

8.1.2.1. Last Observation Carried Forward

The primary efficacy analyses will also be performed using LOCF imputation as a sensitivity analysis. This analysis will use the ITT Set.

The change from baseline in MGYLS and OSDI total scores will be analyzed as described in Section 8.1.1, based on observations using LOCF imputation as described in Section 5.3.2.

8.1.2.2. Evaluation of Potentially Confounding Medications/Therapies at Month 3

The use of potentially confounding medications or therapies at Month 3 will be evaluated by tabulating the number of patients with medications that potentially affect Month 3 OSDI results, and, if a sufficient number of patients meet those criteria, repeating the OSDI analysis with a dichotomous variable indicating the presence/absence of such medications or therapies.

Potentially confounding medications or therapies will be identified as those having a Grade 4 protocol deviation with deviation class of concomitant medications/therapies. The duration of the deviation will include both the duration of medication/therapy usage and the subsequent washout period. Therefore, any such deviation whose start and stop dates overlap with the Month 3 visit date record on the Study Visits eCRF, will classify that patient as having a potentially confounding treatment for the Month 3 visit.

The number of patients with potentially confounding treatments at the Month 3 visit will be tabulated. Those patients will also be flagged in listings. If >10% of patients in the ITT Set have potentially confounding treatments at Month 3, an additional sensitivity analysis of the OSDI change from baseline will be performed. Specifically, the change from baseline in OSDI will be analyzed using an ANCOVA model similar to that described in Section 8.1, with baseline MGYLS score as a covariate and treatment, duration of disease category, and baseline MGS score category as factors, with the presence of a potentially confounding treatment at Month 3 (i.e., yes or no) as an additional factor in the model. This analysis will be performed on the ITT Set, using multiple imputation.

The following pseudocode will be used:

```
PROC GENMOD data=xxx;
      Where visit='Month 3';
      CLASS treatment (ref = 'AZR-MD-001 PLACEBO') duration baseMGS;
      MODEL chg =treatment base duration baseMGS confound;
      LSMEANS treatment;
      run;
```

If this analysis is performed, the p-value associated with the presence of potentially confounding treatment will be presented in conjunction with the other OSDI results, and the least squares means and treatment differences from this model will be presented.

8.2. Secondary Efficacy Endpoints and Analyses

The following endpoints will be presented using the ITT Set. Multiple imputation will be applied, as described in Section 5.3. These analyses will include all data collected through Month 3.

8.2.1. Key Secondary Efficacy Analyses

Proportion of MGYLS responders based on change from baseline ≥5 will be analyzed through Month 3 using a CMH test to compare the proportions between each AZR-MD-001 group and placebo, stratifying by disease duration category (i.e., <5 or ≥5 years) and baseline MGS score category (<6 or ≥6 and ≤12). If the CMH statistic is not estimable, the treatment difference will be evaluated using Pearson's chi-square test, or Fisher's exact test (if the expected cell count is <5 for at least 25% of the cells).

The following pseudocode will be used:

```
PROC FREQ data=xxx;
      BY visit;
      TABLE baseMGS * duration * treatment * response/CMH;
      ODS OUTPUT  CMH = outcmh (where=(STATISTIC=2));
```

```
      Run;

PROC FREQ data=xxx;
      BY visit;
      TABLE treatment * response/EXACT;
      ODS OUTPUT  CHISQ = outc (where=(STATISTIC='Chi-Square'))
                  FISHERSEXACT=outf  (where=(NAME1='XP2_FISH'));
      Run;
```

Proportion of OSDI responders based on OSDI total score <13 will be analyzed through Month 3 as described for the proportion of MGYLS responders, using a CMH test (or chi-square/Fisher's Exact if CMH is not estimable) to evaluate the difference between treatments, controlling for duration of disease category and baseline MGS score category.

Change from baseline in SPEED score at Day 14, Month 1.5 and Month 3 will be analyzed as described for MGYLS in Section 8.1.1.

Change from baseline in Eye Dryness VAS at Day 14, Month 1.5 and Month 3 will be analyzed as described for MGYLS in Section 8.1.1.

8.2.2. Secondary Efficacy Analyses

Change from baseline in MGS will be analyzed through Month 3 using an ANCOVA model with (continuous) baseline MGS score as a covariate and treatment (AZR-MD-001 ointment/semi-solid drug or placebo) and duration of disease category (i.e., <5 or ≥5 years) as factors in the model. This ANCOVA model will be performed for each AZR-MD-001 ointment/semi-solid drug dosing level versus placebo. The least square means for the differences between treatments will be presented along with two-sided (95%) confidence intervals.

The following pseudocode will be used:

```
PROC GENMOD data=xxx;
      BY visit;
      CLASS treatment (ref = 'AZR-MD-001 PLACEBO') duration;
      MODEL chg =treatment base duration;
      LSMEANS treatment;
      run;
```

Proportion of MGS responders based on MGS >12 will be analyzed at Day 14, Month 1.5, and Month 3 as described for the proportion of MGYLS responders, using a CMH test (or chi-square/Fisher's Exact if CMH is not estimable) to evaluate the difference between treatments, controlling for duration of disease category and baseline MGS score category.

Change from baseline in MGYLS at Day 14 and Month 1.5 will be analyzed as described for Month 3 in Section 8.1.1.

Change from baseline in OSDI total score at Day 14 and Month 1.5 will be analyzed as described for Month 3 in Section 8.1.1.

8.3. Exploratory Efficacy Analyses

The following endpoints will be presented using the ITT Set, unless otherwise specified. Where applicable, actual values and changes from baseline will be summarized descriptively for all time points at which the endpoint is collected.

8.3.1. Exploratory Efficacy Analyses Performed at Month 3

Proportion of MGYLS responders based on MGYLS > 2 will be analyzed through Month 3 as described for the proportion of MGYLS responders, using a CMH test (or chi-square/Fisher's Exact if CMH is not estimable) to evaluate the difference between treatments, controlling for duration of disease category and baseline MGS score category.

Change from baseline in MGYOLS at Day 14, Month 1.5 and Month 3 will be analyzed as described for MGYLS in Section 8.1.1.

Proportion of MGYOLS responders based on MGYOLS >2 will be analyzed through Month 3 as described for the proportion of MGYLS responders, using a CMH test (or chi-square/Fisher's Exact if CMH is not estimable) to evaluate the difference between treatments, controlling for duration of disease category and baseline MGS score category.

Proportion of OSDI responders based on a reduction of >4.5 will be analyzed through Month 3 as described for the proportion of MGYLS responders, using a CMH test (or chi square/Fisher's Exact if CMH is not estimable) to evaluate the difference between treatments, controlling for duration of disease category and baseline MGS score category.

Change from baseline in OSDI subscales at Day 14, Month 1.5 and Month 3 will be analyzed as described for MGYLS in Section 8.1.1.

Proportion of SPEED responders based on SPEED <6 will be analyzed through Month 3 as described for the proportion of MGYLS responders, using a CMH test (or chi-square/Fisher's Exact if CMH is not estimable) to evaluate the difference between treatments, controlling for duration of disease category and baseline MGS score category.

Change from baseline in TBUT at Day 14, Month 1.5 and Month 3 will be analyzed as described for MGYLS in Section 8.1.1.

Proportions of TBUT >5 and >10 responders will be analyzed through Month 3 as described for the proportion of MGYLS responders, using a CMH test (or chi-square/Fisher's Exact if

CMH is not estimable) to evaluate the difference between treatments, controlling for duration of disease category and baseline MGS score category.

Change from baseline in Average VAS and Worst VAS at Day 14, Month 1.5 and Month 3 will be analyzed as described for MGYLS in Section 8.1.1.

Proportion of Average VAS responders based on decrease ≥5 and **proportion of Worst VAS responders based on decrease ≥5** will be analyzed through Month 3 as described for the proportion of MGYLS responders, using a CMH test (or chi-square/Fisher's Exact if CMH is not estimable) to evaluate the difference between treatments, controlling for duration of disease category and baseline MGS score category.

Change from Schirmer's assessment at Day 14, Month 1.5 and Month 3 will be analyzed as described for MGYLS in Section 8.1.1.

Proportion of Schirmer's ≥10 mm responders will be analyzed through Month 3 as described for the proportion of MGYLS responders, using a CMH test (or chi-square/Fisher's Exact if CMH is not estimable) to evaluate the difference between treatments, controlling for duration of disease category and baseline MGS score category.

Change from baseline in Burning/Stinging VAS, Itching VAS, Foreign Body Sensation VAS, Eye Discomfort VAS, Photophobia VAS, and Pain VAS at Day 14, Month 1.5 and Month 3 will be analyzed as described for MGYLS in Section 8.1.1.

Proportion of patients with clinical cure, defined as having MGYLS change from baseline ≥5 and OSDI total score <13, will be analyzed through Month 3 as described for the proportion of MGYLS responders, using a CMH test (or chi-square/Fisher's Exact if CMH is not estimable) to evaluate the difference between treatments, controlling for duration of disease category and baseline MGS score category.

Eyelid margin erythema and telangiectasias results will be summarized by time point, in conjunction with other findings from the slit lamp examination. Actual values and shifts from baseline through Month 3 will be summarized by parameter and time point. Changes from baseline will be analyzed at each time point using CMH statistics to evaluate the differences between each AZR-MD-001 treatment group and placebo, controlling for baseline value, using the following pseudocode:

```
PROC FREQ data=xxx;
      BY visit;
      TABLE treatment * base * result / CMH;
      ODS output CMH=outcmh (where=(ALTHYPOTHESIS='General Association'));
      run;
```

Corneal and conjunctival staining (sodium fluorescein corneal staining and lissamine green conjunctival staining) are assessed on a 6-point scale using grades 0, I, II, III, IV, and V, and are summarized by grade and shift from baseline. Shift from baseline through Month 3 will be analyzed using CMH statistics as described for eyelid margin erythema and telangiectasias.

8.3.2. Exploratory Efficacy Analyses Performed at Month 6

These analyses will be performed using the ITT, mITT, and PP6 sets, as indicated. P-values will be provided for descriptive purposes only.

Change from baseline in MGYLS at Month 4.5 and Month 6 will be analyzed as described for MGYLS in Section 8.1.1. This analysis will utilize multiple imputation based on data from the entire 6-month study duration, as described in Section 5.3.1.2, on the ITT, mITT, and PP6 sets. It will be repeated using LOCF on the ITT Set, as described in Section 8.1.2.1.

Change from baseline in OSDI total score at Month 4.5 and Month 6 will be analyzed as described for MGYLS in Section 8.1.1. This analysis will utilize multiple imputation based on data from the entire 6-month study duration, as described in Section 5.3.1.2, on the ITT, mITT, and PP6 sets. It will be repeated using LOCF on the ITT Set, as described in Section 8.1.2.1. Additionally, an analysis of potentially confounding medication, as described in Section 8.1.2.2, will be performed at Month 6, utilizing the ITT Set with multiple imputation.

Proportion of MGYLS responders based on change from baseline ≥5 at Month 4.5 and Month 6 will be analyzed as described in Section 8.2.1, using a CMH test (or chi-square/Fisher's Exact if CMH is not estimable) to evaluate the difference between treatments, controlling for duration of disease category and baseline MGS score category.

Proportion of OSDI responders based on OSDI total score <13 at Month 4.5 and Month 6 will be analyzed as described in Section 8.2.1, using a CMH test (or chi-square/Fisher's Exact if CMH is not estimable) to evaluate the difference between treatments, controlling for duration of disease category and baseline MGS score category.

Change from baseline in SPEED score at Month 4.5 and Month 6 will be analyzed as described for MGYLS in Section 8.1.1.

Change from baseline in individual VAS scores, Average VAS, and Worst VAS at Month 4.5 and Month 6 will be analyzed separately as described for MGYLS in Section 8.1.1.

Change from baseline in MGS at Month 4.5 and Month 6 will be analyzed using an ANCOVA model with (continuous) baseline MGS score as a covariate, and treatment and duration of disease category as factors, as described in Section 8.2.2.

Proportion of MGS responders based on MGS >12 at Month 4.5 and Month 6 will be analyzed as described for the proportion of MGYLS responders, using a CMH test (or chi-square/Fisher's Exact if CMH is not estimable) as described in Section 8.2.2.

Proportion of MGYLS responders based on MGYLS > 2 at Month 4.5 and Month 6 will be analyzed as described for the proportion of MGYLS responders, using a CMH test (or chi-square/Fisher's Exact if CMH is not estimable), as described in Section 8.2.2.

Change from baseline in MGYOLS at Month 4.5 and Month 6 will be analyzed as described for MGYLS in Section 8.1.1.

Proportion of MGYOLS responders based on MGYOLS > 2 at Month 4.5 and Month 6 will be analyzed as described for the proportion of MGYLS responders, using a CMH test (or chi-square/Fisher's Exact if CMH is not estimable), as described in Section 8.3.1.

Proportion of OSDI responders based on a reduction of >4.5 at Month 4.5 and Month 6 will be analyzed as described for the proportion of MGYLS responders, using a CMH test (or chi square/Fisher's Exact if CMH is not estimable), as described in Section 8.3.1.

Change from baseline in OSDI subscales at Month 4.5 and Month 6 will be analyzed as described for MGYLS in Section 8.1.1.

Proportion of SPEED responders based on SPEED <6 at Month 4.5 and Month 6 will be analyzed as described for the proportion of MGYLS responders, using a CMH test (or chi-square/Fisher's Exact if CMH is not estimable), as described in Section 8.3.1.

Change from baseline in TBUT at Month 4.5 and Month 6 will be analyzed as described for MGYLS in Section 8.1.1.

Proportions of TBUT >5 and >10 responders at Month 4.5 and Month 6 will be analyzed as described for the proportion of MGYLS responders, using a CMH test (or chi-square/Fisher's Exact if CMH is not estimable), as described in Section 8.3.1.

Proportion of Average VAS responders based on decrease ≥5 and **proportion of Worst VAS responders based on decrease ≥5** at Month 4.5 and Month 6 will be analyzed as described for the proportion of MGYLS responders, using a CMH test (or chi-square/Fisher's Exact if CMH is not estimable) to evaluate the difference between treatments, controlling for duration of disease category and baseline MGS score category.

Change from Schirmer's assessment at Month 4.5 and Month 6 will be analyzed as described for MGYLS in Section 8.1.1.

Proportion of Schirmer's ≥10mm responders at Month 4.5 and Month 6 will be analyzed as described for the proportion of MGYLS responders, using a CMH test (or chi-square/Fisher's Exact if CMH is not estimable), as described in Section 8.3.1.

Proportion of patients with clinical cure, defined as having MGYLS change from baseline ≥5 and OSDI total score <13, will be analyzed at Month 4.5 and Month 6 as described for the proportion of MGYLS responders, using a CMH test (or chi-square/Fisher's Exact if CMH is not estimable), as described in Section 8.3.1.

Eyelid margin erythema and telangiectasias changes from baseline will be analyzed at Month 4.5 and Month 6, using CMH statistics as described in Section 8.3.1.

Corneal and conjunctival staining shifts from baseline will be analyzed using CMH statistics, as described in Section 8.3.1.

9. ANALYSIS OF PHARMACOKINETICS

Pharmacokinetics are not measured in the Expansion Cohort.

10. SAFETY

The Safety Set will be used for safety analyses reports. Safety will be assessed based on adverse events, vital signs, BCVA (Logarithmic visual acuity chart), biomicroscopy, ophthalmoscopy, IOP, and conjunctival hyperemia (redness).

The primary safety analysis will be performed after all patients have completed the Month 3 visit or discontinued from the study. An additional 3-month safety follow-up (including Month 4.5 and Month 6 visits) will be conducted, and supplemental safety results will be produced after the completion of the Month 6 visits.

A combined analysis of Cohort 1 and Expansion Cohort data will not be produced, as Cohort 1 includes different dosing regimens (once daily vs. twice weekly) as well as including different treatments (AZR-MD-001 0.1%, vehicle).

10.1. Extent of Exposure and Compliance

During the Baseline visit, the patient will be dispensed Vaseline, which will be administered while on site and the prospective patient will be observed by the physician or a designee. Eligible patients will also be dispensed randomized study medication (AZR-MD-001 or placebo), which will be administered twice weekly at home. Patients are expected to apply the first application of randomized study medication on the same date, in the evening.

Application, dispensation, and return of randomized study treatment will be listed chronologically by patient and visit. A separate listing of Physician Observation of Drug Application, for observation of Vaseline applied during the Baseline visit, will be provided.

Compliance for randomized study treatment, in the form of numbers of doses administered and missed, is collected in 6-week intervals. Approximately 12 doses are expected to be administered during each of those 6-week periods, but slightly more or less may be expected depending on actual visit dates and visit windows. The expected number of doses for a given period is calculated as 2*(end date - start date + 1)/7, rounded to the nearest whole number. Compliance is then calculated as 100*(number of doses taken)/(number of expected doses).

Overall compliance for the 3 month study period will be based on the expected numbers of doses calculated as 2×([Month 3 visit date or date of discontinuation]-[date of first dose] +1) /7, for the 3 month study period, and 2×([Month 6 visit date or date of discontinuation]-[date of first dose]+1)/7, for the 6 month period including follow-up. The number of patients with compliance <80%, 80%-120%, and >120% will be tabulated.

For the safety follow-up period, if the final study drug is returned after the Month 6 visit (based on the visit date as compared to the final study drug return date), compliance will be calculated based on the Month 6 visit date. If dates of dispensation or return are not recorded on the eCRF (e.g., visit restrictions were in place and study treatment was mailed to patients), compliance calculations will be based on the assumption that 12 doses should have been administered.

Compliance through the Month 3 visit will be presented at the completion of the 3-month study period. Compliance through the end of the safety follow-up period (i.e., through Month 6) will be presented as part of the supplemental safety analyses.

10.2. Adverse Events

Adverse events will be classified into SOC and PT using MedDRA version 20.0 or higher. Treatment-emergent adverse events (TEAEs) are defined as events beginning or worsening on or after the date of first dose of study medication. If the start date of the event is incomplete or missing, the event will be categorized as a TEAE unless sufficient information (from partial start date, or from end date) clearly indicates that the event started prior to the date of first dose. If event severity or relationship to study intervention is missing, the event will be summarized at the worst possible severity (severe) and strongest possible relationship (very likely/certain).

All events attributed to the application of Vaseline during the Baseline visit will be noted in the verbatim event term by the investigator and identified programmatically from the verbatim term. All such events will be listed by patient, and summarized by SOC and PT overall, since patients

are not randomized to treatment at the time of Vaseline application. AEs attributed to application of Vaseline will also be listed.

Adverse events will be listed by subject, event, and date, with non-TEAEs flagged in the listings, as follows:

- All adverse events
- All serious adverse events (SAEs)
- Adverse events leading to drug withdrawal

TEAEs will be summarized by treatment as follows, using both numbers of events and number and percent of patients. Patients are counted at most one-time per SOC and at most one time per PT, at the highest recorded severity or relationship (where applicable). A patient with multiple events within an SOC or PT will have all events reflected in the total numbers of events in that classification.

- Overall summary of events and patients with different types of TEAEs.
- Summary of TEAEs by SOC and PT.
- Summary of Ophthalmic TEAEs by SOC and PT.
- Summary of Ophthalmic TEAEs Occurring in the Study Eye by SOC and PT.
- Summary of Ophthalmic TEAEs Occurring in the Non-Study Eye by SOC and PT.
- Summary of Non-Ophthalmic TEAEs by SOC and PT.
- Summary of Serious TEAEs by SOC and PT.
- Summary of TEAEs Leading to Drug Withdrawal by SOC and PT.
- Summary of TEAEs Possibly, Probably, or Certainly Related to Study Intervention by SOC and PT.
- Summary of TEAEs by SOC, PT, and Severity.
- Summary of TEAEs by SOC, PT, and Relationship to Study Intervention.
- Summary of TEAEs by SOC, PT, and Site.
- Summary of TEAEs by PT.

10.3. Prior and Concomitant Medication

Prior and concomitant medications and treatments will be coded using the World Health Organization Drug Dictionary (WHODRUG).

Medications used prior to the date of first dose of study medication will be classified as prior medication, and those used on or after the date of the first study treatment (including Vaseline) will be classified as concomitant medications (including those started prior to the first study

treatment which is ongoing during the study). A medication may be classified as both prior and concomitant.

Medication with a missing or partial start date will be considered as prior medication if the first date implied by the available start date is prior to the first study treatment date. Medications with partial end dates will be considered as concomitant if the last available date implied by the available data is on or after the first study treatment date.

Concomitant medication will be summarised by treatment, Anatomical Therapeutic Chemical (ATC) Level 4, PT, and category (Non-ophthalmic medication and ophthalmic medication), using the Safety Set.

Prior and concomitant medications will be listed. Ophthalmic medications in the study eye will be flagged in the prior and concomitant medication listing. Medication use through the Month 3 visit will be presented at the end of the 3-month study period, and medication use through the end of the safety follow-up period (i.e., through Month 6) will be presented as part of supplemental safety analyses.

10.4. Laboratory Evaluations

Aside from urine pregnancy test, clinical laboratory samples are not collected in the Expansion Cohort.

Urine pregnancy test data will be listed chronologically by patient and visit.

10.5. Best-corrected Visual Aacuity; Logarithmic Visual Acuity Chart

BCVA Total letter score, LogMAR (calculated as per Section 5.2.9), axis, and cylinder will be summarized by time point, and treatment, using absolute values and changes from baseline. Changes in letter scores will also be tabulated as: increases of 5 or more letters, decreases of 5 or more letters, or changes of less than 5 letters; and increases of 10 or more letters, decreases of 10 or more letters, or changes of less than 10 letters. Results for sphere refraction will be tabulated. All results, including Snellen equivalents, will be listed chronologically by patient and visit.

10.6. Vital Signs

Vital signs will consist of systolic and diastolic blood pressure (mmHg) and pulse rate (bpm). Vital signs data (absolute values) will be summarized by parameter, time point, and treatment, and listed chronologically.

10.7. Slit-lamp Biomicroscopy, Including Conjunctival Hyperemia

Slit-lamp biomicroscopy results, including the safety endpoint of conjunctival hyperemia (redness), will be summarized in a shift table as described in Section 8.3. CMH analyses will only be performed for the exploratory efficacy endpoints of study eye erythema and telangiectasias. Results will be listed chronologically.

10.8. Ophthalmoscopy

Lens status (categorized as phakic, pseudophakic, or aphakic) will be summarized by time point, and treatment using a shift table. Cataract status (rated on a 4-point scale from None to Severe), vitreous (normal or abnormal), and fundus (normal or abnormal) will be recorded for phakic eyes, and also tabulated in a shift table. Ophthalmoscopy results, including specifics of any vitreous or fundus abnormalities, will be listed chronologically by patient and visit. Dilation status (dilated or undilated) will be presented in listings, but both dilated and undilated results will be tabulated together in a shift table.

10.9. Intraocular Pressure

IOP results will be categorized as <18, 18-25, or >25 mmHg separately in the study eye and non-study eye and summarized using a shift table. Results will be listed chronologically by patient and visit.

10.10. Meibography/Meiboscopy

Meibography results will be collected in each eye and summarized using a shift table.

11. INTERIM ANALYSES

No official interim analysis will be performed.

As described in Section 1.2 and Section 2.3.2, a sample size re-estimation will be performed, in a masked fashion, after all patients complete Month 3. These analyses will be limited to calculation of pooled standard deviations for MGYLS and OSDI total score, and the sample size re-estimation using pseudocode presented in Section 2.3.2. No data summaries or comparisons between treatment groups will be created, and no unmasking will occur.

12. CHANGES FROM ANALYSIS PLANNED IN PROTOCOL

The following are some changes in the analysis of the Expansion Cohort, as compared to protocol.

- The primary objective of the study was shifted from evaluating safety and tolerability, to evaluating safety and efficacy, following discussion with the FDA.

- Some secondary endpoints described in protocol errors 8.1.2, 8.1.5, and 9.4.3 have been reclassified as exploratory efficacy analyses. Results (i.e., actual values) for efficacy assessments were listed as endpoints in the protocol but are not explicit endpoints in the SAP; actual values are summarized in conjunction with changes from baseline throughout.

- Clinical cure, as stated in AZ201801 Protocol Section 9.4.3, has been redefined as having MGYLS change from baseline ≥5 and OSDI total score <13, to correspond with responder criteria for the primary endpoints, and is evaluated using the CMH test instead of a shift table.

- The ITT analysis set has been added as the primary efficacy analysis set, per feedback from the FDA.

- While the mITT Set is defined in the AZ201801 Protocol Section 9.2 as being all randomized patients who have values at randomization and post-baseline values, the definition has been simplified to be randomized patients who met inclusion/exclusion criteria and had post-baseline values. However, it is expected that randomized patients do have values collected at the time of randomization (baseline visit). Further, since randomized study treatment is not administered onsite during this cohort, the mITT now requires that subjects be administered 1+ doses of randomized study treatment.

- The mITT2 population, defined in protocol synopsis as patients in the mITT Set who have baseline MGS scores of 6-12 but not included in the description of analysis sets in protocol section 9.2, is not utilized in the Expansion Cohort analyses.

- Pairwise comparisons between active and placebo groups in ANCOVA models are based on least square means of the differences, which use a z test as produced by the software (not a t-test, as stated in AZ201801 Protocol Section 9.4.3).

- Responder analyses will be performed using CMH analyses, in lieu of logistic regression as described in AZ201801 Protocol Section 9.4.3. This non-parametric approach permits a treatment comparison while controlling for covariates, without assuming an underlying distribution.

- The subgroup analyses specified in AZ201801 Protocol Section 9.4.7 are not utilized in the Expansion Cohort analyses.

- Urine pregnancy test results will not be evaluated as a safety endpoint.

13. REFERENCE LIST

DeSouza CM, Legedza ATR, Sankoh AJ. An overview of practical approaches for handling missing data in clinical trials. J Biopharm Stat. 2009 Nov;19(6):1055-1073.

Dmitrienko A, D'Agostino R Sr. Traditional multiplicity adjustment methods in clinical trials. Stat Med. 2013 Dec 20;32(29):5172–5218.

Tang L, Song J, Belin TR, Unützer J. A comparison of imputation methods in a longitudinal randomized clinical trial. Stat Med. 2005 Jul 30;24(14), 2111-2128.

14. PROGRAMMING CONSIDERATIONS

All statistical computations and construction of tables and listings will be performed using SAS® for Windows Version 9.4 or higher (SAS® Institute Inc., Cary, NC, USA).

The table and listing shells will be developed in a separate document and approved by the sponsor and other stakeholders. Any subsequent changes determined to be necessary will be documented and approved by the sponsor and statistical team. SDTM datasets will be created from the clinical database and external data, following the Study Data Tabulation Model Implementation Guide version 3.2 or higher. Analysis will be based on ADaM datasets created from the SDTM datasets and will follow the Analysis Dataset Model Implementation Guide version 1.3 or higher.

Patient participation will be ongoing at the time of the analyses based on Month 3 data, and some patients could have already completed the Month 4.5 and/or Month 6 visits at that time. At the time of the Month 3 sample size re-estimation, data necessary for the re-estimation (e.g., Screening and Baseline visit information and all MGYLS and OSDI assessments through Month 3) will be fully cleaned for all patients. At the time of the Month 3 database freeze, data will be fully cleaned through the Month 3 visit for all patients. All patient information in the database will be transferred to the statistical team for analyses. The statistical team will programmatically limit the data used in analysis datasets, tables, and listings to the information collected through Month 3, including any unscheduled visits collected during that time and any early termination visits in subjects who did not have a Month 3 visit. Tables and listings presenting information such as disposition, adverse events, medications, and other information not summarized in a by-visit fashion will be presented through Month 3.

Any adverse events that are ongoing at the Month 3 visit and resolve after the Month 3 visit, even if resolution information has been entered in the database at the time of database freeze, will programmatically have the stop date removed, be categorized as Ongoing, and have

outcome assigned to Not Yet Resolved. Any patients who do not have a Month 3 visit but are not discontinued (i.e., did not attend Month 3 visit but remained on trial) will utilize the expected date of the Month 3 visit in this algorithm.

Similarly, non-study medications (e.g., prior and concomitant) that are ongoing at the Month 3 visit and have end date information entered in the database from a later study visit (e.g., Month 4.5 or 6) at the time of database freeze, will be programmatically have stop date removed, and be categorized as Ongoing.

After all patients have completed the Month 6 visit (e.g., completed the safety follow-up period), all patient data after the Month 3 visit will be fully cleaned, and the database locked.

14.1. General Considerations

- One SAS program can create multiple tables (or listings). One program is expected to create both the 3-month and 6-month output (e.g., one program is used to create both Table 17 and Table 17.1, or to create Listing 1 and Listing 1.1).

- Output files will be delivered in Word format. Tables and listings (TLs) will be bundled separately with a table of contents for each.

14.2. Table and Listing Formatting

14.2.1. General

- All TLs will be produced in landscape format, using the Courier New font, size 8 with approximately 1-inch margin on all 4 sides.
- Each table or listing will have a solid line at the top, one underneath the column headers, and one underneath the body of the text.

14.2.2. Headers

- All output should have the following header at the top left of each page:

  Protocol AZ201801 Expansion Cohort
  Azura Ophthalmics

- All output should have **Page n of N** at the top right corner of each page. TLs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).

14.2.3. Display Titles

- The titles should be formatted as follows, with the title text wrapping to a second line where necessary. The title and table designation will be single spaced. Listings will include all available data and will not have an analysis set displayed.

Table x
Title Text
(Analysis Set)

14.2.4. Body of the Data Display

14.2.4.1. General Conventions

Data in the body of a table or listing are formatted as follows:

- Alphanumeric values that do not wrap are centered; those that do wrap are left-justified
- Whole numbers (e.g., counts) are centered
- Numbers containing fractional portions are decimal aligned or centered, as appropriate.

14.2.4.2. Table Conventions

- Analysis population sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of patients in the analysis population.
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category are presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter.
- Where percentages are presented in these tables, zero percentages will not be presented; that is, it will be presented as 0 and not as 0 (0%).
- An Unknown or Missing category are added to each parameter for which information is not available for 1 or more patients.
- Percentage values are printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8), 13 (5.4)). Values that round to 0.0 will be displayed as 0.0. Percentages equating or rounding to 100% are presented as 100, without decimal places. Percent sign may be indicated in column header or row label and not displayed in the body of the results, or included in the results (e.g., 7 (12.8%)) as indicated in the shells.
- Missing descriptive statistics or p-values which cannot be estimated are reported as "N/E".

- The percentage of patients is normally calculated as a proportion of the number of patients assessed in the relevant treatment group (or overall) in the column header. If the percentage is calculated based on a different number, it will be indicated with a footnote (such as in a disposition table) or with the inclusion of a "n" line reflecting the denominator (such as a by-visit analysis).

14.2.4.3. Listing Conventions

- Assessments collected at the early termination visit (recorded as occurring at Month 6, where the assessment date is equal to the End of Study visit date [in the Subject Visits dataset] or the date of early termination [recorded as the date of completion or early termination on the End of Study eCRF page, where study completion status is no]) will be relabeled to "Early Term" in the listings. Any assessments recorded as a scheduled visit other than Month 6 will not be relabeled in this manner.
- Missing data will be left blank, unless otherwise specified.
- Dates are printed in SAS DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates may be represented on patient listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the patient will be left blank, unless otherwise specified.
- All observed time values are to be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26, or 11:26:45). Time will only be reported if it was measured as part of the study.
- Where data is presented by study eye vs. non-study eye, patients without study eye assigned (i.e., unrandomized patients) will have the right eye displayed in the study eye column(s) and left eye displayed in the non-study eye column(s), as indicated in footnotes.

14.2.5. Footnotes

- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with "Note:" if an informational footnote, or [a], [b], etc. if a reference footnote. Each new footnote should start on a new line, where possible.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, whether it is draft or final, and the listing source (i.e., 'Program : myprogram.sas DRAFT Listing source: xxx).

15. APPENDICES

Appendix 1 Visual Analogue Scale (VAS)

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%

Appendix 2 Ocular Surface Disease Index (OSDI)

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

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

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

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

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

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

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

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

Appendix 3 Standard Patient Evaluation of Eye Dryness (SPEED) Questionnaire

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

Appendix 4 List of Tables and Listings Produced at the 3 Month Analysis

The following tables and listings will be produced at Month 3. Shells are provided for each unique table and listing in a separate document.

Comprehensive efficacy and safety analyses will be produced after the completion of the Month 3 visits. Additional safety information will be collected through the Month 6 visit and presented in supplemental safety tables and listings.

Table 1 Summary of Patient Disposition Through Month 3 – Expansion Cohort (All Patients)

Table 2A Summary of Demographic and Baseline Characteristics – Expansion Cohort (Safety Set)

Table 2B Summary of Demographics and Baseline Characteristics – Expansion Cohort (ITT Analysis Set)

Table 2C Summary of Demographics and Baseline Characteristics – Expansion Cohort (mITT Analysis Set)

Table 2D Summary of Demographics and Baseline Characteristics – Expansion Cohort (Per-Protocol Set)

Table 3A Summary of Ophthalmic Medical History – Expansion Cohort (Safety Set)

Table 3B Summary of Ophthalmic Medical History – Expansion Cohort (ITT Set)

Table 3C Summary of Ophthalmic Medical History – Expansion Cohort (mITT Set)

Table 3D Summary of Ophthalmic Medical History – Expansion Cohort (Per-Protocol Set)

Table 4A Summary of Non-Ophthalmic Medical History – Expansion Cohort (Safety Set)

Table 4B Summary of Non-Ophthalmic Medical History – Expansion Cohort (ITT Set)

Table 4C Summary of Non-Ophthalmic Medical History – Expansion Cohort (mITT Set)

Table 4D Summary of Non-Ophthalmic Medical History – Expansion Cohort (Per-Protocol Set)

Table 5A Summary of Protocol Deviations by Grade Through Month 3 – Expansion Cohort (Safety Set)

Table 5B Summary of Protocol Deviations by Grade Through Month 3 – Expansion Cohort (ITT Analysis Set)

Table 5C Summary of Protocol Deviations by Grade Through Month 3 – Expansion Cohort (mITT Analysis Set)

Table 5D Summary of Protocol Deviations by Grade Through Month 3 – Expansion Cohort (Per-Protocol Set)

Table 6A Analysis of Meibomian Glands Yielding Liquid Secretion (MGYLS) Through Month 3 – Expansion Cohort (ITT Analysis Set)

Table 6B Analysis of Meibomian Glands Yielding Liquid Secretion (MGYLS) Through Month 3 – Expansion Cohort (mITT Analysis Set)

Table 6C Analysis of Meibomian Glands Yielding Liquid Secretion (MGYLS) Through Month 3 – Expansion Cohort (PP Analysis Set)

Table 6D Sensitivity Analysis of Meibomian Glands Yielding Liquid Secretion (MGYLS), based on LOCF Imputation Through Month 3 – Expansion Cohort (ITT Analysis Set)

Table 7A Analysis of Ocular Surface Disease Index (OSDI) Total and Subscale Results Through Month 3 – Expansion Cohort (ITT Analysis Set)

Table 7B Analysis of Ocular Surface Disease Index (OSDI) Total and Subscale Results Through Month 3 – Expansion Cohort (mITT Analysis Set)

Table 7C Analysis of Ocular Surface Disease Index (OSDI) Total and Subscale Results Through Month 3 – Expansion Cohort (PP Analysis Set)

Appendix 5 List of Tables and Listings Produced at the end of the Safety Follow-up Period

The following tables and listings will be produced at the completion of the 3-month safety follow-up period (i.e., Month 6), and will include all information from the earlier period. Shells are provided for each unique table and listing in a separate document.

These tables and listings will be used for supplemental safety analyses, and for additional exploratory efficacy analyses.

Table 1.1 Summary of Patient Disposition – Expansion Cohort (All Patients)

Table 5.1A Summary of Protocol Deviations by Grade – Expansion Cohort (Safety Set)

Table 5.1B Summary of Protocol Deviations by Grade – Expansion Cohort (ITT Analysis Set)

Table 5.1C Summary of Protocol Deviations by Grade – Expansion Cohort (mITT Analysis Set)

Table 5.1D Summary of Protocol Deviations by Grade – Expansion Cohort (Per-Protocol Set)

Table 6.1A Analysis of Meibomian Glands Yielding Liquid Secretion (MGYLS) – Expansion Cohort (ITT Analysis Set)

Table 6.1B Analysis of Meibomian Glands Yielding Liquid Secretion (MGYLS) – Expansion Cohort (mITT Analysis Set)

Table 6.1C Analysis of Meibomian Glands Yielding Liquid Secretion (MGYLS) – Expansion Cohort (PP6 Analysis Set)

Table 6.1D Sensitivity Analysis of Meibomian Glands Yielding Liquid Secretion (MGYLS), based on LOCF Imputation – Expansion Cohort (ITT Analysis Set)

Table 7.1A Analysis of Ocular Surface Disease Index (OSDI) Total and Subscale Results – Expansion Cohort (ITT Analysis Set)

Table 7.1B Analysis of Ocular Surface Disease Index (OSDI) Total and Subscale Results – Expansion Cohort (mITT Analysis Set)

Table 7.1C Analysis of Ocular Surface Disease Index (OSDI) Total and Subscale Results – Expansion Cohort (PP6 Analysis Set)

Table 7.1D Sensitivity Analysis of Ocular Surface Disease Index (OSDI) Total and Subscale Results, based on LOCF Imputation – Expansion Cohort (ITT Analysis Set)

Table 8.1 Analysis of Standard Patient Evaluation of Eye Dryness (SPEED) – Expansion Cohort (ITT Analysis Set)

Table 9.1 Analysis of Visual Analogue Scale (VAS) Results – Expansion Cohort

Table 10.1 Analysis of Meibomian Gland Score – Expansion Cohort (ITT Analysis Set)

Table 11.1 Analysis of Tear Break-up Time (TBUT) – Expansion Cohort (ITT Analysis Set)

Table 12.1 Analysis of Meibomian Glands Yielding Optimal Liquid Secretion (MGYOLS) – Expansion Cohort (ITT Analysis Set)

Table 13.1 Analysis of Schirmer's Test without Anesthesia – Expansion Cohort (ITT Analysis Set)

Table 14.1 Analysis of Responder Status – Expansion Cohort (ITT Analysis Set)

Table 15A.1 Shift Table and Analysis of Slit Lamp Results, Including Erythema, Telangiectasias, and Conjunctival Hyperemia – Expansion Cohort (ITT Analysis Set)