A Randomized, Controlled Trial to Evaluate the Role of Oral Azithromycin in the Treatment of Symptomatic Meibomian Gland Disease and its effect on the Ocular Surface Microbiome

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i. Background and Significance

Dry eye syndrome (DES) is a persistent feeling of ocular discomfort that encompasses dryness, irritation, foreign body sensation and burning. In the United States, it is the most common non-refractive cause of visits to eye care providers[1], and has been shown to have a significant impact on quality of life of patients who suffer from this condition[2]. It is not one disease state, but rather is composed of multiple different entities whose end stage results in the symptoms encompassed by DES. The most common cause of DES is Meibomian gland disease (MGD).[3]

The Meibomian glands are modified sebaceous glands that line the upper and lower eyelids and have orifices opening onto the eyelid margin.[4] The secretory product of the Meibomian glands is a finely tuned mixture of lipids with high spreadability and low surface tension that coat the ocular surface and provide an evaporative barrier against aqueous tear loss.[5] A change in the composition of the lipids can cause the tear film to become unstable, either breaking up prematurely or failing to spread properly after blinking, which leaves the underlying corneal epithelium exposed.[6]

Numerous treatments for MGD have been proposed, ranging from heating the glands[7] to topical anti-inflammatories[8, 9], oral omega-3 fatty acids[10, 11], and topical[12] or oral[13, 14] antibiotics. The role of topical anti-inflammatories as effective has been well-established, but the role of antibiotics is less clearly defined. Some clinicians advocate using antibiotics to reduce the burden of bacteria on the ocular surface[15], but the utility of this has never been established[16], nor have there been any causal relationship demonstrated between a bacterial pathogen and MGD[17].

A competing theory for the use of antibiotics to treat MGD is that they exhibit an anti-inflammatory effect on the Meibomian glands, thereby improving the composition of secreted lipid. The macrolide and tetracycline antibiotics have been shown to have a anti-inflammatory effects in addition to their antimicrobial action.[18] Azithromycin has also been shown to affect the lipid composition of cultured human Meibomian gland cells.[19, 20]

The use of antibiotics in the treatment of MGD is an important question to address, as MGD is both an extremely common and chronic disease, and patients are often treated repeatedly. It has been well established that the use of topical and oral antibiotics can induce resistance in bacteria, and thus use of antibiotics should be limited only to cases where there is a definite treatment benefit. Given the widespread use of antibiotics in treatment of MGD, one would hope that there is solid evidence as to the benefit of oral antibiotics as compared to placebo, however evidence based on well-designed clinical trials is sorely lacking.[16]

The pathogenicity of bacteria in MGD has never been demonstrated.[17] It may be because MGD is a non-infectious disease, or it may be because the organism is difficult to identify using standard culture techniques. With the dawn of 16s ribosomal DNA amplification techniques, it has become apparent that the microbiological inhabitants of the ocular surface are far more diverse and numerous than what has been identified using standard culture techniques. Although studies on the ocular microbiome are still in their infancy, differences in microbiological populations have been identified in patients with DES and in contact lens wearers. The microbiome in patients with MGD and in patients who have been treated for MGD remains

unstudied using modern DNA-based techniques and is a ripe area for research, which this project proposes to address.

ii. Preliminary Studies

There have been two published studies looking at oral azithromycin in the treatment of MGD. Oral azithromycin dosed at 1 gram per week for 3 weeks, has been previously studied in a retrospective case series conducted at the F.I. Proctor Foundation at UCSF. In this study, seventy-five percent of subjects reported symptomatic improvement in ocular surface discomfort at a mean follow up time of 5.6 weeks.[13] This was a retrospective analysis, and subjects were on multiple different medications during the study period, which may have affected the outcome. Oral azithromycin has also been studied at a dose of 500mg/day for 3 days, repeated every 7 days for 3 cycles, in a prospective, open-label trial of 13 patients. In this study, the authors reported improvement in both the symptoms and signs of MGD at an undefined end point.[21]

Topical azithromycin has been studied in several open-label studies which demonstrated a benefit in improvement of both the signs and the symptoms of MGD.[22, 23] However, a well-designed randomized controlled double-masked trial of 904 patients comparing topical azithromycin alone to topical azithromycin plus dexamethasone to dexamethasone alone to placebo both demonstrated no additional benefit of azithromycin to dexamethasone in the treatment of MGD, but did show that dexamethasone was effective in improving the signs of MGD.[12] The differing results of these trials demonstrate the need for well-designed randomized controlled trials in evaluating interventions for MGD.

iii. Study Design

Randomized, controlled, double-masked clinical trial of oral azithromycin vs placebo in the treatment of symptomatic Meibomian gland disease.

Patient will be randomized with a 1:1allocation ratio into two groups.

- Group 1 will receive oral azithromycin, 1 gram per week for 3 weeks, plus instruction to perform warm compresses.
- Group 2 will receive oral azithromycin, 1 gram per week for 3 weeks, plus instruction to perform warm compresses.

IV. Study Location:

1. Ophthalmology clinic at the University of California, San Francisco
2. Ophthalmology clinic at the F.I. Proctor Foundation, San Francisco

V. Criteria

Inclusion

1. Symptomatic Meibomian gland disease, defined as patient-reported ocular surface symptoms such as dryness, grittiness, foreign body sensation, or eye fatigue in combination with clinically identifiable Meibomian gland disease with Grade 2 or greater involvement on the Meibomian Gland Grading Scale (Section XV, item 2).
2. OSDI Score $\geq$ 20

3. Ability to give informed consent

Exclusion

1. Age less than 18 years
2. Allergy or intolerance to oral azithromycin or topical dexamethasone
3. Allergy or intolerance to the preservatives used in topical ophthalmic 0.1% dexamethasone: sodium bisulfite, phenylethyl alcohol, benzalkonium chloride
4. History of prolonged QT interval, history of torsades des pointes, congenital long QT syndrome, bradyarrhythmias, heart failure
5. Patients currently taking medications that prolong the QT interval (Table 1)
6. Aqueous deficiency dry eye defined as Schirmer's strip testing without anesthesia with $\leq$ 5mm of tears on two separate tests.
7. Ocular surface inflammatory disease, including cicatrizing conjunctivitis, graft versus host disease, Stevens Johnson syndrome
8. Atopic disease with ocular involvement
9. Limbal stem cell deficiency
10. Oral or topical ophthalmic antibiotic use within the last 90 days
11. Oral prednisone use >5mg per day
12. Topical ophthalmic steroid use within the past 30 days
13. Topical ophthalmic anti-inflammatory (including non-steroidal anti-inflammatories, lifitegrast, or cyclosporine) use within the past 30 days

Table 1: Medications that Prolong QT Interval

Medication	Use	Medication	Use
Amiodarone	Antiarrhythmic	Flecainide	Antiarrhythmic
Amisulphride	Antipsychotic	Haloperidol	Antipsychotic
Amitryptyline	Antidepressant	Hydroxychloroquine	Anti-Malarial
Astemizole	Antihistamine	Imipramine	Antidepressant
Chloroquine	Anti-Malarial	Loratadine	Antihistamine
Chlorpromazine	Antipsychotic	Nortriptyline	Antidepressant
Clarithromycin	Antibiotic	Olanzapine	Antipsychotic
Desipramine	Antidepressant	Procainamide	Antiarrhythmic
Diphenhydramine	Antihistamine	Quetiapine	Antipsychotic
Disopyramide	Antiarrhythmic	Quinidine	Antiarrhythmic
Doxepin	Antidepressant	Quinine	Anti-Malarial
Droperidol	Antipsychotic	Sotalol	Antiarrhythmic
Encainide	Antiarrhythmic	Terfanadine	Antihistamine
Erythromycin	Antibiotic	Thioridazine	Antipsychotic

VII. Main Outcome Measure

The primary outcome will be change in OSDI score from enrollment to 1 month.

Secondary Outcome Measures

1. Difference in alpha diversity of ocular surface microbiome as assessed by Shannon's diversity index between azithromycin and placebo groups at 1 and 3 months.
2. Change in alpha diversity of ocular surface microbiome as assessed by Shannon's diversity index between azithromycin and placebo groups between 0 and 1 month.
3. Change in OSDI score from enrollment to 3 months
4. Change in Neuropathic Pain Score Inventory for the Eye (NPSI-E) from enrollment to 1 and 3 months
5. Change in 5-Item Dry Eye Questionnaire (DEQ-5) from enrollment to 1 and 3 months
6. Change in meibomian gland grading from enrollment to 1 and 3 months
7. Change in SICCA score from enrollment to 1 and 3 months
8. Change in OSI (Ocular Surface Index) score at 1 and 3 months

VIII. Statistical Analysis

For continuous outcomes, a two-tailed t test for significance will be used.

For microbiome outcomes, the alpha diversity (local species pool) of the population will be analyzed and compared pre-and post-treatment within and between the azithromycin and control groups. The difference between the bacterial microbiome in the azithromycin and placebo arm will be assessed using a PERMANOVA with an L^2 norm distance measure. Secondary analyses will include L^1 and L^0 norms, as well as a phylogenetic distance. In addition, we will assess whether bacterial alpha diversity is decreased in the antibiotic treated arm with the primary outcome being the Simpson's index (L^2), with secondary analyses assessing Shannon's (L^1) and Richness (L^0).

IX. Study Sizing

The number of patients was calculated by assuming a 20% difference in Ocular Surface Disease Index (OSDI)[24] score at the primary outcome between treatment and placebo groups, with 80% power and a significance level of 0.05. This yielded a total of 16 patients per arm. To account for loss to follow up, a total of 19 patients per arm will be recruited.

X. Placebo

The oral azithromycin placebo will be a sugar pill, and will be made by the UCSF Investigational Pharmacy.

XI. Non-Medication Intervention

All patients will receive education regarding non-medication interventions for their Meibomian gland disease. This will be instruction to perform warm compresses over both eyes for 10 minutes twice per day. The handout that will be given to patients is available in the Manual of Procedures (MOP).

XII. Masking

The UCSF Investigational pharmacy will perform randomization according to randomization schedule. All masking of investigational medications will be performed by the UCSF Investigational Pharmacy.

Azithromycin tablets will be over-encapsulated for masking purposes to match the placebo pills. Artificial tears will be used as the placebo for dexamethasone, and both will be in identical eye dropper vials.

Both patients and physicians will be masked as to study assignment. The clinical coordinator and the Investigational Pharmacy will have access to the randomization key.

XIII. Schedule of Procedures

The initial visit will be at enrollment. The 1 month visit will be 21-35 days after the initial visit, and the 3 month visit will be 76-96 days after the initial visit.

Procedure	Initial	1 Month	3 Months
Visual Acuity	x	x	x
Refraction	x		
IOP	x	x	x
Schirmer's	x	x	x
TBUT	x	x	x
MGE	x	x	x
SICCA Score	x	x	x
NSPI-E	x	x	x
DEQ-5	x	x	x
OSDI	x	x	x
PHQ-9	x		

XIV. Patient-Reported Instruments

1. NPSI-E – Neuropathic pain inventory
    i. Number of Questions – 12
    ii. Time to Complete -

2. DEQ-5 – Dry eye questionnaire 5
    i. Number of Questions –
    ii. Time to Complete –

3. OSDI – Ocular surface disease index
    i. Number of Questions – 12
    ii. Time to Complete - 5 minutes

4. PHQ-9 –
    i. Number of Questions – 9
    ii. Time to Complete – 5 min

XV. Ocular Surface Evaluation Procedures

The evaluation procedures should be performed in the order specified below to minimize disruption of the ocular surface.

1. Tear Breakup Time

Two people are required to measure tear breakup time, one who does the examination and one who holds timer. The tear breakup time should be measured prior to instillation of any anesthetic drops. A dry fluorescein strip should be touched lightly to the tear meniscus, and the patient instructed to blink several times. After even distribution of the fluorescein, the patient should be asked to blink again and then hold the eye open. The instant the patient holds their eye open an assistant should start a stopwatch. The examiner will remain looking at the ocular surface with the cobalt blue light at the slit lamp, and signal to the timer when the first break in the tear film occurs. This should be repeated a total of three times, and all three times recorded.

2. Meibomian Gland Grading

Meibomian glands will be evaluated using the handheld Meibomian gland expression device (MGED)[25] using the procedure described in Meadows, et al.[26]

Two areas of the lower lid will be used for Meibomian gland grading – the temporal lower lid from the 4^{th}-9^{th} observable Meibomian gland orifice (counting from the lateral canthus) and the central lower lid from the 15^{th}- 20^{th} Meibomian gland orifice (counting from the lateral canthus).

The first step is observation of the glands, with assignment of a morphology score (Table 2). Following this, the glands will be expressed using the MGED, and meibum quality score will be assigned (Table 2).

Lid Morphology	Assigned Grade	Meibum Quality
No plugged glands	0	Clear, fluid meibum
Mild (1-2 glands plugged)	1	Granular or yellowish meibum
Moderate (3-4 glands plugged)	2	Whitish, semi-solid meibum
Severe (5+ glands plugged)	3	Solid, toothpaste-like meibum
-	4	No expressible meibum

Table 2: Meibomian gland scoring system, adapted from Meadows, et al[26]

3. Schirmer Testing

Schirmer testing will be performed using commercially available filter paper Schirmer strips. The strips should be placed at the outer canthus with the tip of the strip tucked between the lower lid and the bulbar conjunctiva, with both eyes being tested at the same time. The strips should be left in place for 5 minutes or until the length of the strip is saturated. The result should be recorded in mm of paper wetted by tears. No anesthetic drops should be given prior to testing.

4. SICCA Scoring

A drop of 0.25% fluorescein should be administered to the conjunctiva of each eye and the patient allowed to wait for approximately 5 minutes. Following this, the corneal epithelium should be examined for staining following the method of Whitcher, et al[27], and the number of puncate epithelial erosions (PEE) counted. A Lissamine green strip should then be saturated with 0.05% proparicaine and the proparicaine allowed to sit on the surface for 30 seconds, this should then be applied to the conjunctiva and the number of conjunctival PEE counted. A score will be assigned according to the following system, from Whitcher, et al[27]. The scores will range from 0 (no staining) to 12 (severe dry eye findings).

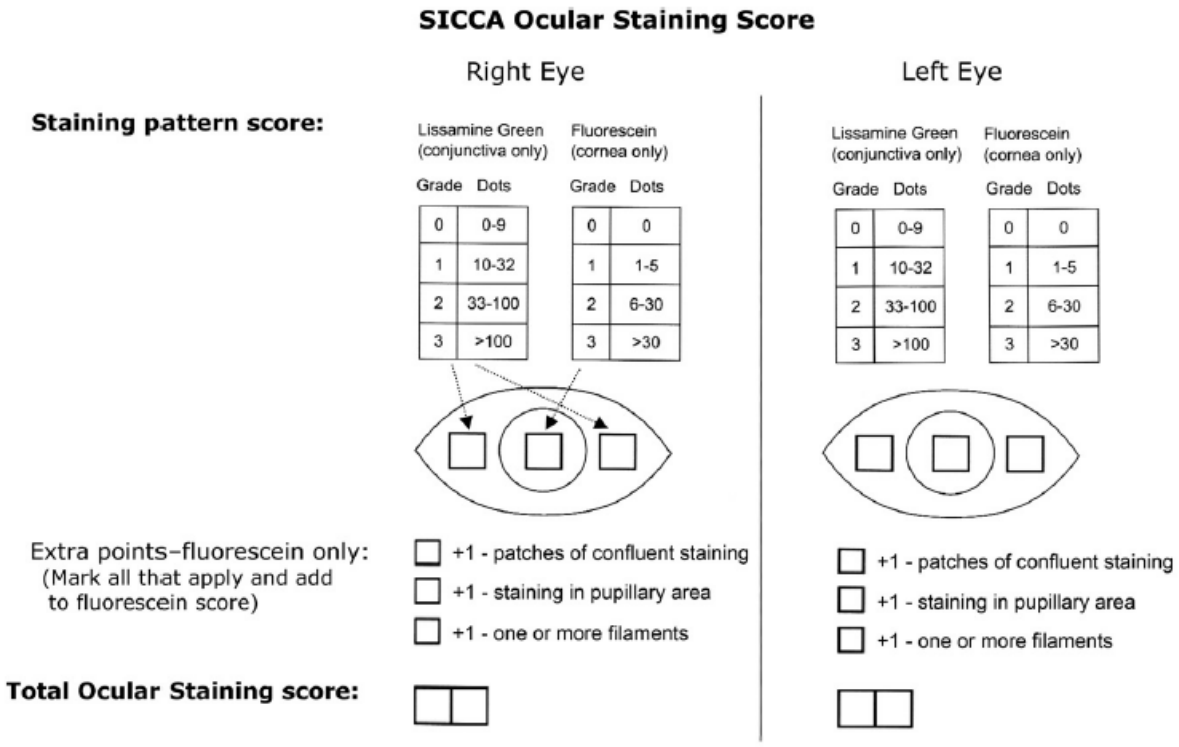

Figure 1: SICCA scoring system[27]

5. HD Analyzer

The HD Analyzer is a FDA approved device to measure ocular surface light scatter. As the tear film is the first surface that light encounters as it enters the eye, disruption of the tear film from Meibomian gland disease can have optical sequelae.

Subjects will receive HD Analyzer measurements of the OSI (ocular surface index) at enrollment, 1 month, and 3 month timepoints per manufacturer instructions.

XVI. Safety and Data Monitoring

a. Adverse Events

All adverse events will be recorded and reported via the Adverse Event Reporting Form (AERF, MOP), and entered into an Adverse Event Log for the patient (MOP). Below is a list of adverse events (AE) and serious adverse events (SAE).

Ocular Adverse Event	**Non-Serious**	**Serious**
Ocular Irritation	Mild to moderate irritation treatable with adjuvant lubricant drops.	Impairs patient's ability to complete activities of daily living, after normal surgical recovery period.
Ocular Hypertension	≥ 24 mm Hg	Surgery required (laser or incisional)
Subconjunctival hemorrhage	Subconjunctival hemorrhage greater than 5mm indiameter after injection	
Cataract	Visually significant cataract, cataract surgery indicated	
Infectious scleritis or keratitis		Any occurrence is a serious adverse event
Corneal or scleral perforation		Any occurrence is a serious adverse event

Systemic Adverse Event	**Non-Serious**	**Serious**
Nausea	Any nausea	Severe discomfort, minimal food intake for 3 or more days **or** at least a 2.5 kg weight loss resulting from nausea
Vomiting	Any vomiting	Severe: vomiting all food or fluids in 24 hours or orthostatic hypotension **or** at least a 2.5 kg weight loss resulting from vomiting
Diarrhea	Any diarrhea	Severe, bloody diarrhea or 8-9 loose stools in 24 hours or orthostatic hypotension **or** at least a 2.5 kg weight loss resulting from diarrhea
Dyspnea	Breathlessness on significant exertion **or** breathlessness at normal level of activity	Breathlessness at rest
Headache	Moderate, non-narcotic analgesic therapy required	Severe, requires narcotic therapy
Fatigue	Self-reported fatigue	Normal activity reduced >50%; cannot work or unable to care for self
Fever for 12 hours	> 100.6 to 103°F/39.5°C	≥ 103°F/39.5°C
Muscle strength	Subjective weakness, no objective symptoms **or** mild objective weakness, no decrease in function	Objective weakness, function limited, or worse

Mood	Self-reported mood changes or psychiatric diagnosis not requiring medical therapy (specify):_ _____	Psychiatric diagnosis requiring medical treatment or hospitalization
Cardiac function	Mild congestive heart failure (CHF) or arrhythmia not requiring treatment or moderate CHF or worse, arrhythmia requiring treatment, stable angina	Unstable angina, severe CHF, myocardial infarction, or arrhythmia requiring hospitalization
Neurologic function	Numbness or tingling	Total loss sensation
Allergic reaction*	Pruritis without rash or erythema or localized urticaria, diffuse maculopapular rash, dry desquamation	Generalized urticaria, angioedema or worse, vesiculation, moist desquamation, ulceration up to and including: exfoliative dermatitis; mucous membrane involvement; **or** Stevens-Johnson Syndrome, **or** erythema multiforme, **or** necrosis requiring surgery
Systemic infection	Any systemic infection.	Systemic infection requiring hospitalization.
Other systemic	No treatment required and no limitations or mild impairment of usual activities	Vigorous treatment, hospitalization usually required, immediate risk of death
Seizure		Any occurrence is a serious adverse event
Cancer		Any occurrence is a serious adverse event
Congenital Anomaly/Birth Defect		Any occurrence is a serious adverse event
Disability or Permanent Damage		Any occurrence is a serious adverse event
Hospitalization		Any occurrence is a serious adverse event
Life-threatening event		Any occurrence is a serious adverse event

Serious adverse event collection begins after the patient has signed informed consent and has undergone pterygium excision. If a patient experiences an SAE after signing informed consent, but prior to undergoing surgery, the event will be treated as unrelated to the study unless the investigator feels the event may have been caused by a protocol procedure. Adverse events (SAEs) occurring after a patient has received the last injection of the study drug will be collected for 30 days after the last dose of study drug, regardless of the investigator's opinion of causation. Thereafter, SAEs are not required to be reported unless the investigator feels the events were related to the study drug or a protocol procedure.

b. Adverse Event Reporting

Study personnel must alert the medical monitory of any **SAE** within 24 hours of investigator awareness of the event. Alerts issued via telephone are to be immediately followed with official notification on the Serious Adverse Event Reporting form (MOP). All serious or unexpected Adverse Events judged to be definitely, possibly, or probably related to study participation will be reported to the UCSF CHR (Committee on Human Research) within 5 working days of their occurrence. All reporting will be performed following CHR guidelines. The study physician must report new significant follow-up information for these events to the principal investigator immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

c. Determination of Causality

Causality of the adverse event will be determined by the study investigators and the DSMB. Events will be determined to be one of the following:

- **Definitely Related:** if it is clear that the event was caused by study participation. A definitely related event has a strong temporal relationship and an alternative cause is unlikely.
- **Probably Related:** If there is a possibility that the event is likely to have been caused by study participation. The AE has a timely relationship to the study procedure(s) and follows a known pattern of response, but a potential alternative cause may be present.
- **Possibly Related:** If there is a reasonable possibility that the event might have been caused by study participation. A possibly related event may follow no known pattern of response and an alternative cause seems more likely. An event may also be considered possibly related if there is significant uncertainty about the cause of the event, or a possible relationship to study participation cannot reasonably be ruled out.
- **Unrelated:** The cause of the AE is known and the event is in no way related to any aspect of study participation.

Uncertain Causality: If there is *any* uncertainty regarding AE causality then the event must be assessed as possibly related to research participation and reported to the IRB as indicated.

d. Emergency Medical Contacts

Principal investigator: Julie Schallhorn.
Email: Julie.schallhorn@ucsf.edu
Phone: 310-709-6105

e. Investigator Follow-Up:

The investigator will follow all unresolved treatment-related adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, new therapy is initiated, the patient is lost to follow-up, or the patient withdraws consent. Every effort will be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the patient's Adverse Event Log (MOP) and in the patient's medical record to facilitate source data verification. If, after follow- up, return to baseline status or stabilization cannot be established, an explanation will be recorded on the patient's Adverse Event Log.

f. Data Review

The DSMC will review of data from enrolled patients at bi-annual committee meetings. The discussion will include the number of patients and any significant adverse events. If necessary, the Study Coordinator will provide unmasked treatment assignment to the committee.

g. Interim Analysis

Interim analyses of efficacy are not planned for this study.

h. Early Stopping of the Study

Stopping for harm will be done at the judgment of the DSMC.

Committee

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Michele Bloomer, MD (michele.bloomer@ucsf.edu)

i. Loss to Follow up

All patients will be offered enrollment in the text-messaging appointment reminder service. Patients that do not show up for scheduled study visits will be contacted by the study coordinator the day following their visit via phone and offered rescheduling. If they are unable to be contacted that day, repeated attempts will be made weekly for 4 weeks to contact patients lost to follow up. Additional attempts will be made at the 6- and 12-month points.

XVII. TREATMENT STOPPING RULES

a. Discontinuation:

Patients who discontinue one of the study treatments due to intolerability or side effects will be observed to the end of the study period unless they are unwilling or unable to return.

In addition, the investigator will discontinue patients from the study drug in the following circumstances:

- The investigator decides that the patient should be withdrawn from the study. If a SAE occurs and the investigator deems stopping study therapy is necessary, the investigator will discontinue the study therapy and take appropriate measures.
- The patient or attending physician requests withdrawal of the patient from the study.
- The investigator or the study sponsor stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP).
- The patient becomes pregnant or fails to use adequate birth control (for women with reproductive potential).
- The patient is noncompliant with study procedures.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the Patient Dropout Form (MOP).
Study agents assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced.

References

1. Pflugfelder SC. Prevalence, burden, and pharmacoeconomics of dry eye disease. The American journal of managed care 2008;14:S102-6.
2. The epidemiology of dry eye disease: report of the Epidemiology Subcommittee of the International Dry Eye WorkShop (2007). The ocular surface 2007;5:93-107.
3. Schaumberg DA, Nichols JJ, Papas EB, Tong L, Uchino M, Nichols KK. The international workshop on meibomian gland dysfunction: report of the subcommittee on the epidemiology of, and associated risk factors for, MGD. Invest Ophthalmol Vis Sci 2011;52:1994-2005.
4. Foulks GN, Bron AJ. Meibomian gland dysfunction: a clinical scheme for description, diagnosis, classification, and grading. The ocular surface 2003;1:107-26.

5. Knop E, Knop N, Millar T, Obata H, Sullivan DA. The international workshop on meibomian gland dysfunction: report of the subcommittee on anatomy, physiology, and pathophysiology of the meibomian gland. Invest Ophthalmol Vis Sci 2011;52:1938-78.
6. King-Smith PE, Bailey MD, Braun RJ. Four characteristics and a model of an effective tear film lipid layer (TFLL). The ocular surface 2013;11:236-45.
7. Lane SS, DuBiner HB, Epstein RJ, et al. A new system, the LipiFlow, for the treatment of meibomian gland dysfunction. Cornea 2012;31:396-404.
8. Lee H, Chung B, Kim KS, Seo KY, Choi BJ, Kim TI. Effects of topical loteprednol etabonate on tear cytokines and clinical outcomes in moderate and severe meibomian gland dysfunction: randomized clinical trial. Am J Ophthalmol 2014;158:1172-1183.e1.
9. Prabhasawat P, Tesavibul N, Mahawong W. A randomized double-masked study of 0.05% cyclosporine ophthalmic emulsion in the treatment of meibomian gland dysfunction. Cornea 2012;31:1386-93.
10. Macsai MS. The role of omega-3 dietary supplementation in blepharitis and meibomian gland dysfunction (an AOS thesis). Transactions of the American Ophthalmological Society 2008;106:336-56.
11. Deinema LA, Vingrys AJ, Wong CY, Jackson DC, Chinnery HR, Downie LE. A Randomized, Double-Masked, Placebo-Controlled Clinical Trial of Two Forms of Omega-3 Supplements for Treating Dry Eye Disease. Ophthalmology 2017;124:43-52.
12. Hosseini K, Lindstrom RL, Foulks G, Nichols KK. A randomized, double-masked, parallel-group, comparative study to evaluate the clinical efficacy and safety of 1% azithromycin-0.1% dexamethasone combination compared to 1% azithromycin alone, 0.1% dexamethasone alone, and vehicle in the treatment of subjects with blepharitis. Clin Ophthalmol 2016;10:1495-503.
13. Greene JB, Jeng BH, Fintelmann RE, Margolis TP. Oral azithromycin for the treatment of meibomitis. JAMA ophthalmology 2014;132:121-2.
14. Yoo SE, Lee DC, Chang MH. The effect of low-dose doxycycline therapy in chronic meibomian gland dysfunction. Korean journal of ophthalmology : KJO 2005;19:258-63.
15. Ta CN, Shine WE, McCulley JP, Pandya A, Trattler W, Norbury JW. Effects of minocycline on the ocular flora of patients with acne rosacea or seborrheic blepharitis. Cornea 2003;22:545-8.
16. Wladis EJ, Bradley EA, Bilyk JR, Yen MT, Mawn LA. Oral Antibiotics for Meibomian Gland-Related Ocular Surface Disease: A Report by the American Academy of Ophthalmology. Ophthalmology 2016;123:492-6.
17. Watters GA, Turnbull PR, Swift S, Petty A, Craig JP. Ocular surface microbiome in meibomian gland dysfunction in Auckland, New Zealand. Clinical & experimental ophthalmology 2016.
18. Giamarellos-Bourboulis EJ. Macrolides beyond the conventional antimicrobials: a class of potent immunomodulators. International journal of antimicrobial agents 2008;31:12-20.
19. Liu Y, Ding J. The combined effect of azithromycin and insulin-like growth factor-1 on cultured human meibomian gland epithelial cells. Invest Ophthalmol Vis Sci 2014;55:5596-601.
20. Liu Y, Kam WR, Ding J, Sullivan DA. Effect of azithromycin on lipid accumulation in immortalized human meibomian gland epithelial cells. JAMA ophthalmology 2014;132:226-8.

21. Igami TZ, Holzchuh R, Osaki TH, Santo RM, Kara-Jose N, Hida RY. Oral azithromycin for treatment of posterior blepharitis. Cornea 2011;30:1145-9.
22. Haque RM, Torkildsen GL, Brubaker K, et al. Multicenter open-label study evaluating the efficacy of azithromycin ophthalmic solution 1% on the signs and symptoms of subjects with blepharitis. Cornea 2010;29:871-7.
23. Luchs J. Azithromycin in DuraSite for the treatment of blepharitis. Clin Ophthalmol 2010;4:681-8.
24. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the Ocular Surface Disease Index. Arch Ophthalmol 2000;118:615-21.
25. Korb DR, Blackie CA. Meibomian gland diagnostic expressibility: correlation with dry eye symptoms and gland location. Cornea 2008;27:1142-7.
26. Meadows JF, Ramamoorthy P, Nichols JJ, Nichols KK. Development of the 4-3-2-1 meibum expressibility scale. Eye Contact Lens 2012;38:86-92.
27. Whitcher JP, Shiboski CH, Shiboski SC, et al. A simplified quantitative method for assessing keratoconjunctivitis sicca from the Sjogren's Syndrome International Registry. Am J Ophthalmol 2010;149:405-15.