STATISTICAL ANALYSIS PLAN

PROTOCOL TITLE:	A Randomized, Multicenter, Double-Masked, Placebo-Controlled Study of the Safety and Efficacy of OmegaD Softgels in the Treatment of Dry Eye Disease
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LIST OF ABBREVIATIONS

Abbreviation	Explanation
AA	Arachidonic acid
AE	Adverse event
ATC-WHO-DD	Anatomical Therapeutic Chemical World Health Organization Drug Dictionary
BID	Twice daily
DHA	Docosahexaenoic acid
DOB	Date of birth
eCRF	Electronic case report form
eDC	Electronic data capture
EPA	Eicosapentaenoic acid
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IL	Interleukin
IRB	Institutional Review Board
ITT	Intent-to-treat
LASIK	Laser-assisted in situ keratomileusis
LTB4	Leukotriene B_4
MedDRA	Medical Dictionary for Regulatory Activities
MMP	Matrix metalloproteinase
NSAID	Nonsteroidal anti-inflammatory drug
OSDI	Ocular Surface Disease Index
OTC	Over-the-counter
PGE	Prostaglandin E
PP	Per protocol
PRK	Photorefractive keratectomy
PRN	Physician Recommended Nutriceuticals
PT	Preferred term
SAE	Serious adverse event

Abbreviation	**Explanation**
SOC	System organ class
SOP	Standard operating procedures
TBUT	Tear break-up time
TEAE	Treatment-emergent adverse event
TNF-α	Tumor necrosis factor alpha
US	United States

1. INTRODUCTION

Dry eye disease is a common multifactorial ophthalmologic disorder of the tears and ocular surface. Dry eye affects approximately 4.9 million people (3.2 million women and 1.7 million men) 50 years and older in in the United States (US). Inflammation is an integral component of this disease, as shown by increased expression of inflammatory mediators on the ocular surface such as interleukin 1 (IL-1), tumor necrosis factor alpha (TNF-α) and matrix metalloproteinase 3 and 9 (MMP-3, MMP-9). This is supported by the observation that Restasis® (cyclosporine ophthalmic emulsion, 0.05%), a drug that targets the immune system, is approved for the indication of increased tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca and effectively treats these symptoms in some patients. The efficacy of Restasis is considered to be modest and ocular burning after instillation, the most common adverse reaction, sometimes limits patient compliance and leads to discontinuation of the drug. There is a clear medical need for more effective therapies.

1.1. Rationale for the Development of OmegaD softgels for the Treatment of Dry Eye

Among alternative drug treatments for dry eye, oral treatment with omega-3 fatty acid supplements, in particular the marine omega-3s eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), appears to be promising. Essential fatty acids have been shown to diminish inflammatory responses in many human inflammatory diseases.

EPA and DHA compete for the same enzymes as the omega-6 fatty acid, arachidonic acid (AA). As omega-3 levels increase relative to omega-6 levels, the competition for cyclooxygenase and 5-lipoxygenase suppresses AA synthesis of inflammatory mediators prostaglandin E_2 (PGE_2) and leukotriene B_4 (LTB4), and increases EPA and DHA synthesis of anti-inflammatory (PGE_1) and weakly inflammatory (PGE_3) mediators. This shifts the balance to a less inflammatory mixture of eicosanoids. EPA and DHA supplementation also decreases monocyte synthesis of cytokines TNF-α and IL-1β, with cytokine synthesis decreasing as cellular EPA concentrations increase. More recently, EPA and DHA derivatives, resolvins and protectins, have been shown to act to initiate the resolution of inflammation by enhancing macrophage clearance of leukocytes.

Because inflammation is a key component of dry eye disease and increasing the systemic levels of omega-3 fatty acids relative to omega-6 levels can mediate immune responses, it is important to evaluate whether omega-3 supplementation can improve dry eye disease signs, symptoms and associated measures of inflammation. In clinical studies conducted with patients with dry eye, oral supplementation with omega-3s has been found to produce significant improvement in dry eye symptoms, and improvement in various dry eye signs has been observed, most often increased tear break-up time (TBUT), with increased Schirmer's test scores and improved meibum characteristics reported by several investigators.

On the basis of the clinical development conducted by Physician Recommended Nutriceuticals (PRN) with PRN Dry Eye Omega Benefits®, OmegaD is now developing OmegaD softgels. A randomized, masked clinical trial was conducted with 105 subjects with dry eye who were randomized to 4 Dry Eye Omega Benefits or placebo (safflower oil) softgels daily and treated for

3 months. Statistically significantly decreased tear osmolarity and dry eye Ocular Surface Disease Index (OSDI) symptoms, and significantly increased TBUT were observed for subjects who received Dry Eye Omega Benefits versus placebo. The safety profile appeared to be satisfactory; 4 subjects in each treatment group reported adverse events (AEs) (Omega Benefits 7.5%, placebo 8.0%). All the AEs reported for the Omega Benefits group were mild; these included stomach upset (2 subjects), diarrhea, headache, upper respiratory infection, and flu. The stomach upset reported for one subject and the diarrhea reported for another were considered possibly related to study drug. OmegaD softgels is a formulation that is similar to Dry Eye Omega Benefits with only slightly different amounts of EPA and DHA.

Although numerous clinical studies have been conducted to study the efficacy of various doses and formulations of omega-3 fatty acids, the commercially available omega-3 supplements used for dry eye disease are supported by general health claims, and while subject to Food and Drug Administration (FDA) regulation as food supplements, the FDA may not have reviewed the clinical data to support activity in dry eye disease. OmegaD LLC plans to conduct a clinical program to evaluate the safety and efficacy of a controlled, pharmaceutical grade omega-3 oral supplement for dry eye disease.

2. STUDY DESCRIPTION

2.1. Primary Objective

The primary objective of this study is to evaluate the safety and efficacy of twice daily (BID) dosing of OmegaD softgels in subjects with dry eye disease.

2.2. Study Design

This will be a randomized, multicenter, double-masked, placebo-controlled study. Subjects will be randomized to 1 of 2 treatment arms and treated for 84 days (12 weeks) as follows:

- OmegaD softgels (N = 82 subjects); 2 softgels BID (2 softgels 5 – 10 minutes before breakfast and 2 softgels 5 – 10 minutes before dinner) for 84 days
- Placebo softgels (N = 82 subjects); 2 softgels BID (2 softgels 5 – 10 minutes before breakfast and 2 softgels 5 – 10 minutes before dinner) for 84 days

At Screening (Day -7 to Day -1), sites will obtain signed informed consent, demographic information, medical/ocular and concomitant medication histories, perform a urine pregnancy test (women of childbearing potential only), conduct screening examinations (tear osmolarity testing, meibomian gland dysfunction grading, TBUT, Schirmer's test), and assess AEs. Inclusion/exclusion criteria will then be reviewed.

Subjects who meet eligibility criteria at Screening will return to the site at Baseline (Day 0) and the site will update concomitant medications and conduct baseline examinations beginning with the OSDI questionnaire. Continuing eligibility for enrollment will require tear osmolarity ≥ 312 mOsm/L and meibomian gland dysfunction grade 1 or 2 on the meibomian orifice size scale **in at least one eye** at **both Screening and Baseline,** TBUT ≤ 7 seconds in **both eyes** at **both Screening and Baseline**, and the Schirmer's test score from **Screening** must be ≥ 5 mm in **both eyes**. The qualifying osmolarity level and meibomian orifice size grade must be present in the same eye at both Screening and Baseline if only one eye qualifies. The study eye will be the worse eye at Baseline as defined by lower TBUT score; if both eyes score equally on TBUT, the eye with the higher tear osmolarity score will be chosen, and if still equal, the right eye will be the study eye. After inclusion/exclusion criteria are reviewed, the site will randomize eligible subjects. The Omega-3 Index score will be assessed via fingerstick blood sample and site personnel will dispense study medication and a daily study medication diary and assess AEs.

Subjects will take 2 softgels twice daily 5 to 10 minutes before a meal (i.e., 2 softgels before breakfast and 2 softgels before dinner). Subjects will document their compliance in terms of number of softgels taken in the study medication diary on a daily basis.

Each subject will return to the site at Day 42 (± 7 days) along with all unused study medication and the study medication diary and site personnel will update concomitant medications, conduct a slit-lamp examination, dispense study medication, assess AEs, and perform study medication accountability and diary review.

Subjects will return to the site at Day 84 (± 7 days), along with all unused study medication and the study medication diary, for final safety and efficacy evaluations. Site personnel will update

concomitant medications, perform a urine pregnancy test (women of childbearing potential only), conduct all specified ophthalmic assessments, assess the Omega-3 Index score via fingerstick blood sample, assess AEs, and perform study medication accountability and diary review.

Both eyes will be assessed at each visit. Adverse events and concomitant medications will be documented from signing of informed consent at Screening to Day 84.

Approximately 164 subjects are planned to be enrolled; approximately 82 subjects in each treatment arm at up to 15 clinical sites; however, when 90 subjects have completed treatment a review of treatment compliance will be conducted. If more than 10% of subjects have protocol deviations for treatment compliance, the study will be resized to achieve a study population in which 90% are compliant.

2.3. Inclusion Criteria

1. Subjects age ≥ 18 years and ≤ 90 years on the date of informed consent.
2. All subjects must provide signed written consent prior to participation in any study related procedures.
3. Patient-reported dry eye symptoms.
4. Clinical diagnosis of dry eye disease supported by global clinical assessment.
5. Presence of tear osmolarity in at least one eye ≥ 312 mOsm/L at both Screening and Baseline.
6. Presence of meibomian gland dysfunction as defined by a grade of 1 or 2 on the meibomian orifice size scale in at least one eye at both Screening and Baseline. The qualifying osmolarity level and meibomian orifice size grade must be present in the same eye at both Screening and Baseline if only one eye qualifies.
7. Female subjects of childbearing potential must have a negative urine pregnancy test at Screening. Women of childbearing potential (i.e., women who are not either postmenopausal for one year or surgically sterile) must use an acceptable form of contraception throughout the study.

2.4. Exclusion Criteria

1. Allergy to fish oil or safflower oil (component of placebo softgels) or any component of the softgel material.
2. Schirmer's test score < 5 mm at Screening in either eye.
3. Tear break-up time > 7 seconds at Screening or Baseline in either eye.
4. Clinically significant eyelid deformity or eyelid movement disorder that is caused by conditions such as notch deformity, incomplete lid closure, entropion, ectropion, hordeolum or chalazion.
5. Active seasonal and/or perennial allergic conjunctivitis or rhinitis.

6. Previous ocular disease leaving sequelae or requiring current topical eye therapy other than for dry eye disease, including, but not limited to: active corneal or conjunctival infection of the eye and ocular surface scarring.
7. History or presence of abnormal nasolacrimal drainage.
8. Laser-assisted in situ keratomileusis (LASIK) or photorefractive keratectomy (PRK) performed within one year prior to Screening and throughout the study period.
9. Ophthalmic drop use within 2 hours prior to any study visit. Any over-the-counter (OTC) artificial tear should be continued at the same frequency and with no change in drop brand.
10. Contact lens wear within 12 hours prior to any study visit; subjects determined to have worn contact lenses within 12 hours must be rescheduled.
11. Punctal cauterization or punctal plug placement within 60 days prior to Screening and throughout the study period.
12. Started or changed the dose of systemic medications known to affect tear production within 30 days prior to Screening and throughout the study period. These include but are not limited to the following medications:
    - Immunomodulators
    - Antihistamines
    - Tricyclic antidepressants
    - Diuretics
    - Corticosteroids (intranasal, inhaled, topical dermatological, and perianal steroids are permitted).
13. Use of any topical prescription ophthalmic medications (including cyclosporine [Restasis®, steroids, nonsteroidal anti-inflammatory drugs [NSAIDs], anti-glaucoma medications), oral tetracyclines or topical macrolides, oral nutraceuticals [fish, flax, black currant seed oils, etc.] within 21 days prior to Screening and throughout the study period.
14. Chronic daily use (defined as > 7 consecutive days at the recommended dosing frequency) of oral NSAIDs during the study period. ANY use of oral NSAIDS during the study period must be discussed with the Medical Monitor.
15. Participation in any drug or device clinical investigation within 30 days prior to entry into this study and/or during the period of study participation.

2.5. Permitted Medications and Treatments

Therapy considered necessary for the subject's welfare that will not interfere with the evaluation of the study medication may be given at the discretion of the Investigator. If there is any question as to whether the medication may interfere, the Investigator should contact the Medical Monitor or Sponsor. Whenever possible, medications should be administered in dosages that remain constant throughout the study duration.

Artificial tear use is permitted during the study period, but it should be continued at the same frequency and with no change in drop brand.

2.6. Prohibited Medications and Treatments

The Medical Monitor should be notified before prohibited medication or therapy is administered unless the safety of the subject requires immediate action. The decision to administer a prohibited medication or therapy should be done with the safety of the subject as the primary consideration. The Medical Monitor MUST be contacted to determine the permissibility of a specific medication or therapy and whether or not the subject should continue with study participation.

For systemic medications known to affect tear production, any new medication or change in the dose of the medication within 30 days prior to Screening and throughout the study period is prohibited as follows:

- Immunomodulators
- Antihistamines
- Tricyclic antidepressants
- Diuretics
- Corticosteroids (intranasal, inhaled, topical dermatological, and perianal steroids are permitted).

Chronic daily use (defined as > 7 consecutive days at the recommended dosing frequency) of oral NSAIDs during the study period is prohibited. ANY use of oral NSAIDS during the study period must be discussed with the Medical Monitor. Aspirin is permitted.

Prohibited ophthalmic medications and therapies within 21 days prior to Screening and throughout the study period include the use of any topical prescription ophthalmic medications as follows:

- Cyclosporine (i.e., Restasis)
- Steroids
- NSAIDs
- Antiglaucoma medications
- Macrolides

Additionally, oral nutraceuticals [fish, flax, black currant seed oils, etc.] are prohibited within 21 days prior to Screening and throughout the study period.

The following procedures are prohibited as specified:

- LASIK or PRK performed within one year prior to Screening and throughout the study period.
- Punctal cauterization or punctal plug placement within 60 days prior to Screening and throughout the study period.

2.7. Treatment Compliance

Treatment compliance will be monitored by study medication accountability and subjects' daily study medication diaries. The amount of unused softgels returned at the Day 42 and Day 84 visits and the information provided in the study medication diaries by subjects will be documented by study site personnel in the electronic data capture (eDC) system.

2.8. Withdrawal from Study and Discontinuation of Study Medication

The following are the criteria for considering withdrawal from the study:

- Withdrawal of subject consent.
- Subject is lost to follow-up.

Subjects may be discontinued from study medication for any of the following reasons:

- The subject has a clinically significant or serious AE that would not be consistent with continuation in the study, as determined by the Investigator or Medical Monitor
  - It is possible for subjects to experience a skin rash or other allergic reaction related to the components of the softgels; if this occurs, the subject should discontinue the medication.
- Pregnancy

If a subject is discontinued from study medication or is generally noncompliant with the protocol, every effort should be made to encourage the subject to continue to attend study visits to be followed for safety, rather than withdrawing the subject from the study. Reasons for considering subject withdrawal from the study are discussed above.

3. STUDY ASSESSMENTS

3.1.1. Demographic Information

Demographic information including date of birth, gender, race, ethnicity, and date of informed consent will be recorded.

3.1.2. Medical/Ocular History

Clinically significant medical and ophthalmic history will be documented and will include any previously diagnosed ophthalmic abnormalities and ocular surgeries, including laser and non-laser procedures.

3.1.3. Concomitant Medications History

All concomitant medications (prescription and OTC) taken at Screening and for 3 months prior to Screening and throughout the course of the study will be recorded in the Concomitant Medications page of the electronic case report form (eCRF). Information regarding the dates of first and last dose, site of dosing (e.g., right eye, left eye, both eyes, systemic), and the reason the concomitant medication is being taken must be recorded in the eCRF. When a concomitant medication has been taken at a stable dose for longer than 6 months, an estimation of the start date is adequate.

3.1.4. Urine Pregnancy Test

A urine pregnancy test will be performed at Screening and repeated at the End of Treatment Visit (Day 84) or the Early Discontinuation Visit for women of childbearing potential only.

3.2. Efficacy Assessments

3.2.1. Signs

3.2.1.1. Tear Osmolarity

Tear osmolarity will be tested via the TearLab Osmolarity Test.

3.2.1.2. Meibomian Gland Dysfunction Grading

Using a slit-lamp at a magnification of 10 to 16X, the eyelids of each eye will be evaluated utilizing the following scales:

Meibomian Gland Dysfunction Grading Scales

A. Meibomian Orifice Size Scale

GRADE	EYELID MARGIN MEIBOMIAN ORIFICE SIZE FINDINGS
0	Orifice barely visible.
1	Orifice easily visible in at least 5 orifices.
2	Orifice dilated with meibum plug which may extend above the lid margin in at least 5 orifices.
3	Orifice keratinized over in at least 5 orifices.

B. Telangiectasia Scale

GRADE	EYELID MARGIN TELANGIECTASIA FINDINGS
0	No blood vessels present between meibomian glands.
1	One (1) blood vessel present between 4 pairs of glands/orifices
2	More than 1 vessel between 4 pairs of glands/orifices
3	More than 1 vessel with vasodilation between 4 pairs of glands/orifices.
4	More than 1 vessel with vasodilation between 4 pairs of glands/orifices with erythema of the tissue.

3.2.1.3. Tear Break-Up Time

The TBUT procedure is conducted 3 times for each eye and the TBUT for each is measured in seconds and recorded in the eCRF. The average for each eye will be calculated by the eDC system.

3.2.1.4. Schirmer's Test (Anesthetized)

An anesthetized Schirmer's test will be performed and the amount of moisture on each strip in millimeters (mm) will be measured and recorded in the eCRF.

3.2.2. Symptoms

The OSDI questionnaire will be provided to the study subject, who will be asked to circle the number that corresponds with the frequency of dry eye symptoms experienced over the past week. Site personnel will enter the scores in the eCRF. The eDC system will automatically calculate the final score.

3.3. Safety Assessments

3.3.1. Slit-Lamp Examination

A routine slit-lamp examination will be performed to evaluate the anterior segment of the eye, including lids, cornea, conjunctiva, anterior chamber, iris, and lens. Abnormalities will be documented.

3.4. Pharmacokinetic Assessment

3.4.1. Omega-3 Index Test

The Omega -3 Index Test measures the concentration of two specific omega-3 fatty acids, EPA and DHA, as a percent of total fatty acids in red blood cell membranes. This test is performed by using a contact-activated lancet to collect a drop or two of blood on a collection card. Each card is identified and packaged to be submitted to OmegaQuant (Sioux Falls, SD) for analysis.

3.5. Adverse and Serious Adverse Events

3.5.1. Definition of Adverse Events

3.5.1.1. Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical study subject administered a study medication (pharmaceutical/biological product) that does not necessarily have a causal relationship to this medication. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with the use of the study medication, whether or not related to the study medication. Study medication includes the investigational drug under evaluation and the comparator product or vehicle placebo that is given during any phase of the study.

Medical conditions/diseases present before starting the investigational treatment are only considered AEs if they worsen after starting the investigational treatment. Abnormal test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of AEs should be sought by open-ended questioning of the subject at each visit during the study. At each clinic visit, study personnel should ask the following question: "Have you had any problems since your last visit?" AEs also may be detected when they are volunteered by the subject during or between visits or through study assessments.

3.5.1.2. Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,

Note: The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Results in persistent or significant disability/incapacity (excluding progression/outcome of the disease under study);
- Is a congenital anomaly/birth defect,
- Requires inpatient hospitalization or prolongation of existing hospitalization, or

- Is medically significant; i.e., defined as an event that jeopardizes the health of the subject or may require medical or surgical intervention to prevent one of the outcomes listed above.

Treatment on an outpatient emergency basis that does not result in hospital admission, or a hospitalization that is elective or is a preplanned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of the study, is not considered an SAE.

All SAEs that are ongoing at the time of completion or discontinuation from the study will be followed until stabilization (i.e., no other change in the condition is expected) or resolution of the event.

3.6. Relationship to Study Drug

The relationship of AEs to the study medication should be assessed by the Investigator using the definitions below.

Not suspected: The temporal relationship of the event to the study medication makes a causal relationship unlikely, or, other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

Suspected: The temporal relationship of the event to the study medication makes a causal relationship possible or other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the study medication and the occurrence of the AE, then the AE should be considered “suspected.”

If the relationship between the AE/SAE and the investigational product is determined by the Sponsor or designee to be “suspected” the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting (see Section 9.8).

3.7. Recording Adverse Events

Adverse events spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation, regardless of severity or potential association with the study medication or study procedures, will be recorded in the eCRF. Clinically significant changes in blood pressure and heart rate should be reported as AEs; however, Omega-3 treatment has been demonstrated to have beneficial effects on blood pressure and heart rate. Only clinically significant changes (increase or decrease) in heart rate should be reported as AEs. All AEs that occur after a subject has signed the informed consent form until the final study visit, Visit 4 (Day 84), should be collected and recorded on the AE eCRF page. AEs that occur after informed consent is provided but before the first dose of study medication will be summarized separately from AEs that occur from the first dose of double-masked treatment on Day 0 to the Day 84 visit. Serious adverse events will be followed until the event is resolved or stabilized.

Medical conditions/diseases occurring before the signing of Informed Consent Form during Visit 1 (Screening) should be collected on the medical/ocular history pages of the eCRF.

The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the following:

- Onset (date and time);
- Resolution (date and time);
- Severity grade (mild, moderate, severe);
- Relationship to study medication (not suspected, suspected);
- Action taken (none, study medication temporarily interrupted, study medication permanently discontinued; concomitant medication taken; hospitalization/prolonged hospitalization; other);
- Serious outcome (yes/no).

The severity grade should be determined by the Investigator using the definitions below.

- Mild: Discomfort noticed but no disruption of normal daily activity
- Moderate: Discomfort sufficient to cause interference with normal daily activity
- Severe: Incapacitating, with inability to perform normal activities

Table 2: Schedule of Procedures

Procedures	**Visit 1 Screening**	**Visit 2 Baseline**	**Visit 3**	**Visit 4/Early Discontinuation**
Days	**-7 to -1**	**0**	**42 ± 7 days**	**84 ±7 days**
Informed consent	X			
Demographics	X			
Medical/ocular history	X			
Concomitant medication history/review	X	X	X	X
Urine pregnancy test [a]	X			X
Ocular Surface Disease Index Questionnaire		X		X
Tear osmolarity	X	X		X
Meibomian gland dysfunction grading at slit-lamp using meibomian orifice size and telangiectasia scales	X	X		X
Slit-lamp examination		X	X	X
Tear break-up time (TBUT)	X	X		X
Schirmer's test (anesthetized)	X			X
Review inclusion/exclusion criteria	X	X		
Randomization		X		
HS-Omega-3 Index Test (fingerstick)		X		X
Study medication and study medication diary distribution		X	X	
Adverse event assessment [b]	X	X	X	X
Study medication accountability [c]		X	X	X
Study medication diary review			X	X

[a] Women of childbearing potential only.
[b] Collection of AEs extends from signing of informed consent until the last study visit.
c Clinical site personnel will document all dispensed or returned study medication as applicable at Baseline, and Days 42 and 84.

4. SAMPLE SIZE AND POWER CONSIDERATIONS

TBUT: A sample size of 82 in each group will have 95% power to detect a difference in means of 2.07 seconds assuming that the common standard deviation is 3.5 using a two-group t-test with a 0.05 two-sided significance level.

OSDI: A sample size of 82 in each group will have approximately 95% power to detect a difference in means of 11.390 assuming that the common standard deviation is 20.0 using a two-group t test with a 0.05 two-sided significance level.

When 90 subjects have completed treatment a review of treatment compliance will be conducted. If more than 10% of subjects have protocol deviations for treatment compliance, the study will be resized to achieve a study population in which 90% are compliant.

5. ANALYSIS POPULATIONS

5.1.1. Populations for Efficacy Analysis

5.1.1.1. Intent-to-Treat Population

The intent-to-treat (ITT) population is defined as all randomized subjects. The primary efficacy analysis will be performed on the ITT population.

5.1.1.2. Per Protocol Population

The per protocol (PP) population will include all ITT subjects who remain in the study through Visit 4 and who did not deviate from the protocol in any way likely to seriously affect the primary outcome of the study. Secondary efficacy analyses will be performed on the PP population.

5.1.2. Safety Analysis Population

The safety population will include all subjects who have received at least one dose of the study medication. All safety analyses will utilize the safety population.

6. HANDLING OF MISSING DATA

The planned statistical methods use all available data. To account for the presence of missing data, multiple imputation may be used for ITT analyses on the primary endpoints. Multiple imputation will be carried out using the SAS procedures.

7. STATISTICAL ANALYSIS

Efficacy analysis will be conducted on the ITT population and on the PP population. Safety analyses will be performed using the safety analysis population.

The study eye will be the worse of qualifying eyes at Baseline as defined by lower TBUT score; if both eyes score equally on TBUT, the eye with the higher tear osmolarity score will be chosen, and if still equal the right eye will be the study eye. All statistical analyses and reporting will be performed using the SAS® System Version 9.3 or later.

Unless otherwise specified, continuous variables will be summarized with descriptive statistics (n, mean, median, standard deviation, standard error, minimum, and maximum), and categorical variables will be summarized with counts and percentages.

Definition of Baseline:

Baseline measurements will be the last measurement for the corresponding variable prior to the first randomized dose on Visit 2, Day 0.

Out of Window and Unscheduled Visits:

The protocol defined windows for scheduled visits will not be used in the analyses by visit. Data will be assigned to the scheduled visit closer in time to the scheduled visit. Unscheduled visit data will only be used in an analysis if there is no other available data closer in time to a scheduled visit. All unscheduled visit data will be included in data listings.

7.1. Subject Disposition

Subject disposition, including the number of subjects randomized, treated, and completing the study (and completing each study visit), will be tabulated by treatment group. The percentage of subjects treated and completing the study will be based on the total number randomized. A subject data listing will be provided.

Eligibility criteria exemptions and major protocol deviations will be summarized by treatment group and presented in a listing. Major protocol deviations may include, but are not limited to the following: violation of inclusion or exclusion criteria, using prohibited medications, non-adherence to study treatment schedule. A guideline for classification of patients as belonging to the per protocol analysis dataset will be documented prior to database unmasking as will the masked review of patient data for purposes of classification.

The total number and percentage of subjects included in each of the analysis datasets will be summarized by treatment group, with percentages based on the total number of randomized subjects. A subject data listing will be provided.

Discontinuations and the reasons for discontinuation from the study will be summarized for all randomized subjects. Summaries will include the number and percentage of subjects within each treatment group.

Reasons for discontinuation following the receipt of study drug will include the following:

- Withdrawal of subject consent.
- Adverse event(s).

A subject data listing will be provided.

7.2. Demographic and Baseline Characteristics

Subject demographic and baseline characteristics will be summarized for the ITT analysis population; however, should there be a reasonable difference in the size of the ITT and safety analysis populations, demographic and baseline characteristics will be summarized for both. The comparability of groups used in comparison analyses will be characterized in tables of demographic data. Summary tables will be supported with individual subject data listings.

Continuous variables such as age will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum), and categorical variables such as gender, race, ethnicity, and iris color will be summarized using counts and percentages of subjects.

Age will be determined as the whole integer number of years from the date of birth (DOB) to the date of the screening visit, i.e., the truncated integer difference between the DOB and Visit 1.

7.3. Treatment Compliance and Exposure

The duration of drug exposure and % compliance will be summarized by visit and treatment group. Compliance over all visits will also be summarized.

Duration of drug exposure will be calculated for each subject as the last date of dosing minus the first date of dosing + 1. The number and percentage of subjects by treatment group will be summarized according to the following duration-of-exposure categories: '< 1 wk', '1 to < 9 wks', '9 to < 13 wks', and ≥ 13 wks'.

A subject data listing will be provided.

7.4. Study Endpoints

7.4.1. Primary Efficacy Endpoints

The primary efficacy endpoints comprise a set of hypotheses that will be tested in a hierarchical fashion.

1. Mean change from baseline in average of the 3 TBUT measures in the study eye at Visit 4 (Day 84)
2. Mean change from baseline in OSDI score at Visit 4 (Day 84)
3. Mean change from Screening in Schirmer's test (anesthetized) score in the study eye at Visit 4 (Day 84).

4. Mean change from baseline in tear osmolarity in the study eye at Visit 4 (Day 84).

Groups will be compared using an analysis of covariance model where treatment group is a fixed factor and baseline score is a covariate. The treatment difference will be estimated by the adjusted least squares mean. The 95% confidence on the difference will be provided.

The differences between the 2 treatment groups will be tested with a significance level of 0.05. In order to control the Type I error rate these endpoints will be tested sequentially in the order described above. Testing will halt at the first p-value >0.05.

7.4.2. Exploratory Efficacy Endpoint

- Proportion of subjects with meibomian gland dysfunction grade of 0 on both meibomian orifice size and telangiectasia scales in the study eye at Visit 4 (Day 84). Statistical significance will be assessed by a chi-square, Fisher's exact, or Cochran-Mantel-Haenszel test.

Groups will be compared using an analysis of covariance model where treatment group is a fixed factor and baseline score is a covariate. The treatment difference will be estimated by the adjusted least squares mean. The 95% confidence on the difference will be provided.

8. SAFETY EVALUATIONS

8.1. Adverse Events

Treatment-emergent adverse events (TEAEs) are those with onset after randomization or if occurring prior to randomization, worsened after randomization. Only treatment-emergent events will be summarized. All events in the clinical database regardless of when they occurred will be provided in data listings. Adverse events will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA) system to the levels of System Organ Class (SOC) and primary Preferred Term (PT).

An overall summary will be presented which gives the number and percentage of subjects within each treatment group that experienced any TEAE, experienced any treatment related TEAE, permanently discontinued treatment due to a TEAE, experienced a treatment emergent SAE, and that died.

In summary tables, AEs occurring in both eyes will be summarized once at the greater intensity and relationship to study drug.

Events that are possibly or probably related will be counted as an event related to study drug.

The number and percentage of subjects experiencing one or more events within a MedDRA SOC and PT class without regard to intensity, relationship, or seriousness will be tabulated by treatment group. In addition, tables will display events by SOC, PT, and maximum intensity or closest relationship to treatment.

The number of deaths and SAEs will also be presented, and AEs leading to premature discontinuation from the study will be listed and tabulated.

A glossary listing that shows the verbatim terms assigned to each SOC and PT will be provided.

A listing of TEAEs by treatment group ordered by subject, SOC, PT, and onset date will be provided.

A listing of serious TEAEs by treatment group ordered by subject, SOC, PT, and onset date will be provided.

8.2. Concomitant Medications

All concomitant medications listed on the case report form will be provided in data listings in the clinical study report. Each medication will be mapped to their corresponding Preferred Term from the ATC-WHO-DD (Anatomical Therapeutic Chemical World Health Organization Drug Dictionary) A frequency distribution of all concomitant medications used during the study will be provided for each treatment group. Medications used prior to randomization but stopped prior to randomization will be summarized separately from those used concomitantly. A subject data listing will be provided.

8.3. Ocular and Other Medical History

History terms will be classified according to the MedDRA system to the levels of SOC and primary PT.

An overall summary will be presented which gives the number and percentage of subjects within each treatment group that experienced each condition or procedure. A subject data listing will be provided.

8.4. Ophthalmoscopy/Dilated Fundoscopy

The observations of ocular ophthalmoscopy and dilated fundoscopy will be summarized in frequency tables based on the ordinal or categorical scales for each measure for each eye by time point and treatment group. A subject data listing will be provided.

9. CHANGES FROM THE PROTOCOL

TBD

10. INTERIM ANALYSIS

No interim analyses are planned.

11. TABLES, LISTINGS AND FIGURES

Table, listing and figure shells are provided in the Appendix.