CLINICAL TRIAL PROTOCOL

OmegaD-2016-001

A Randomized, Multicenter, Double-Masked, Placebo-Controlled Study of the Safety and Efficacy of OmegaD Softgels in the Treatment of Dry Eye Disease

Study Phase:	Phase 3
Product Name:	OmegaD softgels
Indication:	Treatment of dry eye disease
Sponsor:	OmegaD LLC 740 Nine Gates Road Yorklyn, DE 19736
Medical Monitor:	Charles Slonim, MD
Original Protocol:	24 June 2016

SPONSOR SIGNATURE

Study Title:	A Randomized, Multicenter, Double-Masked, Placebo-Controlled Study of the Safety and Efficacy of OmegaD Softgels in the Treatment of Dry Eye Disease
Study Number:	OmegaD-2016-001
Original Protocol:	24 June 2016

Person authorized to sign the protocol and protocol amendment(s) for the Sponsor, OmegaD LLC:

S. Gregory Smith, MD
Chief Executive Officer, OmegaD LLC
302-383-3948 (Mobile)

S Gregory Smith

Signature

07/12/2016

Date

Medical Monitor
Charles Slonim, MD
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Signature

7/5/2016

Date

INVESTIGATOR'S AGREEMENT

Study Title:	A Randomized, Multicenter, Double-Masked, Placebo-Controlled Study of the Safety and Efficacy of OmegaD Softgels in the Treatment of Dry Eye Disease
Study Number:	OmegaD-2016-001
Original Protocol:	24 June 2016

I have read the OmegaD-2016-001 protocol. The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and in compliance with International Conference of Harmonisation (ICH) Guidelines, and all applicable United States (US) Federal Regulations and local legal and regulatory requirements.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Contact Information
Clinical Study Leader	Roselyn Judd Oculos Clinical Research	615-962-8698 (Office) 586-212-0237 (Mobile) Email: rjudd@pointguardllc.com
Medical Monitor	Charles Slonim, MD Oculos Clinical Research	813-690-0255 (Mobile) 813-443-5865 (Fax) Email: cslonim@pointguardllc.com

1. SYNOPSIS

Name of Sponsor/Company: OmegaD LLC

Name of Investigational Product: OmegaD softgels and placebo softgels

Name of Active Ingredient: Eicosapentaenoic acid (EPA)/docosahexaenoic acid (DHA), Omega-3 fatty acids in the triglyceride form

Title of Study: A Randomized, Multicenter, Double-Masked, Placebo-Controlled Study of the Safety and Efficacy of OmegaD Softgels in the Treatment of Dry Eye Disease

Studied Period (Years):	**Phase of Development:**
Estimated date first patient enrolled: September 2016 Estimated date last patient completed: May 2017	3

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

Methodology: 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

Comparisons of OmegaD softgels to placebo will be double-masked; OmegaD softgels and placebo will be identical-appearing softgels.

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, tear break-up time (TBUT), Schirmer's test), and assess adverse events (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 (Ocular Surface Disease Index (OSDI) questionnaire, tear osmolarity, meibomian gland dysfunction grading, slit lamp examination, TBUT). Continuing eligibility for enrollment will require tear osmolarity ≥ 312 mOsm/L and 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,** 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. 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 (ie, 2 softgels 5 – 10 minutes before breakfast and 2 softgels 5 – 10 minutes before dinner). Daily reminders to take the medication will be provided, and subjects will document their compliance in terms of number of softgels taken in the study medication diary on a daily basis.

Methodology (Continued):

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), conduct all ophthalmic assessments as specified in the Schedule of Procedures, the Omega-3 Index 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.

Number of Patients (Planned): Approximately 164 subjects are planned to be enrolled; approximately 82 subjects in each treatment arm at approximately 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.

Diagnosis and Main Criteria For Inclusion:

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.

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.

Diagnosis and Main Criteria For Inclusion:

Exclusion Criteria (Continued):

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. Aspirin is permitted.
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.

Investigational Product, Dosage and Mode Of Administration: OmegaD softgels, 2 softgels BID (ie, 2 softgels 5 – 10 minutes before breakfast and 2 softgels 5 – 10 minutes before dinner).

Reference Therapy, Dosage and Mode Of Administration: Placebo softgels, 2 softgels BID (ie, 2 softgels 5 – 10 minutes before breakfast and 2 softgels 5 – 10 minutes before dinner).

Duration of Treatment: 84 days (12 weeks)

Study Procedures: Note: Ophthalmic examinations should be conducted in the order listed in the Schedule of Procedures. All ophthalmic examinations are conducted in both eyes. Study medication accountability (documentation of dispensed/returned study medication) will be conducted at each study visit beginning at Baseline.

Visit 1 (Day -7 to Day -1): Screening

The site will obtain signed informed consent, demographics, medical/ocular/concomitant medication

histories, perform a urine pregnancy test (for women of childbearing potential only), conduct screening ophthalmic examinations (tear osmolarity ≥ 312 mOsm/L and meibomian gland dysfunction as defined by a grade of 1 or 2 on the meibomian orifice size scale in at least one eye, TBUT ≤ 7 seconds in both eyes, Schirmer's test score ≥ 5 mm in both eyes), review inclusion/exclusion criteria, and assess AEs. The qualifying osmolarity level and meibomian orifice size grade must be present in the same eye at Screening if only one eye qualifies.

Visit 2 (Day 0): Baseline

The site will update concomitant medications, conduct baseline examinations including the OSDI, tear osmolarity testing, meibomian gland dysfunction grading, slit-lamp examination, and TBUT and then review inclusion/exclusion criteria.

In order to meet inclusion requirements, subjects must have tear osmolarity ≥ 312 mOsm/L and 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**, 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. Site personnel will then randomize eligible subjects, perform the HS-Omega-3 Index Test will be via fingerstick blood sample, dispense/document study medication and a daily study medication diary and provide instructions for use, and assess AEs.

Subjects should be reminded to bring all study medication and the study medication diary to the clinical site at Visit 3 (Day 42). If the study medication and diary are not brought to the site, the visit must be rescheduled.

Visit 3 (Day 42 ± 7 days): Safety and Accountability Visit

The site will collect unused study medication and the study medication diary, update concomitant medications, perform a slit-lamp examination, dispense study medication, assess AEs, and conduct study medication accountability and diary review.

Subjects should be reminded to bring all study medication and the study medication diary to the clinical site at Visit 4(Day 84). If the study medication and diary are not brought to the site, the visit must be rescheduled.

Visit 4 (Day 84 ± 7 days): Final Treatment Visit

The site will collect unused study medication and the daily study medication diary, update concomitant medications, perform urine pregnancy test, conduct final ophthalmic examinations (OSDI, tear osmolarity, meibomian gland grading, slit-lamp examination, TBUT, and Schirmer's test), Omega-3 Index via fingerstick blood sample, assess AEs, and conduct final study medication accountability and diary review.

Clinical site personnel will document all received and returned study medication at each visit and review the study medication diary. Study medication accountability will be conducted by the monitor at each applicable monitoring visit.

If a study subject is discontinued from study medication before Visit 4 or is generally noncompliant with the protocol, every effort should be made to keep the subject in the study and conduct all study visits as scheduled or, failing that, to perform all Visit 4 procedures at the visit the subject is discontinued.

Efficacy Assessments:

Signs: TBUT, tear osmolarity, meibomian gland dysfunction grading, Schirmer's test (anesthetized).

Symptoms: OSDI questionnaire.

Pharmacokinetics: Omega-3 Index Test

Safety Assessments: Safety assessments will include slit-lamp examination, collection of AEs, and documentation of concomitant medications.

Criteria for Evaluation:

Primary Efficacy Endpoints:

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

- Mean change from baseline in TBUT in the study eye at Visit 4 (Day 84).
- Mean change from baseline in OSDI score at Visit 4 (Day 84)

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 two endpoints will be tested sequentially in the order described above. If the null hypothesis for the TBUT endpoint can be rejected at $P \leq 0.05$, the OSDI endpoint will be tested at $P \leq 0.05$.

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).

Secondary Efficacy Endpoint(s):

- Mean change from baseline in tear osmolarity in the study eye at Visit 4 (Day 84).
- Mean change from Screening in Schirmer's test (anesthetized) score in the study eye at Visit 4 (Day 84).

Safety Endpoint:

- Incidence of adverse events.

Statistical Methods:

Analysis Population:

- Intent-to-treat (ITT): The ITT population will include all randomized subjects.
- Per protocol (PP): The 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.
- Safety: The safety population will include all subjects who have received at least one dose of the study medication.

Statistical Methods (Continued):

Statistical Analyses:

Analysis of TBUT, meibomian gland dysfunction, tear osmolarity, and Schirmer's test scores will utilize the designated study eye (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) to assess the significance of the differences between OmegaD and placebo. The unit of analysis for OSDI symptoms will be the subject.

Statistical significance for the comparison of means will utilize the t-test or analysis of covariance. Statistical significance for binary data will be assessed by a chi-square, Fisher's exact, or Cochran-Mantel-Haenszel test.

Descriptive statistics will be used to summarize continuous outcomes (number of subjects, mean, standard deviation or standard error of the mean, median, maximum, and minimum) and categorical variables (frequency and percentage) at each assessment time point. All summary tables will be supported with individual subject data listings.

Sample Size:

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.

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.

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations are used in this study protocol.

Table 3: Abbreviations

Abbreviation	Explanation
AA	Arachidonic acid
AE	Adverse event
BID	Twice daily
DHA	Docosahexaenoic acid
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
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 terms
SAE	Serious adverse event
SOC	System organ class
SOP	Standard operating procedures
TBUT	Tear break-up time

Abbreviation	Explanation
TEAE	Treatment-emergent adverse event
TNF	Tumor necrosis factor
US	United States

4. INTRODUCTION

4.1. Background Information

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) (Schaumberg et al, 2003; Schaumberg et al, 2009). 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) (Pflugfelder, 2004). 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.

4.2. 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 (PGE3) mediators. This shifts the balance to a less inflammatory mixture of eicosanoids (James et al, 2000). EPA and DHA supplementation also decreases monocyte synthesis of cytokines TNF-α and IL-1β, with cytokine synthesis decreasing as cellular EPA concentrations increase (Caughey et al, 1996). 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 (Kohli and Levy, 2009).

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 (Bhargava et al, 2013; Kangari et al, 2013; Kawakita et al, 2013; Macsai, 2008; Oleñik et al, 2013; Wojtowicz et al, 2011).

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 (Donnenfeld et al, 2015). 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.

4.3. Justification for Dose, Regimen, and Treatment Period

The omega-3 daily dose to be utilized in OmegaD-2016-001, 1680 mg of EPA and 560 mg of DHA, is the same dose utilized in the PRN study in which significant separation was observed between OmegaD and placebo in OSDI symptoms, TBUT, and tear osmolarity (Donnenfeld et al, 2015), and it appeared to be well tolerated based on the low number of AEs reported (unpublished data). The daily amount of omega-3 in OmegaD is less than that present in Lovaza® capsules (1860 mg of EPA and 1500 mg of DHA), the FDA-approved EPA/DHA product indicated for the reduction of triglyceride levels in adults with severe hypertriglyceridemia, the safety of which was established in the clinical trials conducted in support of approval. The treatment period of 3 months is considered sufficient to evaluate the efficacy and safety of OmegaD softgels and is a standard study duration in trials of dry eye disease.

4.4. Good Clinical Practices Statement

This study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and in compliance with International Conference of Harmonisation (ICH) guidelines, and all applicable US federal regulations and local legal and regulatory requirements.

4.5. Population to Be Studied

Study subjects will be ≥ 18 years and ≤ 90 years of age, with patient-reported dry eye symptoms and a clinical diagnosis of dry eye disease supported by global clinical assessment. Each subject must have, in at least one eye, tear osmolarity of ≥ 312 mOsm/L and meibomian gland

dysfunction as defined by a grade of 1 or 2 on the meibomian orifice size scale at both Screening and Baseline in at least one eye. In addition, TBUT must be ≤ 7 seconds in both eyes at both Screening and Baseline and the Schirmer's test score in both eye(s) must be ≥ 5 mm at 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. See Section 7 for inclusion and exclusion criteria.

5. TRIAL OBJECTIVES AND PURPOSE

5.1. 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.

6. INVESTIGATIONAL PLAN

6.1. Overall 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

Comparisons of OmegaD softgels to placebo will be double-masked; OmegaD softgels and placebo will be identical-appearing softgels.

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 (ie, 2 softgels 5 - 10 minutes before breakfast and 2 softgels 5 – 10 minutes before dinner). Daily reminders to take the medication will be provided, and 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

6.2. Number of Subjects

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.

6.3. Criteria for Study Termination

The study may be terminated at any time by OmegaD LLC, following appropriate notification.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Subject 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.

7.2. Subject 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.

7.3. Withdrawal Criteria

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

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

If a subject withdraws or is withdrawn from the study, the principal reason for withdrawal will be recorded in the electronic case report form (eCRF).

If a study subject is lost to follow up at any point during the study period, attempts to contact the subject must be documented.

If a study subject is discontinued from study medication before Visit 4 or is generally noncompliant with the protocol, every effort should be made to keep the subject in the study and conduct all study visits as scheduled or, failing that, to perform all Visit 4 procedures at the visit the subject is discontinued.

8. TREATMENT OF SUBJECTS

8.1. Description of Study Drug

8.1.1. Investigational Product

The daily dose of OmegaD softgels, 4 softgels, contains 1680 mg of EPA and 560 mg of DHA, with other naturally occurring omega-3 fatty acids, an antioxidant (alpha tocopherol), and a flavoring agent in a softgel shell composed of gelatin, glycerin, and colorant. The softgel is formulated with the omega-3 fatty acids in the triglyceride form.

8.1.2. Reference Therapy

The placebo softgels contain safflower oil in a softgel shell composed of gelatin, glycerin, and colorant.

8.2. Randomization and Masking

Study medication will be randomized in a 1:1 ratio (OmegaD to placebo). A randomized block design will be used, and the randomization will be created by the biostatistician.

If subjects meet eligibility criteria at Screening and at Baseline (see Section 7 for eligibility criteria), subjects will be randomly assigned to study medication at the Baseline visit. Clinical sites will assign the next subject kit, taken sequentially, from the lowest to the highest numbered kits from within each shipment of study medication. The drug kit randomization number will be recorded in the subject's eCRF.

A supply of randomized study medication from the assigned kit sufficient to last until Day 42 will be dispensed to the subject at the Baseline visit; and at the Day 42 visit a supply of randomized study medication from the assigned kit sufficient to last until Day 84 will be dispensed.

8.2.1. Unmasking During the Study Period

Should it be necessary to unmask a subject's treatment assignment in case of emergency, the investigator may obtain the treatment code for a given randomized subject from the 2-part tear-off label from the subject's study medication kit. The randomization code is to be obtained only if a medical emergency exists and knowledge of the medication being taken will influence the medical management of the subject. In the event of emergency or life-threatening condition, the investigator may need to unmask the subject. The following procedure should be followed:

1. The Investigator should contact the Medical Monitor via phone immediately before unmasking a subject, unless it is not possible to do so without risk to the subject.
2. The Investigator should document the serious adverse event (SAE) and justification for unmasking in the Study Summary and Comments pages of the eCRF.
3. The Subject may continue to participate in the study at the Investigator's discretion. If the subject is to be discontinued from study participation, then ALL procedures described in the Early Discontinuation Visit (Section 10.5) should be completed.

4. The Investigator should contact Oculos Clinical Research, the clinical research organization, at OmegaD-safety@pointguardllc.com within 24 hours with the randomization number, subject initials, details of the AE or SAE, any action taken, and whether the subject is continuing in the study.

8.3. Concomitant Medications

8.3.1. 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.

8.3.2. Prohibited Medications

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.

Contact lens and ophthalmic drop use (e.g., artificial tears), while permitted during the study period, are prohibited within designated time periods prior to any study visit. Contact lens wear is prohibited within 12 hours prior to any study visit (subjects determined to have worn contact lenses within 12 hours must be rescheduled), and ophthalmic drop use is prohibited within 2 hours prior to any study visit.

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.

8.4. 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.

8.5. Discontinuation of Study Medication

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 in Section 7.3.

8.6. Study Medication Materials and Management

8.6.1. Packaging and Labeling

Study medication will be packaged and labeled at a central packaging facility. Each subject kit will consist of a single box with 5 bottles of study medication. Upon randomization each eligible subject will receive 2 bottles of study medication. The study site will retain 3 bottles, 2 of which will be dispensed at the Day 42 visit, and 1 extra bottle in case of loss or damage.

8.6.2. Storage

Store at controlled room temperature: 15° to 30°C (59° to 86°F). Do not freeze. Keep out of reach of children.

8.6.3. Administration

Following randomization, site personnel will dispense study medication and instruct the subject on administration procedures. The daily dose is 4 softgels daily, which is recommended to be taken as 2 softgels 5 – 10 minutes before breakfast and 2 softgels 5 – 10 minutes before dinner. Taking the softgels just before meals is important to minimize any digestive upset, such as belching and indigestion. If the subject can tolerate it, all 4 softgels may be taken 5 - 10 minutes before a single meal; the timing of the dose is not as important as taking all 4 softgels.

8.6.4. Dispensing

At randomization, a kit with 2 bottles of study medication (sufficient study medication to last until the Day 42 visit with a little overage) and a study medication diary will be dispensed to the subject with instructions to return the kit along with all unused study medication and the completed study diary at the Day 42 visit. At the Day 42 visit, the unused study medication will be counted, and the site will dispense 2 bottles of study medication (sufficient study medication to last until the Day 84 visit with a little overage) and the study medication diary with instructions to return the kit along with all unused study medication and the completed study diary at the Day 84 visit.

8.6.5. Study Medication Accountability

The Investigator or designee (e.g., study coordinator or pharmacist) will maintain a full accountability record for the study medication and will be responsible for recording the receipt, dispensing, and return of all supplies of the study medication using the inventories supplied by Oculos. Clinical site personnel will document all dispensed and returned study medications at Baseline (Day 0), Day 42, and Day 84 and study drug accountability will be conducted by the monitor at each applicable monitoring visit.

As described in Section 8.6.4, the subject will return all unused study medication and the study medication diary at Days 42 and 84. The monitor will review dispensing and drug accountability records during site visits and at the completion of the study and note any discrepancies.

All investigational study medication must be stored in a secure facility, with access limited to the Investigator and authorized staff.

9. STUDY ASSESSMENTS

Prior to entry into the study or initiation of any study-related procedures, the subject must read, sign, and date the current Institutional Review Board (IRB)-approved version of the informed consent form. A full discussion of informed consent is presented in Section 13.3.

9.1. Demographic and Background Characteristics

9.1.1. Demographic Information

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

9.1.2. 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.

9.1.3. 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 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. Standard procedural medications will not go into the eCRF but are recorded on a standard procedural medication log provided by Oculos Clinical Research.

9.1.4. 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.

9.2. Efficacy Assessments

9.2.1. Signs

9.2.1.1. Tear Osmolarity

Tear osmolarity will be tested via the TearLab Osmolarity Test. The osmolarity testing must precede all other diagnostic examinations (except the OSDI at Visits 2 and 4), and the subject must refrain from administrating any tear supplements within two hours prior to the tear osmolarity test.

9.2.1.2. 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.

A grade of 1 or 2 in meibomian orifice size in at least one eye is required for eligibility into the study. A grade of 0 or 3 in both eyes excludes the patient from study participation. 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.

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.

A certain score on the telangiectasia scale is not required for study entry, nor is it an exclusion criterion. The telangiectasia and meibomian orifice size scales will provide additional detailed information with which to track the progress/resolution of meibomian gland disease.

9.2.1.3. Tear Break-Up Time

A drop of Fluress® is added to the eye and the patient may blink once to disperse it. Then while the subject avoids blinking, the tear film is observed under the slit-lamp through a cobalt blue filter and timed until tiny dry spots develop. The 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.

9.2.1.4. Schirmer's Test (Anesthetized)

An anesthetized Schirmer's test will be performed to insure that only basal tear secretion is being measured and to prevent tearing due to the irritation from the filter paper (the eyes will already

have been anesthetized for the TBUT procedure). Filter paper strips will be placed in both eyes inside the lower eyelid (conjunctival sac) at the same time. The eyes are closed for 5 minutes. The paper is then removed and the amount of moisture on each strip in millimeters (mm) is measured and recorded in the eCRF.

9.2.2. Symptoms

The OSDI questionnaire (Appendix A) 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.

9.3. Safety Assessments

9.3.1. 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.

9.4. Pharmacokinetic Assessment

9.4.1. 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.

9.5. Adverse and Serious Adverse Events

9.5.1. Definition of Adverse Events

9.5.1.1. 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.

9.5.1.2. Serious Adverse Event

An 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; ie, 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.

9.6. 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).

9.7. 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 first dose of study medication during Visit 1 (Day 1) 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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity (as defined directly above) whereas seriousness is defined by the criteria under Section 9.5.1.2 . An AE of severe intensity may not be considered serious.

Should a pregnancy occur, it must be reported and recorded on the pregnancy form. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

9.8. Reporting Adverse Events

All SAEs (related and unrelated) will be recorded from signing of informed consent until the final study visit, Visit 3 (Day 42), following the end of treatment exposure. Any SAEs "suspected" to be related to the investigational product and discovered by the Investigator at any time after the study should be reported to Oculos.

Any SAE that occurs must be reported to Oculos within 24 hours of its occurrence or within 24 hours of learning of its occurrence. Recurrent episodes, complications, or progression of the initial SAE must be reported to Oculos as follow-up to the original episode within 24 hours of the Investigator receiving the information. Information about all SAEs will be collected and recorded on the SAE form. All pertinent medical records and information collected during the treatment and follow-up of the subject should be maintained at the site with a copy emailed to OmegaD-safety@pointguardllc.com. The Investigator must assess the SAE relationship and complete the SAE form. Oculos may request additional information. Follow-up information (e.g., discharge summary) will be retained in the subject's chart and a copy will be emailed to OmegaD-safety@ pointguardllc.com.

In addition, all SAEs should be recorded on the Adverse Event eCRF page with the serious question marked "Yes".

It is the investigator's responsibility to notify the approving IRB of any SAEs on a timely basis as instructed by the Sponsor or designee following the Sponsor's determination of causality.

All subjects who experience an SAE should be followed clinically and undergo the appropriate diagnostic evaluations until stabilization or resolution of the event.

Oculos will report all SAEs to the US FDA on the appropriate schedule depending if the event is drug related or not drug related, expected, unexpected (based on the available information in the Investigator's Brochure).

Any death occurring during the study and follow up period should be reported as an SAE. For any death occurring through the end of the study, regardless of the degree of relationship to study drug, the SAE resulting in the death must be reported to Oculos. A death occurring after completion of the study at Visit 4 (Day 84) does not require completion of the SAE form.

10. STUDY ACTIVITIES

Note: Ophthalmic examinations should be conducted in the order listed in the Schedule of Procedures. All ophthalmic examinations are conducted in both eyes. Subjects must not have used any ophthalmic drop within 2 hours and must not have worn contact lenses within 12 hours of the study visit. Subjects determined to have used ophthalmic drops or worn contacts within the specified durations prior to study visits must be rescheduled.

10.1. Visit 1 (Day -7 to Day -1)/Screening

At Visit 1 (Day -7 to Day -1)/Screening subjects will provide written informed consent before any study-related procedures are conducted and participate in screening procedures to establish eligibility for the study. Procedures performed at Screening will include the following:

- Obtain written informed consent
- Inclusion/exclusion criteria
- Demographics
- Medical and ocular histories
- Concomitant medication history
- Urine pregnancy test (women of childbearing potential only)
- Tear osmolarity test
- Meibomian gland dysfunction grading
- TBUT
- Schirmer's test (anesthetized)
- Review inclusion/exclusion criteria
- AE assessment

Only subjects with tear osmolarity ≥ 312 mOsm/L and meibomian gland dysfunction grade **1 or 2** on the meibomian orifice size scale in at least one eye, and TBUT ≤ 7 seconds and Schirmer's test score ≥ 5 mm in both eyes will be scheduled to return to the clinical site for Visit 2. The qualifying osmolarity level and meibomian orifice size grade must be present in the same eye at Screening if only one eye qualifies.

10.2. Visit 2 (Day 0)/Baseline

At Visit 2 (Day 0)/Baseline the site will conduct confirmatory examinations of eligibility and subjects who continue to meet eligibility criteria will participate in baseline dry eye disease examinations, be randomized, and receive a supply of study medication. Procedures performed at Baseline include:

- Concomitant medication review
- OSDI questionnaire

- Tear osmolarity test
- Meibomian gland dysfunction grading
- Slit-lamp examination
- TBUT
- Review inclusion/exclusion criteria to confirm eligibility. Subjects who do not meet the following criteria will be considered to have failed screening at this point:
  - Subjects must have tear osmolarity ≥ 312 mOsm/L and meibomian gland dysfunction grade 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.
  - TBUT ≤ 7 seconds in **both eyes** at **both Screening and Baseline**
  - The Schirmer's test score from **Screening** must be ≥ 5 mm in **both eyes** (Schirmer's test is not conducted at Baseline).
- Randomization
- Omega-3 Index test (fingerstick blood sample)
- Dispense and document dispensing of study medication and provide instructions for administration
- Dispense study medication diary and provide instructions for use
- AE assessment

10.3. Visit 3 (Day 42)/Safety and Accountability Visit

Subjects should be reminded at scheduling and confirmation to bring all unused study medication and the study medication diary to Visit 3. If the study medication and diary are not brought to the site, the visit must be rescheduled.

Procedures performed at Visit 3 (Day 42), a mid-treatment safety and accountability visit, will include the following:

- Collect unused study medication and study medication diary
- Concomitant medication review
- Slit-lamp examination
- Dispense study medication for the remainder of the study
- AE assessment
- Conduct study medication accountability and review study medication diary

10.4. Visit 4 (Day 84)/Final Study Visit

Subjects should be reminded at scheduling and confirmation not to use ophthalmic drops within 2 hours or wear contact lenses within 12 hours prior to the study visit and to bring all unused study medication and the study medication diary to Visit 4. If the study medication and diary are not brought to the site, the visit must be rescheduled.

At Visit 4 (Day 84), the final study visit, subjects will participate in final efficacy and safety evaluations. Procedures performed at Day 84 will include the following:

- Collect unused study medication and study medication diary
- Concomitant medication review
- Urine pregnancy test (women of childbearing potential only)
- OSDI
- Tear osmolarity test
- Meibomian gland dysfunction grading
- Slit-lamp examination
- TBUT
- Schirmer's test (anesthetized)
- Omega-3 Index test (fingerstick blood sample)
- AE assessment
- Conduct study medication accountability and review study medication diary

10.5. Early Discontinuation

If the subject discontinues the study early, procedures performed will include the following:

- Collect all unused study medication materials and the study medication diary, if available; otherwise arrange for the subject to return them
- Concomitant medication review
- Urine pregnancy test (women of childbearing potential only)
- OSDI
- Tear osmolarity test
- Meibomian gland dysfunction grading
- Slit-lamp examination
- TBUT
- Schirmer's test (anesthetized)
- Omega-3 Index test (fingerstick blood sample)

- AE assessment
- Conduct study medication accountability and review study medication diary

11. STATISTICS

11.1. General Considerations

This is a randomized, multicenter, double-masked, placebo-controlled study to evaluate the safety and efficacy of BID dosing of OmegaD softgels for 84 days (12 weeks) in the treatment of subjects with dry eye disease.

Subjects will be randomized in a 1:1 ratio as follows:

- OmegaD softgels (N = 82 subjects); 2 softgels BID
- Placebo softgels (N = 82 subjects); 2 softgels BID

A biostatistician will perform statistical analyses as agreed with the Sponsor according to the Statistical Analysis Plan. Any additional or supplemental data analysis performed independently by an Investigator shall be submitted to the Sponsor for review.

Efficacy analysis will be conducted on the intent-to-treat (ITT) population and on the per protocol (PP) population. Safety analyses will be performed using the safety analysis population. Definitions for all of the analysis populations can be found in Section 11.3.

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.

11.2. 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.

11.3. Determination of Sample Size

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.

11.4. Analysis Populations

11.4.1. Populations for Efficacy Analysis

11.4.1.1. Intent-to-Treat Population

The ITT population is defined as all randomized subjects. The primary efficacy analysis will be performed on the ITT population.

11.4.1.2. Per Protocol Population

The 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.

11.4.2. 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.

11.5. Demographics 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.

11.6. Efficacy Analysis

Primary efficacy analyses will be performed on the ITT population. Analysis of TBUT, meibomian gland dysfunction, tear osmolarity, and Schirmer’s test scores will utilize the designated study eye (worse eye at Baseline as defined by lower TBUT; 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) to assess the significance of the differences between OmegaD and placebo. The unit of analysis for OSDI symptoms will be the subject.

Statistical significance for the comparison of means will utilize the t-test or analysis of covariance. Statistical significance for binary data will be assessed by a chi-square, Fisher's exact, or Cochran-Mantel-Haenszel test.

Descriptive statistics will be used to summarize continuous outcomes (number of subjects, mean, standard deviation or standard error of the mean, median, maximum, and minimum) and categorical variables (frequency and percentage) at each assessment time point. All summary tables will be supported with individual subject data listings.

11.6.1. Primary Efficacy Endpoints

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

- TBUT in the study eye
- OSDI score

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 two endpoints will be tested sequentially in the order described above. If the null hypothesis for the TBUT endpoint can be rejected at $P \leq 0.05$, OSDI endpoint will be tested at $P \leq 0.05$.

11.6.2. 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).

11.6.3. Secondary Efficacy Endpoints

- Mean change from baseline in tear osmolarity in the study eye at Visit 4 (Day 84).
- Mean change from Screening in Schirmer's test (anesthetized) score in the study eye at Visit 4 (Day 84).

11.7. Safety Analyses

Safety data will be presented in tables of descriptive statistics and frequency distribution. All summary tables will be supported with individual subject data listings.

12. QUALITY CONTROL AND QUALITY ASSURANCE

Oculos/OmegaD LLC and/or their contracted agents utilize standard operating procedures (SOPs) designed to ensure that research procedures and documentation are consistently conducted/prepared to the highest quality standards. These SOPs require compliance with FDA regulations and the ICH Good Clinical Practice (GCP) guidance.

The study will be monitored by Oculos to verify that the rights and well-being of human subjects are being protected, the reported data are accurate, complete, and verifiable, and that the conduct of the study is in compliance with the currently approved protocol, with ICH GCP, and with the applicable regulatory requirements.

To insure compliance with GCP and all applicable regulatory requirements, Sponsor or its agent may conduct a quality assurance audit at any time during or after completion of a study. The investigator will be given adequate notice if he/she is selected for an audit. The audit will include, but is not limited to: a review of all informed consent forms, medical records, and regulatory documentation; an assessment of study conduct and protocol compliance; and a review of the investigational drug product receipt, storage, and administration. At the conclusion of an audit, the auditor will conduct a brief meeting with the investigator to review the findings of the audit.

13. ADMINISTRATIVE CONSIDERATIONS

13.1. Institutional Review Board (IRB)

The IRB must review, approve, and provide continuing review of the clinical study protocol, protocol amendments, the informed consent documents, subject recruitment advertisements, and any other written information to be provided to the subjects. Initial IRB approval is an affirmative decision that the clinical study has been reviewed and may be conducted at the study site within the constraints set forth by the IRB, the institution, GCP, and applicable regulatory requirements. A copy of the IRB approval letter for the protocol, the informed consent, the intended advertising, and any written material to be provided to the subject must be submitted to Oculos prior to release of investigational supplies to the study site. Progress reports and notifications of serious adverse drug reactions will be provided to the IRB according to local regulations and guidelines. The IRB must be notified of completion or termination of the study. The study site must maintain an accurate and complete record of all reports, documents, and other submissions made to the IRB concerning this protocol.

13.2. Ethical Conduct of the Study

The study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and in compliance with ICH guidelines, and all applicable US federal regulations and local legal and regulatory requirements.

13.3. Written Informed Consent

A sample informed consent form containing the required elements of informed consent will be provided by Oculos. Any changes made to this sample must be approved by Oculos prior to submission to the IRB. After approval by Oculos, the informed consent form must be submitted to and approved by the IRB. The informed consent must be written in a language in which the subject is fluent. Regulations require that foreign language informed consent forms be submitted to the IRB for approval. The foreign language translation is required to contain a statement of certification of the translation. The investigator must forward a copy of the consent forms, the certified foreign language translation, and an IRB approval letter to Oculos.

It is the responsibility of the Investigator to inform each subject of the purpose of this clinical trial, including possible risks and benefits, and to document the informed consent process. Prior to undergoing any study-related procedures, the subject must read, sign, and date the current IRB-approved version of the informed consent form. The original informed consent form is to be retained by the study site, and a copy is to be given to the subject.

13.4. Subject Confidentiality and Confidentiality of Data

Data generated for the study should be stored in a limited-access file area and be accessible only to representatives of the study site, Oculos/OmegaD LLC, the IRB, and FDA/relevant regulatory agencies. Medical information resulting from a subject's participation in this study may be given to the subject's personal physician or to the appropriate medical personnel responsible for the subject's welfare. No information that can be related to a specific individual subject will be

released or used in any fashion without the signed written consent of that subject. All reports and communications relating to study subjects will identify subjects only by initials and subject identification number. Complete subject identification will be kept by the Investigator for purposes of long-term follow-up, if needed. This information will be treated with strict adherence to professional standards of confidentiality.

13.5. Study Monitoring

The study will be monitored by Oculos on behalf of OmegaD LLC in accordance with current GCP to assure compliance with the study protocol and the quality of the data collected. Monitoring visits will occur as required and could include a study initiation visit, a monitoring visit, and a study close-out visit. Training will be provided for key investigative personnel in all aspects of study conduct. The Investigator will be responsible for making sure that clinical site personnel are provided adequate training on conducting their designated tasks.

This study will utilize eDC to optimize the eCRF source verification process with limited separate source documentation. Monitors will review e-source data and overall study data/consistency remotely and query discrepancies based upon eCRF entries (eCRF initial entry is the source). During this monitoring, data are reviewed as entered by the site, and the monitors will flag any abnormalities, trends, or safety signals for Medical Monitor review and monitor follow-up onsite, if necessary.

During visits to the study site, the monitor may review the source documents including but not limited to signed informed consent forms, study medication diaries, study medication accountability and storage, and the reporting procedures for AEs and SAEs. All data generated during this study and the medical records/documents from which they originated are subject to inspection by Oculos, the study Sponsor, the FDA, and other regulatory agencies. The investigator must notify Oculos promptly of any inspections scheduled by regulatory authorities.

Upon completion of the study, the clinical monitor will conduct a final visit (closeout) to the site. The objectives of this visit are to ascertain that all regulatory records and reports are complete, verify that the study drug and other supplies have been accounted for, and ensure that the Investigators are aware of their responsibilities once the study ends.

The Investigator is responsible for permitting Oculos direct access to any study documents for monitoring and auditing purposes, for providing adequate space for monitoring, and for addressing any questions or issues that might be raised by the monitor or auditor on a timely basis.

13.6. Case Report Forms and Study Records

All data relating to study procedures will be entered by site personnel directly onto eCRFs provided by Oculos. The eCRF is the first place the majority of the study data will be recorded; and therefore, considered to be the source document. In general, paper source documents will not be created, but when generated, source documents (e.g., discharge summaries, etc.) will be retained at the study site.

13.7. Protocol Violations/Deviations

The Investigator should not deviate from the requirements of this protocol without prior written approval of the Medical Monitor at Oculos, with the exception of a medical emergency.

A significant protocol violation must be reported to Oculos upon discovery. Protocol deviations should be reported to the IRB in accordance with IRB guidelines.

All changes to the protocol will be made by Oculos, or designee as an approved amendment to the protocol, submitted to the FDA, and approved by the IRB prior to implementation.

13.8. Access to Source Documentation

A trial-related monitoring audit, review by the IRB, and/or regulatory inspection may be conducted at any time during or after completion of a study (Section 12). The Investigator will be given adequate notice if he/she is selected for an audit and must provide direct access to study documentation. The audit may include, but is not limited to, a review of all informed consent forms; a review of medical records; a review of regulatory documentation; an assessment of study conduct and protocol compliance; and a review of the investigational drug product receipt, storage, and administration.

13.9. Data Generation and Analysis

Management of data and the production of the clinical study report will be the responsibility of Oculos or its designee.

During the course of the trial, data queries will be generated for data items that are potentially erroneous and require appropriate clarification or correction. Such clarifications and corrections will be discussed with and approved by study site personnel and appropriately documented. Prior to database lock, data listings will be generated and anomalous values investigated.

13.9.1. Retention of Data

Investigators should retain study-related records at the site until informed by the Sponsor. The Investigator will not discard any records without notifying OmegaD, LLC. If the Principal Investigator moves from the current clinical site, OmegaD LLC should be notified of the name of the person who will assume responsibility for maintenance of the records at the clinical site or the new address at which the records will be stored. The Investigator will notify OmegaD, LLC as soon as possible in the event of accidental loss or destruction of any study documentation. If it becomes necessary for Oculos Clinical Research, OmegaD LLC, or the FDA or relevant regulatory authorities to review any documentation relating to the study, the Investigator must permit access to such records.

13.10. Publication And Disclosure Policy

All information concerning OmegaD softgels and the operations of OmegaD LLC, such as patent applications, formulas, manufacturing processes, basic scientific data or formulation information not previously published, are considered CONFIDENTIAL and shall remain the sole property of OmegaD LLC. The Investigator agrees to use this information only in accomplishing this study and will not use it for other purposes without the written consent of OmegaD LLC

The publication policy is addressed in a separate agreement.

14. LIST OF REFERENCES

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APPENDIX A. OCULAR SURFACE DISEASE INDEX (OSDI) QUESTIONNAIRE

Ocular Surface Disease Index© (OSDI©)[2]

Ask your patient the following 12 questions, and circle the number in the box that best represents each answer. Then, fill in boxes A, B, C, D, and E according to the instructions beside each.

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?	4	3	2	1	0
2. Eyes that feel gritty?	4	3	2	1	0
3. Painful or sore eyes?	4	3	2	1	0
4. Blurred vision?	4	3	2	1	0
5. Poor vision?	4	3	2	1	0

Subtotal score for answers 1 to 5 (A)

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	
6. Reading?	4	3	2	1	0	N/A
7. Driving at night?	4	3	2	1	0	N/A
8. Working with a computer or bank machine (ATM)?	4	3	2	1	0	N/A
9. Watching TV?	4	3	2	1	0	N/A

Subtotal score for answers 6 to 9 (B)

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	
10. Windy conditions?	4	3	2	1	0	N/A
11. Places or areas with low humidity (very dry)?	4	3	2	1	0	N/A
12. Areas that are air conditioned?	4	3	2	1	0	N/A

Subtotal score for answers 10 to 12 (C)

ADD SUBTOTALS A, B, AND C TO OBTAIN D (D = SUM OF SCORES FOR ALL QUESTIONS ANSWERED) (D)

TOTAL NUMBER OF QUESTIONS ANSWERED (DO NOT INCLUDE QUESTIONS ANSWERED N/A) (E)

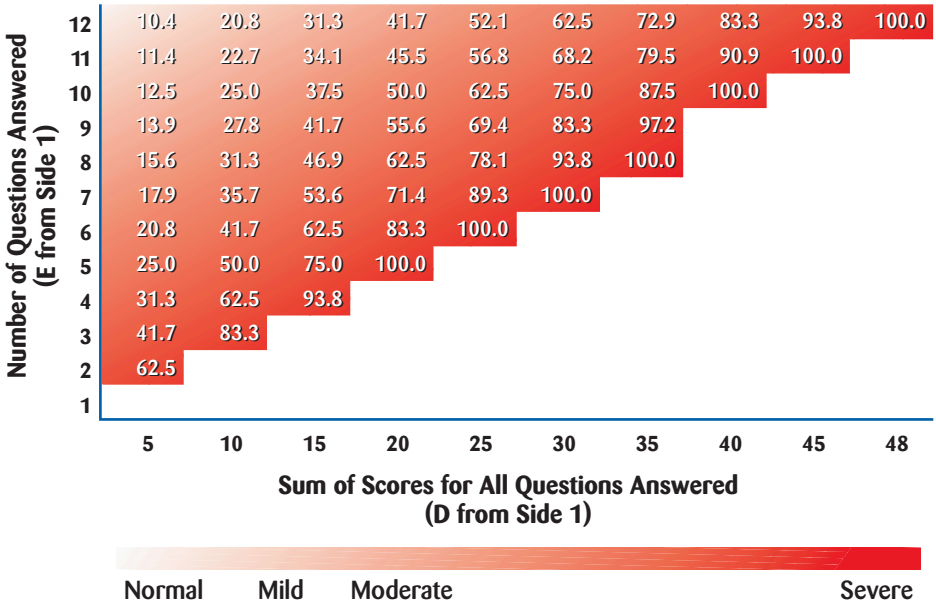
Please turn over the questionnaire to calculate the patient's final OSDI© score.

Evaluating the OSDI© Score[1]

The OSDI© is assessed on a scale of 0 to 100, with higher scores representing greater disability. The index demonstrates sensitivity and specificity in distinguishing between normal subjects and patients with dry eye disease. The OSDI© is a valid and reliable instrument for measuring dry eye disease severity (normal, mild to moderate, and severe) and effect on vision-related function.

Assessing Your Patient's Dry Eye Disease[1,2]

Use your answers D and E from Side 1 to compare the sum of scores for all questions answered (D) and the number of questions answered (E) with the chart below.*
Find where your patient's score would fall. Match the corresponding shade of red to the key below to determine whether your patient's score indicates normal, mild, moderate, or severe dry eye disease.



*Values to determine dry eye disease severity calculated using the OSDI© formula:

$$\text{OSDI©} = \frac{(\text{sum of scores}) \times 25}{(\#\text{ of questions answered})}$$

Patient's Name: _____ **Date:** _____

How long has the patient experienced dry eye? _____

Eye Care Professional's Comments: _____

Tear and place in patient's chart for follow-up care on next visit.

Reference: 1. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the Ocular Surface Disease Index. *Arch Ophthalmol.* 2000;118:615-621. **2.** Data on file, Allergan, Inc.

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