CLINICAL TRIAL PROTOCOL

OmegaD-2019-002

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:	07 October 2019
Amended Protocol V2.0:	28 October 2019
Amended Protocol V3.0:	18 December 2019
Amended Protocol V4.0:	05 May 2020

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-2019-002
Amended Protocol:	05 May 2020

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 MD

Signature

5/7/2020

Date

Medical Monitor
Charles Slonim, MD
Oculos Development Services, LLC
813-690-0255 (Mobile)
Email: chuck.slonim@oculoscr.com

Signature

Date

SPONSOR SIGNATURE

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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-2019-002
Amended Protocol:	05 May 2020

I have read the OmegaD-2019-002 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 Council for 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 Development Services, LLC	586-212-0237 (Mobile) Email: roselyn.judd@oculoscr.com
Medical Monitor	Charles Slonim, MD Oculos Development Services, LLC	813-690-0255 (Mobile) Email: chuck.slonim@oculoscr.com

1. SYNOPSIS

Name of Sponsor/Company: OmegaD LLC	
Name of Investigational Products: 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): Estimated date first subject enrolled: November 2019 Estimated date last subject completed: July 2020	**Phase of Development:** 3
Objectives: The primary objective of this study is to evaluate the safety and efficacy of once daily 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 =150 subjects): 4 softgels to be taken daily at bedtime. No other orally taken medications (including vitamins) should be taken within 2 hours of taking the study medication. If necessary to minimize any digestive upset, subjects may take 2 softgels twice daily (BID), provided that dosing of study medication is not within 2 hours of a meal or orally taken administration of other medications, including vitamins. Under these circumstances, the first dose should be taken between meals and the second dose should be taken at bedtime • Placebo softgels (N =150 subjects): 4 softgels to be taken daily at bedtime. No other orally taken medications (including vitamins) should be taken within 2 hours of taking the study medication. If necessary to minimize any digestive upset, subjects may take 2 softgels BID, provided that dosing of study medication is not within 2 hours of a meal or orally taken administration of other medications, including vitamins. Under these circumstances, the first dose should be taken between meals and the second dose should be taken at bedtime Comparisons of OmegaD softgels to placebo will be double-masked; OmegaD softgels and placebo will be identically 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 (Ocular Surface Disease Index [OSDI] questionnaire [to be completed by subjects], tear osmolarity testing, meibomian gland dysfunction grading, tear break-up time [TBUT], Schirmer's test [anesthetized]), 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 1) and the site will update concomitant medications, perform a urine pregnancy test (women of childbearing potential only), and conduct baseline examinations. Continuing eligibility for enrollment will require a negative pregnancy test result (if performed), 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 **Screening**, Schirmer's test score (anesthetized) at **Screening** must be ≥ 5 mm in **both eyes**, and OSDI score **at Screening** must be ≥ 20. 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 higher tear osmolarity score; if both eyes score equally on tear osmolarity, the eye with the lower TBUT 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 HS-Omega-3 Index score will be assessed via fingerstick blood sample and site personnel will dispense investigational product (IP) and a daily IP diary and assess AEs.

Subjects will take 4 softgels daily at bedtime. Daily reminders to take the medication will be provided, and subjects will document their compliance in terms of number of softgels taken in the IP diary on a daily basis.

Each subject will return to the site at Day 42 (± 7 days) along with all unused IP and the IP diary. The subject will complete an OSDI questionnaire, and site personnel will update concomitant medications, conduct a slit lamp examination, dispense new IP, assess AEs, and perform IP accountability and diary review.

Subjects will return to the site at Day 84 (± 7 days), along with all unused IP and the IP diary, for final safety and efficacy evaluations. The subject will complete an OSDI questionnaire and answer a question to establish their compliance with dosing of any vitamins (to be taken more than 2 hours before or after study medication) during the study. Site personnel will update concomitant medications, perform a urine pregnancy test (women of childbearing potential only), conduct all specified ophthalmic assessments, assess the HS-Omega-3 Index score via fingerstick blood sample, assess AEs, and perform IP accountability and diary review.

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

Subjects who have already completed their Day 84 Final Study Visit at the time of this Protocol Amendment (V4.0) will be contacted by the site to establish their compliance with dosing of any vitamins (to be taken more than 2 hours before or after study medication) during the study.

Number of Subjects (Planned):

Approximately 300 subjects are planned to be enrolled, with approximately 150 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. Noncompliance will be defined as a total of 28 missed softgels in a 6-week period. 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. At least moderate ocular surface disease as measured by an OSDI score ≥ 20 at Screening.
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. Schirmer's test score (anesthetized) ≥ 5 mm in both eyes at Screening.
7. TBUT ≤ 7 seconds in both eyes at Screening.

8. 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.

Exclusion Criteria:

1. Any previous reconstructive or cosmetic eyelid surgery that may, in the Investigator's opinion, affect the normal function of the lids (eg, blepharoplasty, ptosis repair, entropion/ectropion repair) that could affect study parameters/assessments.
2. Cataract extraction, with or without minimally invasive glaucoma surgery (eg, iStent®), within 90 days prior to Screening.
3. Any previous invasive glaucoma surgery (eg, trabeculectomy, shunts, valves) and/or corneal surgery (eg, penetrating keratoplasty, lamellar keratoplasty, Descemet's stripping endothelial keratoplasty [DSEK]).
4. Lid scrubs with over-the-counter (OTC) products (eg, OCuSOFT® lid scrub, SteriLid®, baby shampoo, etc.) and/or warm compresses within 14 days prior to Screening and throughout the study period.
5. Prescription and OTC ophthalmic mast cell stabilizers and antihistamines within 21 days prior to Screening and throughout the study period (systemic mast cell stabilizers are allowed, and systemic antihistamines are permitted with certain restrictions [see exclusion criterion #16]).
6. Chronic daily use (defined as > 7 consecutive days at the recommended dosing frequency) of systemic narcotics for any chronic pain syndrome (eg, fibromyalgia, rheumatoid arthritis, etc.) during the study period. Short-term, as-needed dosing of a systemic narcotic for ≤ 72 hours is allowed, but not at Screening or on the day of the study visit.
7. Allergy to fish oil or mineral oil (component of placebo softgels) or any component of the softgel material.
8. 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.
9. Active or anticipated seasonal and/or perennial allergic conjunctivitis or rhinitis.
10. 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 or inflammation of the eye and ocular surface scarring.
11. History or presence of abnormal nasolacrimal drainage.
12. Laser-assisted in situ keratomileusis (LASIK) or photorefractive keratectomy (PRK) performed within one year prior to Screening and throughout the study period.
13. Ophthalmic artificial tear drop use within 2 hours prior to any study visit. Any OTC artificial tear (preserved or unpreserved) should be continued at the same frequency and with no change in drop brand.
14. Contact lens wear within 12 hours prior to Screening or any study visit; subjects determined to have worn contact lenses within 12 hours must be rescheduled.
15. History of cauterization of the punctum or existing silicone punctal plug(s); history of silicone plug removal or collagen plug insertion or removal within 12 months prior to Screening and throughout the study period.
16. Started or changed the dose of systemic medications known to affect tear production (including immunomodulators, tricyclic antidepressants, diuretics, and corticosteroids) within 30 days prior to Screening and throughout the study period. However, one short (≤ 72 hour)

course of a systemic medication that affects tear production (including immunomodulators, tricyclic antidepressants, diuretics, and corticosteroids) or systemic antihistamines is allowed but not within 30 days of Screening or on the day before or the day of any other study visit. Any chronic use of systemic antihistamines within 30 days prior to Screening and throughout the study period is prohibited.

17. Use of any topical prescription ophthalmic medications (including cyclosporine [Restasis®, Cequa®] or topical lifitegrast [Xiidra®], steroids, nonsteroidal anti-inflammatory drugs [NSAIDs], anti-glaucoma medications, anti-microbials), topical macrolides, or oral nutraceuticals (fish, flax, black currant seed oils, etc.) within 21 days prior to Screening and throughout the study period.
18. Use of oral tetracyclines or oral macrolides within 21 days prior to Screening and throughout the study period; use of isotretinoin (Accutane®) within 90 days prior to Screening and throughout the study period.
19. 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 of any dosage is permitted.
20. Women of childbearing potential who are pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control. Acceptable methods include the use of at least one of the following: intrauterine device (IUD), hormonal (oral, injection, patch, implant, ring), barrier with spermicide (condom, diaphragm), or abstinence. An adult woman is considered to be of childbearing potential unless she is 1 year postmenopausal or post-surgical hysterectomy. All women of childbearing potential, including those post-tubal ligation, must have a negative urine pregnancy test result at Visit 1 (Screening), Visit 2 (Baseline), and Visit 4 (Day 84) examinations and must intend to not become pregnant during the study.
21. 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: 4 softgels to be taken daily at bedtime. No other orally taken medications (including vitamins) should be taken within 2 hours of taking the study medication. If necessary to minimize any digestive upset, subjects may take 2 softgels BID, provided that dosing of study medication is not within 2 hours of a meal or orally taken administration of other medications, including vitamins. Under these circumstances, the first dose should be taken between meals and the second dose should be taken at bedtime.

Reference Therapy, Dosage and Mode of Administration:

Placebo softgels: 4 softgels to be taken daily at bedtime. No other orally taken medications (including vitamins) should be taken within 2 hours of taking the study medication. If necessary to minimize any digestive upset, subjects may take 2 softgels BID, provided that dosing of study medication is not within 2 hours of a meal or orally taken administration of other medications, including vitamins. Under these circumstances, the first dose should be taken between meals and the second dose should be taken at bedtime.

Duration of Treatment:

84 days (12 weeks)

Study Procedures:

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

The site will obtain signed informed consent, demographics, medical/ocular/concomitant medication histories, perform a urine pregnancy test (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 (anesthetized) ≥ 5 mm in both eyes, OSDI score ≥ 20), review inclusion/exclusion criteria, and assess AEs. The qualifying osmolarity level and meibomian orifice size grade must be present in the same eye at the Screening Visit if only one eye qualifies.

Visit 2 (Day 1): Baseline Visit
The site will update concomitant medications, perform a urine pregnancy test (women of childbearing potential only), conduct baseline examinations including tear osmolarity testing, meibomian gland dysfunction grading, and slit lamp examination and then review inclusion/exclusion criteria.

Site personnel will then randomize eligible subjects, perform the HS-Omega-3 Index Test via fingerstick blood sample, dispense/document IP and a daily IP diary and provide instructions for use, and assess AEs.

Subjects should be reminded to bring all IP and the IP diary to the clinical site at Visit 3 (Day 42). If the IP 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 IP and the IP diary, update concomitant medications, conduct OSDI questionnaire (overseeing subject completion) and slit lamp examination, dispense IP, assess AEs, and conduct IP accountability and diary review.

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

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

The site will collect unused IP and the daily IP diary, update concomitant medications, perform a urine pregnancy test (women of childbearing potential only), conduct final ophthalmic examinations (OSDI questionnaire [overseeing subject completion], tear osmolarity, meibomian gland dysfunction grading, slit lamp examination, TBUT, and Schirmer's test [anesthetized]), HS-Omega-3 Index Test via fingerstick blood sample, assess AEs, record subject's answer to yes/no question, "During the study, did you regularly take any vitamins within 2 hours of taking your study medication?", and conduct final IP accountability and diary review.

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

If a subject is discontinued from IP 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.

Subjects who have already completed their Day 84 Final Study Visit at the time of this Protocol Amendment (V4.0) will be contacted by the site to establish their compliance with dosing of any vitamins (to be taken more than 2 hours before or after study medication) during the study.

Efficacy Assessments:

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

Symptoms: OSDI questionnaire

Pharmacokinetics: HS-Omega-3 Index Test

Safety Assessments:

Safety assessments will include slit lamp examination and collection of AEs.

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 tear osmolarity in the study eye at Visit 4 (Day 84)
- Mean change from Screening 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 2 endpoints will be tested sequentially in the order described above. If the null hypothesis for the tear osmolarity endpoint can be rejected at $P \leq 0.05$, OSDI endpoint will be tested at $P \leq 0.05$.

Secondary Efficacy Endpoints:

- Mean change from baseline in TBUT 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)

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)

Safety Endpoint:

- Incidence of AEs

Statistical Methods:

Analysis Populations:

- 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 IP.

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

Statistical Analyses:

Analysis of TBUT, meibomian gland dysfunction, tear osmolarity, and Schirmer's test scores (anesthetized) will utilize the designated study eye (worse eye at Baseline as defined by higher tear osmolarity score; if both eyes score equally on tear osmolarity, the eye with the lower TBUT 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 an analysis of covariance using treatment, center, and baseline values as covariates. 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 (SD) 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.

A comprehensive Statistical Analysis Plan will be completed prior to completion of data collection.

Sample Size:

A total of 150 subjects per groups is planned. Power considerations for each endpoint are described below.

Tear osmolarity: In the initial placebo-controlled trial of OmegaD, the change from baseline in tear osmolarity was -13 (SD=22). Two natural history studies in dry eye suggest that changes in tear osmolarity can become less or more severe. The former trial reported a mean decrease of 6 mOsm/L, whereas the latter trial reported a mean increase of approximately 20 mOsm/L. A sample size of 150 in each group will have 95% power to detect a difference in changes in tear osmolarity means of 8 mOsm/L (-13 mOsm/L for OmegaD and -5 mOsm/L for placebo), assuming that the common SD of change is 19, using a two-group t-test with a 0.05 two-sided significance level.

OSDI: As OSDI is a subjective subject-reported outcome, some degree of improvement is expected from trial participation. In the initial placebo-controlled trial of OmegaD, the change from baseline in OSDI was -13 points (SD=20). In natural history studies, changes from baseline in OSDI were -7 and -10 points (SD≈16). A sample size of 150 in each group will have approximately 95% power to detect a difference in change in mean OSDI scores of 7 points (-13-point change for OmegaD and -6-point change for placebo), assuming that the common SD of change in OSDI is 17.0, using a two-group t-test with a 0.05 two-sided significance level.

TBUT: In the initial placebo-controlled trial of OmegaD, the change from baseline in TBUT was 1.4 seconds with a SD of 2.8. In natural history studies, changes from baseline in TBUT were 0.4 and 0 seconds (SD≈1.9). A sample size of 150 in each group will have approximately 95% power to detect a difference in changes in mean TBUT of 1 second (1.4-second change for OmegaD and 0.4-second change for placebo), assuming that the common SD of change in TBUT is 2.4, using a two-group t-test with a 0.05 two-sided significance level.

Table 2: Schedule of Procedures

Procedures	Visit 1 Screening	Visit 2 Baseline	Visit 3 Safety and Accountability	Visit 4 Final Study/Early Discontinuation
Days	**-7 to -1**	**1**	**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		X
Ocular Surface Disease Index Questionnaire	X		X	X
Tear osmolarity [b]	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	X
Tear break-up time	X			X
Schirmer's test (anesthetized)	X			X
Review inclusion/exclusion criteria	X	X		
Randomization		X		
HS-Omega-3 Index Test (fingerstick)		X		X
IP distribution		X	X	
IP diary distribution		X		
Unused IP and diary collection			X	X
IP accountability [c]		X	X	X
IP diary review			X	X
Vitamin dosing compliance				X
AE assessment [d]	X	X	X	X

AE, adverse event; IP, investigational product.
[a] Women of childbearing potential only.
[b] Investigators can use up to 3 attempts to obtain a valid reading (with a 10-minute waiting period between attempts). No other diagnostic examinations can be performed until a valid reading is obtained.
[c] Clinical site personnel will document all dispensed or returned IP as applicable at Baseline Visit and at Days 42 and 84 Visits.
[d] Collection of AEs extends from signing of informed consent until the last study visit.

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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
DSEK	Descemet's stripping endothelial keratoplasty
eCRF	electronic case report form
eDC	electronic data capture
EPA	eicosapentaenoic acid
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Council for Harmonisation
IL-1	interleukin 1
IL-1β	interleukin 1 beta
IRB	Institutional Review Board
IP	investigational product
ITT	intent-to-treat
IUD	intrauterine device
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LASIK	laser-assisted in situ keratomileusis
LTB_4	leukotriene B_4
MMP-3	matrix metalloproteinase 3
MMP-9	matrix metalloproteinase 9
NSAID	nonsteroidal anti-inflammatory drug
OSDI	Ocular Surface Disease Index
OTC	over-the-counter
PGE_1	prostaglandin E_1
PGE_2	prostaglandin E_2
PGE_3	prostaglandin E_3
PP	per protocol
PRK	photorefractive keratectomy

Abbreviation	Explanation
PRN	Physician Recommended Nutriceuticals
SAE	serious adverse event
SD	standard deviation
SOP	standard operating procedure
TBUT	tear break-up time
TNF-α	tumor necrosis factor alpha
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 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 metalloproteinases 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 (LTB_4) and increases EPA and DHA synthesis of anti-inflammatory (prostaglandin E_1 [PGE_1]) and weakly inflammatory (prostaglandin E_3 [PGE_3]) 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 interleukin 1 beta (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 (anesthetized) 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 LLC 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 softgels 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, with 4 subjects in each treatment group reporting adverse events (AEs; Omega Benefits 7.5%, placebo 8.0%). All the AEs reported for the Omega Benefits group were mild and 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, having identical amounts of EPA and DHA.

Omega D LLC conducted a multicenter, placebo-controlled, double-masked, randomized clinical trial in subjects with dry eye disease. One hundred and eighty (180) subjects were randomized (OmegaD, n=89; placebo, n=91), with 173 subjects completing the study (OmegaD, n=85; placebo, n=88). After 84 days of treatment, the results of the study showed that although treatment with OmegaD softgels achieved an approximate 30% change from baseline in both TBUT and OSDI, there was no significant difference between OmegaD and placebo for either of these parameters [TBUT ($P = 0.54$), OSDI ($P = 0.52$)]. The lack of significant difference was considered primarily due to the unexpectedly high placebo response rates. The Omega-3 Index score was significantly increased in the OmegaD group compared with placebo ($P < 0.0001$), showing that omega-3 fatty acids in the RBC membranes had increased over the duration of the study in those subjects receiving OmegaD softgels. The safety profile of OmegaD softgels in this study was similar to the previous PRN study. There were no serious adverse events (SAEs) in either group and a total of 56 AEs were reported in 39 subjects (OmegaD, 31 AEs in 23 subjects [25.8%]; placebo, 25 AEs in 16 subjects [17.6%]). Of these, only diarrhea (n=4 subjects), abdominal discomfort (n=2), abdominal pain (n=2), and upper respiratory tract infection (n=4) were reported in more than one subject in either group (> 2%). All AEs were either mild or moderate in intensity. Four subjects in the OmegaD group and 1 subject in the placebo group withdrew from the study due to AEs and 1 further subject in the OmegaD group had study drug interruption.

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 only supported by general health claims. While these omega-3 supplements were subject to Food and Drug Administration (FDA) regulation as food supplements, the clinical data to support activity in dry eye disease may not have been reviewed by the FDA. 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-2019-002, 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 (Epitropoulos,

2016). This dose also 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 Practice Statement

This study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and in compliance with International Council for 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 an OSDI score ≥ 20 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 Screening, and Schirmer's test score (anesthetized) in both eyes must be ≥ 5 mm at Screening. 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 once daily 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 =150 subjects): 4 softgels to be taken daily at bedtime. No other orally taken medications (including vitamins) should be taken within 2 hours of taking the study medication. If necessary to minimize any digestive upset, subjects may take 2 softgels twice daily (BID), provided that dosing of study medication is not within 2 hours of a meal or orally taken administration of other medications, including vitamins. Under these circumstances, the first dose should be taken between meals and the second dose should be taken at bedtime.
- Placebo softgels (N =150 subjects): 4 softgels to be taken daily at bedtime. No other orally taken medications (including vitamins) should be taken within 2 hours of taking the study medication. If necessary to minimize any digestive upset, subjects may take 2 softgels BID, provided that dosing of study medication is not within 2 hours of a meal or orally taken administration of other medications, including vitamins. Under these circumstances, the first dose should be taken between meals and the second dose should be taken at bedtime.

Comparisons of OmegaD softgels to placebo will be double-masked; OmegaD softgels and placebo will be identically 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 [anesthetized], and OSDI), 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 1) and the site will update concomitant medications, perform a urine pregnancy test (women of childbearing potential only), and conduct baseline examinations. Continuing eligibility for enrollment will require a negative pregnancy test result (if performed), tear osmolarity $\geq$ 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 $\leq$ 7 seconds in **both eyes** at **Screening**, Schirmer's test score (anesthetized) must be $\geq$ 5 mm in **both eyes** at **Screening**, and OSDI score must be $\geq$ 20 **at Screening**. 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 higher tear osmolarity score; if both eyes score equally on tear osmolarity, the eye with the lower TBUT 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 HS-Omega-3 Index score will be assessed via fingerstick blood sample and site personnel will dispense investigational product (IP) and a daily IP diary and assess AEs.

Subjects will take 4 softgels daily at bedtime. Daily reminders to take the medication will be provided, and subjects will document their compliance in terms of number of softgels taken in the IP diary on a daily basis.

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

Subjects will return to the site at Day 84 (± 7 days), along with all unused IP and the IP diary, for final safety and efficacy evaluations. The subject will complete an OSDI questionnaire and answer a question to establish their compliance with dosing of any vitamins (to be taken more than 2 hours before or after study medication) during the study. Site personnel will update concomitant medications, perform a urine pregnancy test (women of childbearing potential only), conduct all specified ophthalmic assessments, assess the HS-Omega-3 Index score via fingerstick blood sample, assess AEs, and perform IP accountability and diary review.

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

Note: For those subjects unable or unwilling to attend a scheduled study visit in-person during the COVID-19 pandemic, a “phone visit” will be conducted to allow collection of as many data points as possible, including changes to concomitant medication, AE inquiries, OSDI questionnaire responses, and response to the vitamin dosing compliance question. Subjects who are willing and able will be asked to come into the office for the Final Study Visit, during which all scheduled assessments will be conducted. Additional subject enrollment will occur to compensate for those subjects unable or unwilling to attend their Final Study Visit, to ensure a minimum of 300 evaluable subjects.

6.2. Number of Subjects

Approximately 300 subjects are planned to be enrolled, with approximately 150 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. Noncompliance will be defined as a total of 28 missed softgels in a 6-week period. 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.

Note: Due to the COVID-19 pandemic, some subjects may be unable or unwilling to attend their Final Study Visit (see Section 6.1). Additional subject enrollment will occur to compensate for these subjects, to ensure a minimum of 300 evaluable subjects.

6.3. Criteria for Study Termination

The study may be terminated at any time by OmegaD LLC, following appropriate notification of FDA, the Institutional Review Board (IRB), sites/investigators, and subjects.

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. At least moderate ocular surface disease as measured by an OSDI score ≥ 20 at Screening.
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. Schirmer's test score (anesthetized) ≥ 5 mm in both eyes at Screening.
7. TBUT ≤ 7 seconds in both eyes at Screening.
8. 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.

7.2. Subject Exclusion Criteria

1. Any previous reconstructive or cosmetic eyelid surgery that may, in the Investigator's opinion, affect the normal function of the lids (eg, blepharoplasty, ptosis repair, entropion/ectropion repair) that could affect study parameters/assessments.
2. Cataract extraction, with or without minimally invasive glaucoma surgery (eg, iStent®), within 90 days prior to Screening.
3. Any previous invasive glaucoma surgery (eg, trabeculectomy, shunts, valves) and/or corneal surgery (eg, penetrating keratoplasty, lamellar keratoplasty, Descemet's stripping endothelial keratoplasty [DSEK]).
4. Lid scrubs with over-the-counter (OTC) products (eg, OCuSOFT® lid scrub, SteriLid®, baby shampoo, etc.) and/or warm compresses within 14 days prior to Screening and throughout the study period.
5. Prescription and OTC ophthalmic mast cell stabilizers and antihistamines within 21 days prior to Screening and throughout the study period (systemic mast cell stabilizers are allowed, and systemic antihistamines are permitted with certain restrictions [see exclusion criterion #16]).
6. Chronic daily use (defined as > 7 consecutive days at the recommended dosing frequency) of systemic narcotics for any chronic pain syndrome (eg, fibromyalgia, rheumatoid arthritis, etc.) during the study period. Short-term, as-needed dosing of a

systemic narcotic for ≤ 72 hours is allowed, but not at Screening or on the day of the study visit.

7. Allergy to fish oil or mineral oil (component of placebo softgels) or any component of the softgel material.
8. 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.
9. Active or anticipated seasonal and/or perennial allergic conjunctivitis or rhinitis.
10. 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 or inflammation of the eye and ocular surface scarring.
11. History or presence of abnormal nasolacrimal drainage.
12. Laser-assisted in situ keratomileusis (LASIK) or photorefractive keratectomy (PRK) performed within one year prior to Screening and throughout the study period.
13. Ophthalmic artificial tear drop use within 2 hours prior to any study visit. Any OTC artificial tear (preserved or unpreserved) should be continued at the same frequency and with no change in drop brand.
14. Contact lens wear within 12 hours prior to Screening or any study visit; subjects determined to have worn contact lenses within 12 hours must be rescheduled.
15. History of cauterization of the punctum or existing silicone punctal plug(s); history of silicone plug removal or collagen plug insertion or removal within 12 months prior to Screening and throughout the study period.
16. Started or changed the dose of systemic medications known to affect tear production (including immunomodulators, tricyclic antidepressants, diuretics, and corticosteroids) within 30 days prior to Screening and throughout the study period. However, one short (≤ 72 hour) course of a systemic medications that affect tear production (including immunomodulators, tricyclic antidepressants, diuretics, and corticosteroids) or systemic antihistamines is allowed but not within 30 days of Screening or on the day before or the day of any other study visit. Any chronic use of systemic antihistamines within 30 days prior to Screening and throughout the study period is prohibited.
17. Use of any topical prescription ophthalmic medications (including cyclosporine [Restasis®, Cequa®] or topical lifitegrast [Xiidra®], steroids, nonsteroidal anti-inflammatory drugs [NSAIDs], anti-glaucoma medications, anti-microbials), topical macrolides, or oral nutraceuticals (fish, flax, black currant seed oils, etc.) within 21 days prior to Screening and throughout the study period.
18. Use of oral tetracyclines or oral macrolides within 21 days prior to Screening and throughout the study period; use of isotretinoin (Accutane®) within 90 days prior to Screening and throughout the study period.
19. 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 of any dosage is permitted.

20. Women of childbearing potential who are pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control. Acceptable methods include the use of at least one of the following: intrauterine device (IUD), hormonal (oral, injection, patch, implant, ring), barrier with spermicide (condom, diaphragm), or abstinence. An adult woman is considered to be of childbearing potential unless she is 1 year postmenopausal or post-surgical hysterectomy. All women of childbearing potential, including those post-tubal ligation, must have a negative urine pregnancy test result at Visit 1 (Screening), Visit 2 (Baseline), and Visit 4 (Day 84) examinations and must intend to not become pregnant during the study.
21. 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 subject is lost to follow-up at any point during the study period, attempts to contact the subject must be documented.

If a subject is discontinued from IP before Visit 4 (Day 84) 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 (Day 84) procedures at the visit the subject is discontinued.

8. TREATMENT OF SUBJECTS

8.1. Description of Investigational Product

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 mineral oil in a softgel shell composed of gelatin, glycerin, and colorant.

8.2. Randomization and Masking

An Interactive Web Response System (IWRS)/Interactive Voice Response System (IVRS) will assign a kit number to subjects who qualify for randomization. IP 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), they will be randomly assigned to IP at the Baseline Visit. Clinical sites will utilize the IWRS to assign kits to subjects. The IP kit randomization number will be recorded in the subject's eCRF.

A supply of randomized IP 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 IP 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 IP 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 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 10.4) should be completed.

4. The Investigator should contact Oculos Development Services, LLC (Oculos), the contract research organization, at OmegaD-safety@oculoscr.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 IP 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. Permitted concomitant orally administered medications (including vitamins) should not be taken within 2 hours of study medication dosing.

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.

The initiation or dose modification of systemic medications known to affect tear production is prohibited within 30 days prior to Screening and throughout the study period, but short-term, as-needed dosing of a systemic medication is allowed with certain restrictions. One short ($\leq$ 72 hour) course of a systemic medication that affects tear production (including immunomodulators, tricyclic antidepressants, diuretics, and corticosteroids) or systemic antihistamines is allowed but not within 30 days of Screening or on the day before or the day of any other study visit. Any chronic use of systemic antihistamines within 30 days prior to Screening and throughout the study period is prohibited.

Prescription and OTC ophthalmic mast cell stabilizers and antihistamines are prohibited within 21 days prior to Screening and throughout the study period (systemic mast cell stabilizers are allowed, and systemic antihistamines are permitted with the restrictions outlined above).

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 of any dosage 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 (ie, Restasis and Cequa)
- Lifitegrast (Xiidra)
- Steroids
- NSAIDs
- Antiglaucoma medications
- Anti-microbials
- Macrolides

Additionally, oral nutraceuticals (fish, flax, black currant seed oils, etc.), oral tetracyclines, and oral macrolides are prohibited within 21 days prior to Screening and throughout the study period. Isotretinoin (Accutane®) is also prohibited within 90 days prior to Screening and throughout the study period.

Contact lens and ophthalmic drop use (eg, 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
- History of cauterization of the punctum or existing silicone punctal plug(s); history of silicone plug removal or collagen plug insertion or removal within 12 months prior to Screening and throughout the study period.

8.4. Treatment Compliance

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

8.5. Discontinuation of Investigational Product

Subjects may be discontinued from IP for either 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 IP 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. Investigational Product Materials and Management

8.6.1. Packaging and Labeling

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

8.6.2. Storage

Store at 15° to 25°C (59° to 77°F). Do not freeze. Keep out of reach of children.

8.6.3. Administration

Following randomization, site personnel will dispense IP and instruct the subject on administration procedures. The daily dose is 4 softgels to be taken at bedtime. No other orally taken medications (including vitamins) should be taken within 2 hours of taking the study medication. If necessary to minimize any digestive upset, subjects may take 2 softgels BID, provided that dosing of study medication is not within 2 hours of a meal or orally taken administration of other medications, including vitamins. Under these circumstances, the first dose should be taken between meals and the second dose should be taken at bedtime.

8.6.4. Dispensing

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

8.6.4.1. Interim COVID-19 Pandemic Dispensing Procedures

During the COVID-19 pandemic, sites may dispense to subjects as much IP as necessary (including the fifth/reserve bottle) to allow the subjects to continue to take their study medication until they are able to return for a final visit. In addition, subjects will be dispensed an extra diary with blank study dosing days to be completed if they take IP for more days than originally intended in order to allow continued dosing through to the Final Study Visit.

For those subjects entering the study prior to the pandemic who have not received the remainder of the IP, they can receive the IP and an extra diary with blank study dosing days in any of the following ways:

- In-person during an already scheduled study visit
- In-person pick-up by the subject, or designee, if the subject is unwilling or unable to keep a previously scheduled study visit
- IP and extra diary delivered to the subject by study staff
- IP and extra diary shipped overnight to the subject by study staff

Regardless of the method utilized, study drug accountability records will be maintained, and delivery methods will be documented by the site.

8.6.5. Investigational Product Accountability

The Investigator or designee (eg, study coordinator or pharmacist) will maintain a full accountability record for the IP and will be responsible for recording the receipt, dispensing, and returning all supplies of the IP using the inventories supplied by Oculos. Clinical site personnel will document all dispensed and returned IPs at Baseline (Day 1), Day 42, and Day 84, and IP 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 IP and the IP 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 will note any discrepancies.

All IP 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 IRB-approved version of the informed consent form (ICF). 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 (eg, 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.

9.1.4. Urine Pregnancy Test

A urine pregnancy test will be performed at Screening, at Baseline, and at the Final Study 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 Visit 4), and the subject must refrain from administering any tear supplements within 2 hours prior to the tear osmolarity test. The testing must follow the protocol specified in the Study Procedures Manual. If an invalid reading is obtained (< 275 or > 400 mOsm/L), the investigator should wait at least 10 minutes to retest tear osmolarity. No other diagnostic examinations can be administered until a valid tear osmolarity reading is obtained. Investigators can use up to 3 attempts to obtain a valid reading (with a 10-minute waiting period between attempts).

9.2.1.2. Meibomian Gland Dysfunction Grading

Using a slit lamp at a magnification of 10X 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 subject 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 Altafluor is added to the eye and the subject may blink for 2 seconds 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. If there is break-up in the tear film immediately after the blink, this shall be registered as 0. 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 (see Study Procedures Manual).

9.2.1.4. Schirmer's Test (Anesthetized)

An anesthetized Schirmer's test will be performed to ensure 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). Schirmer strips will be placed in both eyes on the lower eyelid margins at the same time. The eyes are closed for 5 minutes. The strips are then removed and the amount of moisture on each strip in millimeters (mm) is measured and recorded in the eCRF (see Study Procedures Manual).

9.2.2. Symptoms

A laminated copy of the OSDI questionnaire (Appendix A) will be provided to the subject, who will be asked to point to 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. HS-Omega-3 Index Test

The HS-Omega-3 Index Test measures the concentration of 2 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 2 of blood on a collection card. Each card is identified and packaged to be submitted to OmegaQuant (Sioux Falls, SD) for analysis.

9.5. Other Assessment

9.5.1. Vitamin Dosing Compliance Question

At the Final Study Visit, subjects will be asked the yes/no question, "During the study, did you regularly take any vitamins within 2 hours of taking your study medication?" Subjects who have already completed their Day 84 Final Study Visit at the time of this Protocol Amendment (V4.0) will be contacted by the site to establish their compliance with dosing of any vitamins (to be taken more than 2 hours before or after study medication) during the study.

9.6. Adverse and Serious Adverse Events

9.6.1. Definition of Adverse Events

9.6.1.1. Adverse Event

An AE is any untoward medical occurrence in a clinical study subject administered an IP (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 IP, whether or not related to the IP. IP 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.

9.6.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening or sight-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 (ie, no other change in the condition is expected) or resolution of the event.

9.7. Relationship to Investigational Product

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

Not suspected: The temporal relationship of the event to the IP 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 IP 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 IP and the occurrence of the AE, then the AE should be considered "suspected."

If the relationship between the AE/SAE and the IP is determined by the Sponsor or designee to be "suspected," the event will be considered to be related to the IP for the purposes of expedited regulatory reporting (see Section 9.9).

9.8. Recording Adverse Events

AEs 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 IP 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 ICF 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 IP will be summarized separately from AEs that occur from the first dose of double-masked treatment on Day 1 to the Day 84 Visit. Following Visit 4 (Day 84), all AEs "suspected" to be related to the IP should be followed until resolution.

Medical conditions/diseases occurring before the first dose of IP during Visit 2 (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
- Resolution date
- Severity grade (mild, moderate, severe)
- Relationship to IP (not suspected, suspected)

- Action taken (none, IP temporarily interrupted, IP 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 9.6.1.2. 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 IP 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.

9.9. Reporting Adverse Events

All SAEs (suspected and not suspected) will be recorded from signing of informed consent until the Final Study Visit (Visit 4/Day 84), following the end of treatment exposure. Any SAEs "suspected" to be related to the IP 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@oculoscr.com. The Investigator must assess the SAE relationship and complete the SAE form. Oculos may request additional information. Follow-up information (eg, discharge summary) will be retained in the subject's chart and a copy will be emailed to OmegaD-safety@ oculoscr.com.

In addition, all SAEs should be recorded on the AE 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 or unexpected (based on the available information in the Investigator's Brochure).

Any death occurring during the study or 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 IP, 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 (Table 2). 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.

Note: For those subjects unable or unwilling to attend a scheduled study visit in-person during the COVID-19 pandemic, a "phone visit" will be conducted to allow collection of as many data points as possible, including changes to concomitant medication, AE inquiries, OSDI questionnaire responses, and response to the vitamin dosing compliance question. Subjects who are willing and able will be asked to come into the office for the Final Study Visit, during which all scheduled assessments will be conducted. Additional subject enrollment will occur to compensate for those subjects unable or unwilling to attend their Final Study Visit, to ensure a minimum of 300 evaluable subjects.

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 will participate in screening procedures to establish eligibility for the study. Procedures performed at Screening will include the following:

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

Only subjects with a score on the OSDI ≥ 20, tear osmolarity ≥ 312 mOsm/L and meibomian gland dysfunction grade **1 or 2** on the meibomian orifice size scale in at least one eye, TBUT ≤ 7 seconds in both eyes and Schirmer's test score (anesthetized) ≥ 5 mm in both eyes will be scheduled to return to the clinical site for Visit 2 (Day 1). 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 1)/Baseline

At Visit 2 (Day 1)/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 IP. Procedures performed at Baseline include:

- Concomitant medication review
- Urine pregnancy test (women of childbearing potential only)
- Tear osmolarity test
- Meibomian gland dysfunction grading
- Slit lamp examination
- 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 **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 **Screening** (TBUT is not conducted at Baseline)
  - Schirmer's test score (anesthetized) at **Screening** must be ≥ 5 mm in **both eyes** (Schirmer's test is not conducted at Baseline)
  - OSDI ≥ 20 points at **Screening**
- Randomization
- HS-Omega-3 Index Test (fingerstick blood sample)
- Dispense and document dispensing of IP and provide instructions for administration
- Dispense IP 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 IP and the IP diary to Visit 3 (Day 42). If the IP 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:

- Concomitant medication review
- OSDI

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

10.4. Visit 4 (Day 84)/Final Study/Early Discontinuation 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 IP and the IP diary to Visit 4 (Day 84). If the IP and diary are not brought to the site, the visit must be rescheduled. Due to the COVID-19 pandemic precautions, the Final Study Visit may be extended until the subject can safely attend the visit.

At Visit 4 (Day 84), the Final Study Visit, subjects will participate in final efficacy and safety evaluations. Procedures/assessments performed at Day 84 will include the following, regardless of whether the subject had participated in a "phone visit" during the COVID-19 pandemic:

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

11. STATISTICS

A comprehensive Statistical Analysis Plan will be completed prior to completion of data collection.

11.1. General Considerations

This is a randomized, multicenter, double-masked, placebo-controlled study to evaluate the safety and efficacy of once daily 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 =150 subjects); 4 softgels at bedtime
- Placebo softgels (N = 150 subjects); 4 softgels at bedtime

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 11.4.

The study eye will be the worse of qualifying eyes at Baseline as defined by the higher tear osmolarity; if both eyes score equally on tear osmolarity, the eye with the lower TBUT 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

A total of 150 subjects per group is planned. Power considerations for each endpoint are described below.

Tear osmolarity: In the initial placebo-controlled trial of OmegaD, the change from baseline in tear osmolarity was -13 (standard deviation [SD]=22). Two dry eye natural history studies (Smith, data on file and Sullivan, 2012) suggest that changes in tear osmolarity can become less or more severe. The former trial reported a mean decrease of 6 mOsm/L, whereas the latter reported a mean increase of approximately 20 mOsm/L. A sample size of 150 in each group will have 95% power to detect a difference in change in tear osmolarity means of 8 mOsm/L (-13 mOsm/L for OmegaD and -5 mOsm/L for placebo), assuming that the common SD of change is 19, using a two-group t-test with a 0.05 two-sided significance level.

OSDI: As OSDI is a subjective subject-reported outcome, some degree of improvement is expected from trial participation. In the initial placebo-controlled trial of OmegaD, the change from baseline in OSDI was -13 points (SD=20). In the natural history studies described above, changes from baseline in OSDI were -7 and -10 points (SD≈16). A sample size of 150 in each

group will have approximately 95% power to detect a difference in change in mean OSDI scores of 7 points (-13-point change for OmegaD and -6-point change for placebo), assuming that the common SD of change in OSDI is 17.0, using a two-group t-test with a 0.05 two-sided significance level.

TBUT: In the initial placebo-controlled trial of OmegaD, the change from baseline in TBUT was 1.4 seconds (SD=2.8). In the natural history studies described above, changes from baseline in TBUT were 0.4 and 0 seconds (SD≈1.9). A sample size of 150 in each group will have approximately 95% power to detect a difference in change in mean TBUT of 1 second (1.4-second change for OmegaD and 0.4-second change for placebo), assuming that the common SD of change in TBUT is 2.4, using a two-group t-test with a 0.05 two-sided significance level.

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 (Day 84) 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 IP. 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 (anesthetized) 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 an analysis of covariance using treatment, center, and baseline values as covariates. 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, SD 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.

- Mean change from baseline in tear osmolarity in the study eye at Visit 4 (Day 84)
- Mean change from Screening 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 2 endpoints will be tested sequentially in the order described above. If the null hypothesis for the tear osmolarity endpoint can be rejected at $P \leq 0.05$, OSDI endpoint will be tested at $P \leq 0.05$.

11.6.2. Secondary Efficacy Endpoints

- Mean change from baseline in TBUT 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)

11.6.3. 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)

11.7. 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 ensure compliance with GCP and all applicable regulatory requirements, the 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 ICFs, medical records, and regulatory documentation; an assessment of study conduct and protocol compliance; and a review of the IP 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.

12.1. Interim COVID-19 Pandemic Monitoring Procedures

- All onsite monitoring visits will be suspended until further notice.
- ICFs will be uploaded to DataTrak by the sites for remote review by Oculos.

13. ADMINISTRATIVE CONSIDERATIONS

13.1. Institutional Review Board

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 ICF 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 ICF 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 ICFs 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 ICF. The original ICF is to be retained by the study site, and a copy is to be given to the subject.

13.3.1. Version 3.0 Reconsent

All newly consented subjects will follow the usual, in-person consenting procedures. Due to the nature of Version 3.0 involving a dosing change, it is important that the change is implemented as soon as possible for currently enrolled subjects. All efforts will be made to have the subject come to the site and complete the reconsenting procedures in person. If in-person consent cannot be obtained, remote consent may be completed as outlined below:

- Designated site staff will contact the subject to explain that the site will be sending an updated ICF and dosing instructions.
- Once received, the subject will contact the site to set up a time to discuss the dosing changes with the Principal Investigator or Study Coordinator and will be given ample time and opportunity to ask questions.
- If the subject agrees to the new dosing schedule, the subject will sign the ICF and send it back to the site.
- Upon receipt at the site, the person who performed consenting procedures via phone will sign and date with the current date at the time of signature.
- A copy of the fully signed ICF will be mailed to the subject or given to them at their next scheduled visit and the original will be retained onsite.
- The consenting process should be documented in the subject's file and include a notation indicating that the subject's consent was obtained remotely in order to explain the discrepancy between the participant's date of documents and staff's date of documents.

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 ICFs, IP diaries, IP 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 (closeout) visit to the site. The objectives of this visit are to ascertain that all regulatory records and reports are complete, verify that the IP 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.

13.5.1. Interim COVID-19 Pandemic Monitoring Procedures

- All onsite monitoring visits will be suspended until further notice.
- ICFs will be uploaded to DataTrak by the sites for remote review by Oculos.

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 (eg, 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 ICFs, medical records, and regulatory documentation; an assessment of study conduct and protocol compliance; and a review of the IP 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 Development Services, LLC, 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

Bhargava R, Kumar P, Kumar M, Mehra N, Mishra A. A randomized controlled trial of omega-3 fatty acids in dry eye syndrome. *Int J Ophthalmol*. 2013;6(6):811-6.

Caughey GE, Mantzioris E, Gibson RA, Cleland LG, James MJ. The effect on human tumor necrosis factor alpha and interleukin 1 beta production of diets enriched in n-3 fatty acids from vegetable oil or fish oil. *Am J Clin Nutr*. 1996;63(1):116-22.

Donnenfeld ED, Holland EJ, Bucci FA Jr, et al. Effect of oral re-esterified omega-3 nutritional supplementation on dry-eye disease: double-masked randomized placebo-controlled study. In ASCRS ASOA Symposium and Congress 2015 Apr 17-21 San Diego, CA.

Epitropoulos AT, Donnenfeld E, Shah ZA, et al. Effect of oral re-esterified omega-3 nutritional supplementation on dry eyes. *Cornea*. 2016;35(9):1185-91.

Investigator's Brochure. OmegaD softgels for the treatment of dry eye disease. 28 August 2019.

James MJ, Gibson RA, Cleland LG. Dietary polyunsaturated fatty acids and inflammatory mediator production. *Am J Clin Nutr*. 2000;71(1 Suppl):343S-8S.

Kangari H, Eftekhari MH, Sardari S, Hashemi H, Salamzadeh J, Ghassemi-Broumand M, et al. Short-term consumption of oral omega-3 and dry eye syndrome. *Ophthalmology*. 2013;120(11):2191-6.

Kawakita T, Kawabata F, Tsuji T, Kawashima M, Shimmura S, Tsubota K. Effects of dietary supplementation with fish oil on dry eye syndrome subjects: randomized controlled trial. *Biomed Res*. 2013;34(5):215-20.

Kohli P, Levy BD. Resolvins and protectins: mediating solutions to inflammation. *Br J Pharmacol*. 2009;158(4):960-71.

Macsai MS. The role of omega-3 dietary supplementation in blepharitis and meibomian gland dysfunction (an AOS thesis). *Trans Am Ophthalmol Soc*. 2008;106:336-56.

Oleñik A, Jiménez-Alfaro I, Alejandre-Alba N, Mahillo-Fernández I. A randomized, double-masked study to evaluate the effect of omega-3 fatty acids supplementation in meibomian gland dysfunction. *Clin Interv Aging*. 2013;8:1133-8.

Pflugfelder SC. Antiinflammatory therapy for dry eye. *Am J Ophthalmol*. 2004;137(2):337-42.

Schaumberg DA, Sullivan DA, Buring JE, Dana MR. Prevalence of dry eye syndrome among US women. *Am J Ophthalmol*. 2003;136(2):318-26.

Schaumberg DA, Dana R, Buring JE, Sullivan DA. Prevalence of dry eye disease among US men: estimates from the Physicians' Health Studies. *Arch Ophthalmol*. 2009;127(6):763-8.

Data on file. Smith G. A longitudinal natural history study of the signs and symptoms of dry eye disease. 2017.

Sullivan BD, Crews LA, Sönmez B, et al. Clinical utility of objective tests for dry eye disease: variability over time and implications for clinical trials and disease management. *Cornea*. 2012;31(9):1000-8.

Wojtowicz JC, Butovich I, Uchiyama E, Aronowicz J, Agee S, McCulley JP. Pilot, prospective, randomized, double-masked, placebo-controlled clinical trial of an omega-3 supplement for dry eye. *Cornea*. 2011;30(3):308-14.

APPENDIX A. OCULAR SURFACE DISEASE INDEX 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)

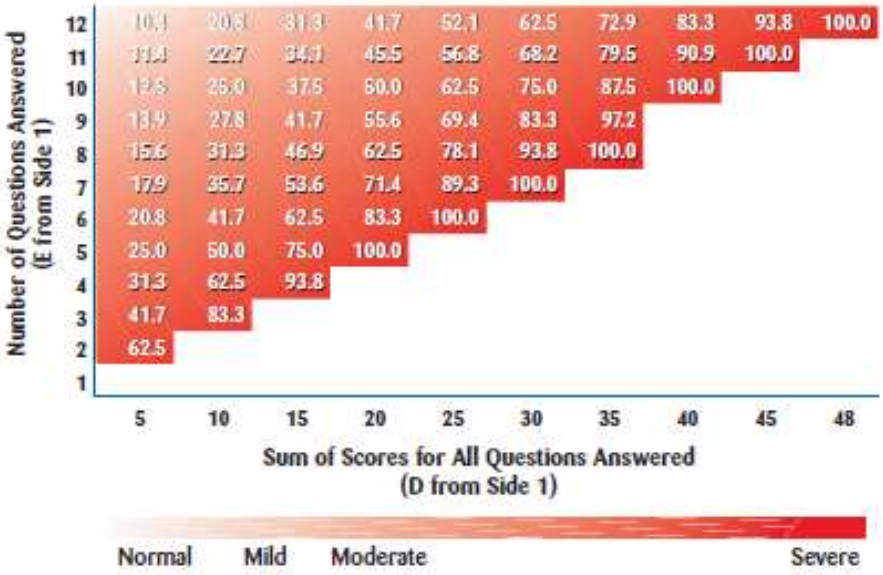
Please turn over the questionnaire to calculate the patient's final OSDI© score.

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: _____

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