



Original Research

The Dry Eye Assessment and Management (DREAM) extension study – A randomized clinical trial of withdrawal of supplementation with omega-3 fatty acid in patients with dry eye disease



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ABSTRACT

Purpose: To determine effects of continued or discontinued use of omega-3 (ω 3) fatty acid supplements through a randomized withdrawal trial among patients assigned to ω 3 supplements in the first year of the DREAM study.

Methods: Patients who were initially assigned to ω 3 (3000 mg) for 12 months in the primary trial were randomized 1:1 to ω 3 active supplements or placebos (refined olive oil) for 12 more months. The primary outcome was change in the Ocular Surface Disease Index (OSDI) score. Secondary outcomes included change in conjunctival staining, corneal staining, tear break-up time, Schirmer test, and adverse events.

Results: Among 22 patients assigned to ω 3 and 21 to placebo supplements, the mean change in OSDI score between month 12 and 24 was similar between treatment groups (mean difference in change -0.6 points, 95% confidence interval [CI], $(-10.7, 9.5)$, $p = 0.91$). There were no significant differences between groups in mean change in conjunctival staining (difference in mean change -0.5 points; 95% CI $(-1.2, 0.3)$), corneal staining (-0.3 points; 95% CI $(-1.2, 0.3)$), tear break-up time (-0.8 s; 95% CI $(-2.6, 0.9)$) and Schirmer test (0.6 mm, 95% CI $(-2.0, 3.2)$). Rates of adverse events were similar in both groups.

Conclusion: Among patients who received ω 3 supplements for 12 months in the primary trial, those discontinuing use of ω 3 for an additional 12 months did not have significantly worse outcomes compared to those who continued use of ω 3.

ClinicalTrials.gov number NCT02128763.

1. Introduction

Dry eye disease (DED) is a common chronic disorder that results in ocular discomfort, fatigue, visual disturbance and pain, thereby affecting overall quality of life [1–5]. DED is one of the most frequently encountered ocular morbidities [6] and is considered one of the top 3 most prevalent chronic eye diseases, together with glaucoma and age-related macular degeneration [7–10]. Nearly 14% of Americans, 50 years and older, of all races, and more commonly women, are affected by dry eye disease [1,11,12]. The average cost of managing DED in the US is estimated at more than \$55 billion annually, including healthcare

costs and loss of productivity [13]. Standard treatments for DED include use of artificial tears and lubricating ointments, anti-inflammatory drops, lid scrubs and punctal occlusion. Although the pathogenesis of DED is multifactorial, inflammation of the ocular surface has been shown to be an important component of dry eye disease [5,14].

There have been several reports of small clinical trials to support the role of ω 3 fatty acids in the treatment of DED [15–20]. However, outcome measures, dosing, composition, and length of treatment with ω 3 have varied across these trials. We are unaware of any previous reports of the effects on DED of withdrawing ω 3 supplements from current users.

Abbreviations: DED, dry eye disease; DHA, docosahexaenoic acid; DREAM, Dry Eye Assessment and Management; EPA, eicosapentaenoic acid; NEL, National Eye Institute; OSDI, Ocular Surface Disease Index; TBUT, tear break-up time

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The Dry Eye Assessment and Management (DREAM) trial was a large-scale, multicenter, randomized controlled trial that reported no difference between $\omega 3$ and placebo supplement groups on symptoms and signs of DED, although both groups showed improvement in symptoms over time [21]. The purpose of the DREAM extension trial is to determine effects of continued use or discontinuation of $\omega 3$ through a randomized withdrawal trial among subjects who were assigned to $\omega 3$ in year one of the study. The extension trial aims to provide information on long-term safety and sustainability of any treatment effect by evaluating data for return of signs and symptoms of DED after withdrawal of $\omega 3$ treatment.

2. Materials and methods

2.1. Subjects

The DREAM Study was a prospective, multi-center, double-masked, randomized, clinical trial. Participants were enrolled from 27 centers throughout the United States. Institutional Review Board approval was obtained at each center and the trial adhered to the principles of the Declaration of Helsinki. The trial was carried out under a Food and Drug Administration Investigational New Drug application and was registered with clinicaltrials.gov (NCT02128763.) A detailed description of the primary trial design and methodology has been published [22]. Participants who completed the DREAM study visit at 12 months and who were assigned to active supplements in the primary trial were eligible for the extension study (Fig. 1). Participants were informed whether they had been taking $\omega 3$ or placebo supplements during the preceding 12 months. Those who agreed to continue taking study supplements for the second year and had a negative urine pregnancy test (women of childbearing potential only) were enrolled after written informed consent was obtained.

The original plan was to offer participation in the extension study to all participants in the primary trial assigned to active supplements with the assumption that approximately 50% would enroll. However, recruitment for the primary trial required more time and resources than anticipated. To remain within budget, recruitment for the extension study was ended at the same time as recruitment for the primary trial. This change was approved by the DREAM Data and Safety Monitoring Committee. As of July 31, 2016, 43 (39.4%) of 109 patients completing the Month 12 visit and assigned to active supplements were enrolled in the extension study.

2.2. Treatment

Patients were randomly assigned, in a 1:1 ratio, to receive either

active or placebo supplements. The active supplements contained a total dose of 2000 mg of eicosapentaenoic acid (EPA) and 1000 mg docosahexaenoic acid (DHA) and the placebo supplements contained a total dose of 5000 mg of refined olive oil. The Access Business Group (Ada, MI) manufactured the supplements (softgel capsules). Participants were instructed to take five capsules per day for 12 months.

2.3. Visit procedures

After the enrollment visit (at month 12 of the primary trial), study visits were conducted at 18 and 24 months with a follow up phone call at months 15 and 21 (Appendix A, Table A1). Visit procedures were conducted in a specific order, in both eyes, and all testing was conducted following a standardized protocol. Standardized supplies were used at all sites. The use of artificial tears or any other topical treatment was not permitted for at least 2 h before any study visit. Participants were asked to complete questionnaires, Ocular Surface Disease Index (OSDI) and Brief Ocular Discomfort Inventory, about their dry eye symptoms and the impact of DED on their daily lives. A slit lamp evaluation (SLE), evaluation of the meibomian glands and eyelids, and tests to determine signs of dry eye disease were performed at each study visit. The four tests to determine key signs of dry eye disease included: 1) lissamine green conjunctival staining using a modified version of the National Eye Institute (NEI)/industry-recommended guidelines, where each of the temporal and nasal areas were graded on a scale of 0–3 under white light of moderate intensity; 2) corneal fluorescein staining using the NEI/industry-recommended guidelines, where each of the temporal, nasal, central, top and bottom areas were graded on a scale of 0–3 using the cobalt blue filter of the slit lamp [23]; 3) tear break up time (TBUT) and 4) Schirmer test with anesthetic.

2.4. Outcome measures

The primary outcome was a change in dry eye symptoms from month 12 to month 24 as measured by the OSDI score. Secondary outcomes included changes in the above described four clinical signs of DED: lissamine green staining, fluorescein corneal staining, TBUT, and Schirmer test from baseline to follow up.

2.5. Adverse events

Patients were asked about incidences of systemic and ocular adverse events during each visit at 18 and 24 months and by telephone at 15 and 21 months. Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) system. All serious adverse events and their codes were reviewed by a medical monitor.

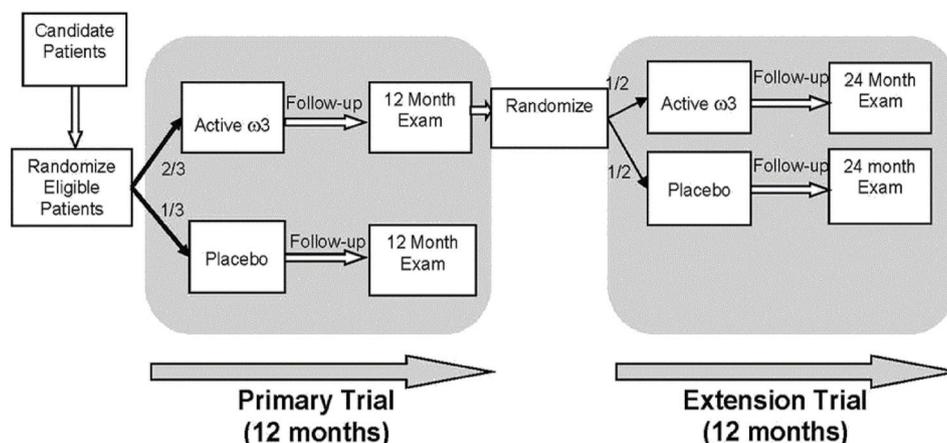


Fig. 1. Schematic overview of the DREAM primary and extension trials.

Table 1
Characteristics of the active and placebo groups at Month 12.

Characteristic	Active (22 Patients)		Placebo (21 Patients)	
	Mean	SD	Mean	SD
Age, years, mean	58.2	± 15.0	58.4	± 14.7
Gender - no. (%)				
Female	19	(86.4)	17	(81.0)
Male	3	(13.6)	4	(19.0)
Race - no. (%)				
White	15	(68.2)	16	(76.2)
Black	2	(9.1)	2	(9.5)
Other	5	(22.7)	3	(14.3)
Ethnicity (self-reported) - no. (%)				
Hispanic or Latino	2	(9.1)	0	(0.0)
Other	20	(90.9)	21	(100)
OSDI score, mean				
Total	27.9	± 19.5	27.8	± 19.6
Vision-related function subscale	24.1	± 24.1	21.9	± 23.6
Ocular symptoms	32.2	± 23.9	34.7	± 22.5
Environmental triggers subscale	32.8	± 26.3	33.1	± 24.7
Short Form –36 score, mean				
Physical health	47.6	± 12.8	48.3	± 9.5
Mental health	51.1	± 10.4	51.4	± 10.0
Brief Ocular Discomfort Index score, mean				
Discomfort subscale	31.7	± 19.4	29.0	± 16.2
Pain interference subscale	16.5	± 21.3	14.9	± 14.1
Use of dry eye treatments, n (%)				
Artificial tears, drops or gel	13	(59.1)	14	(66.7)
Cyclosporine drops	7	(31.8)	4	(19.0)
Warm lid soaks	4	(18.2)	3	(14.3)
Lid scrubs or baby shampoo	3	(13.6)	1	(4.8)
Any other treatment	6	(27.3)	7	(33.3)
Systemic disease - no. (%) ^a				
Sjögren syndrome	4	(18.2)	2	(9.5)
Thyroid disease	4	(18.2)	2	(9.5)
Rheumatoid arthritis	3	(13.6)	4	(19.0)
None of the above	14	(63.6)	15	(71.4)
Fatty acid in red blood cells, mean ^b				
Eicosapentaenoic, %	3.0	± 1.0	3.3	± 1.0
Docosahexaenoic, %	6.1	± 0.7	6.2	± 0.7
Oleic, %	10.6	± 1.2	11.4	± 1.4
		44 Eyes		42 Eyes
Conjunctival staining score, mean	2.7	± 1.7	2.1	± 1.7
Corneal staining score, mean	3.3	± 2.9	3.9	± 3.3
Tear break-up time, secs, mean	4.3	± 4.8	3.3	± 2.0
Schirmer test, mm, mean	7.1	± 3.4	7.7	± 5.9

Plus-minus values are means ± SD.

^a Ongoing or past history by patient report; may have more than 1 disease.

^b Missing values for 1 in the Active group.

Table 2
Changes in primary and secondary outcome measures from 12 months to 24 months.

Change from baseline	Active Patients			Placebo Patients			Between Group Difference ^a		
	n	Mean	SD	n	Mean	SD	Mean	(95% CI)	p
Ocular Surface Disease Index score									
Total, mean	19	3.1	± 15.1	20	3.7	± 17.8	-0.6	(-10.7, 9.5)	0.91
Vision-related function, mean	19	2.8	± 18.0	20	2.5	± 20.3	0.3	(-11.4, 12.0)	0.96
Ocular symptoms, mean	19	-0.0	± 18.8	20	3.1	± 16.5	-3.1	(-14.0, 7.7)	0.57
Environmental triggers, mean	17	5.4	± 17.4	20	5.4	± 26.7	-0.0	(-14.0, 13.9)	1.00
≥ 10 increase, n (%)	19	6	(32%)	20	5	(25%)	7%	(-33%, 21%)	0.65
Brief Ocular Discomfort Index, mean									
Discomfort	19	-5.1	± 14.3	20	3.5	± 19.3	-8.6	(-19.0, 1.7)	0.10
Interference	19	-1.7	± 16.0	20	2.6	± 13.3	-4.3	(-13.3, 4.7)	0.35
Short Form-36 score, mean									
Physical health	19	-1.6	± 11.2	20	-3.3	± 4.9	1.8	(-3.6, 7.1)	0.52
Mental health	19	-4.1	± 5.0	20	-0.5	± 7.0	-3.6	(-7.3, 0.1)	0.055
Fatty acid in red blood cells, % mean									
Eicosapentaenoic	18	-0.6	± 0.8	19	-2.5	± 0.7	1.9	(1.4, 2.4)	< 0.001
Docosahexaenoic	18	-0.6	± 0.6	19	-1.9	± 0.7	1.3	(0.9, 1.7)	< 0.001
Oleic	18	0.51	± 0.69	19	0.17	± 1.51	0.3	(-0.4, 1.1)	0.36
Signs, mean									

(continued on next page)

Table 2 (continued)

Change from baseline	Active Patients			Placebo Patients			Between Group Difference ^a		
	n	Mean	SD	n	Mean	SD	Mean	(95% CI)	p
Conjunctival staining score	38	-0.4	± 1.0	40	0.1	± 1.9	-0.4	(-1.2, 0.3)	0.26
Corneal staining score	38	-0.1	± 1.7	40	0.2	± 2.1	-0.3	(-1.2, 0.7)	0.60
Tear break-up time, seconds	38	-0.6	± 4.6	40	0.2	± 1.9	-0.8	(-2.6, 0.9)	0.35
Schirmer test, mm	38	2.4	± 3.8	40	1.8	± 5.4	0.6	(-2.0, 3.2)	0.65
Safety, mean									
Visual acuity, letters	38	0.0	± 3.8	40	-0.1	± 3.9	0.1	(-1.6, 1.9)	0.89
Intraocular pressure, mmHg	38	0.2	± 2.6	40	-0.3	± 2.7	0.5	(-1.0, 2.0)	0.48

^a Differences are the value in the active group minus the value in the placebo group.

2.6. Statistical analysis

Change between 12 and 24 months within treatment groups was assessed with tests for linear trend across months 12, 18, and 24. Comparisons of mean change in continuous measures between treatment groups and associated 95% confidence intervals (95% CI) were based on linear regression using a robust variance estimator.

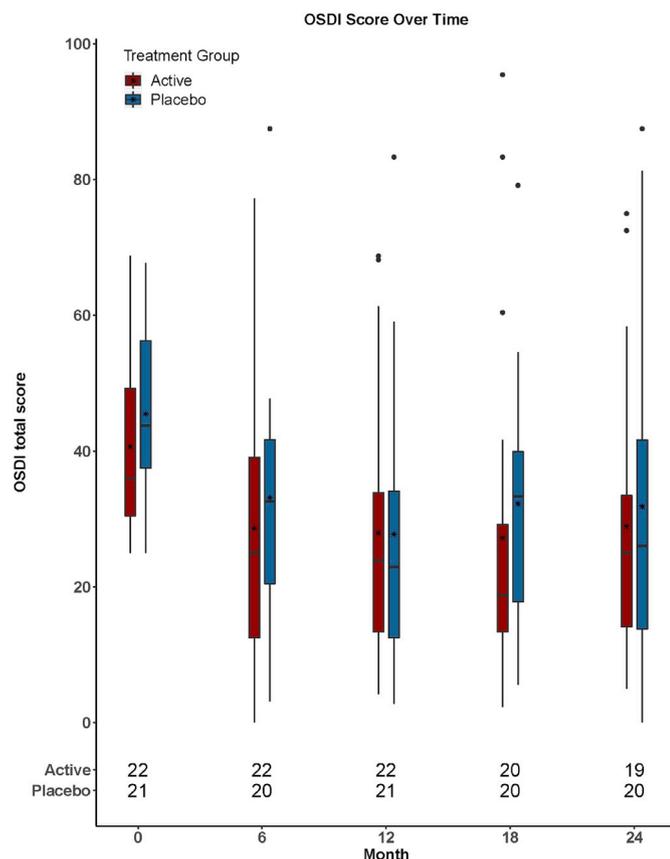


Fig. 2. Ocular Surface Disease Index (OSDI) scores over time. Box and whisker plots: Box upper and lower edges correspond to the 75th and 25th percentiles, respectively. Within the box, the asterisk corresponds to the mean value and the line corresponds to the 50th percentile (median). Ends of whiskers correspond to the lowest score within 1.5 times the interquartile range of the 25th percentile and the highest score within 1.5 times the interquartile range of 75th percentile. Each circle outside of the whiskers corresponds to one score.

Generalized estimating equations were used for ocular measures to accommodate the correlation between eyes of the same person [24]. Comparisons of categorical outcomes were made using chi-square tests; and 95% CI's for the difference in proportions were calculated using Wilson's method [25]. The difference between groups in the number of adverse events per person was assessed with a Poisson regression model.

3. Results

A total of 22 participants were assigned to the active supplement group and 21 to the placebo group. The characteristics of the participants, at enrollment into the extension study, were comparable between treatment groups across all characteristics listed in Table 1 (p > 0.05 for all comparisons). Participants were predominantly female and white. The mean OSDI score, conjunctival and corneal staining, tear breakup time, Schirmer test, and the use of dry eye treatments were similar in the 2 groups at enrollment into the extension trial. At entry into the primary trial, mean values for these 43 patients were 43.0 for the total OSDI score, 3.1 for conjunctival staining, 4.5 for corneal staining, 3.3 s for tear breakup time, and 8.9 mm for Schirmer test. Between entry into the primary trial and 12 months, the mean percent fatty acid level increased by 2.5% for EPA and by 2.0% for DHA.

Completion of follow-up visits at 18 and 24 months was ≥86% in both treatment groups. The mean values of the % of EPA and DHA in red blood cell membranes decreased more in the placebo group than in the active group (-2.5% vs -0.6% for EPA and -1.9% vs -0.6% for DHA; p < 0.001 for both; Table 2). Mean changes in oleic acid, the main constituent of olive oil, were similar between the 2 groups.

The mean (± SD) change between month 12 and month 24 in total OSDI score was 3.1 ± 15.1 (p = 0.52) in the active group and 3.7 ± 17.8 (p = 0.28) in the placebo group (Table 2). The difference in mean change between groups was -0.6 (95% confidence interval CI (-10.7, 9.5); p = 0.91). (Table 2; Fig. 2).

Among the secondary outcome measures of DED signs, most of the changes between 12 and 24 months within the treatment groups were not statistically significantly different from 0 (p ≥ 0.28; Fig. 3). However, the mean (± SD) conjunctival staining score decreased in the active group (-0.4 ± 1.0; p = 0.04) while the mean (± SD) Schirmer test mm increased in both the active group (2.4 ± 3.8; p = 0.004) and the placebo group (1.8 ± 5.4; p = 0.03). Mean (95% CI) differences in change between active and placebo groups were -0.4 ((-1.2, 0.3); p = 0.26) for the conjunctival staining score and -0.3 ((-1.2, 0.7); p = 0.60) for the corneal staining score (Fig. 3A and B). The mean

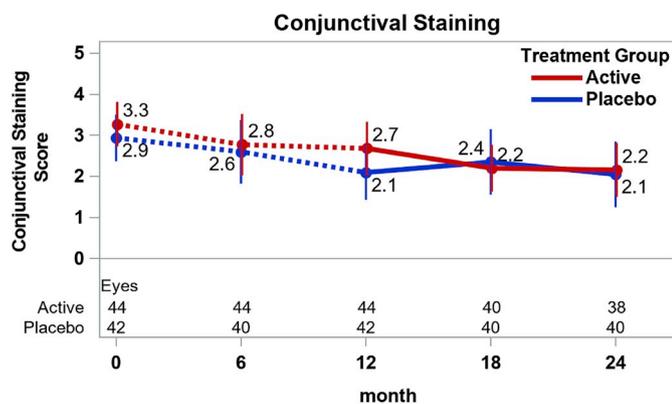


Fig. 3. Signs of dry eye disease over time by treatment group. Mean values and associated 95% confidence intervals for signs of dry eye disease by treatment group, over time. Dotted lines connect values prior to randomization in the extension trial. A. Conjunctival staining; B. Corneal staining; C. Tear break-up time; D. Schirmer test.

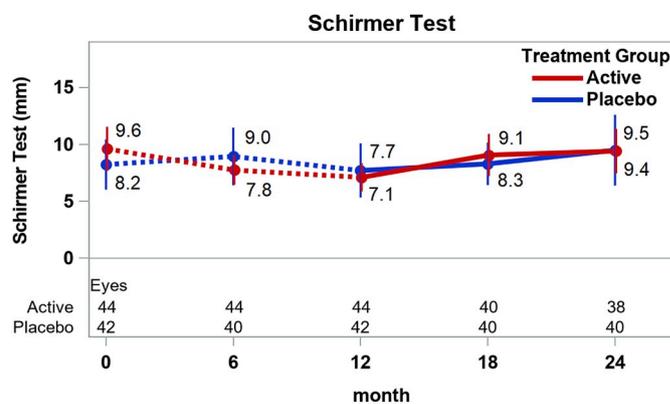


Fig. 3. (continued)

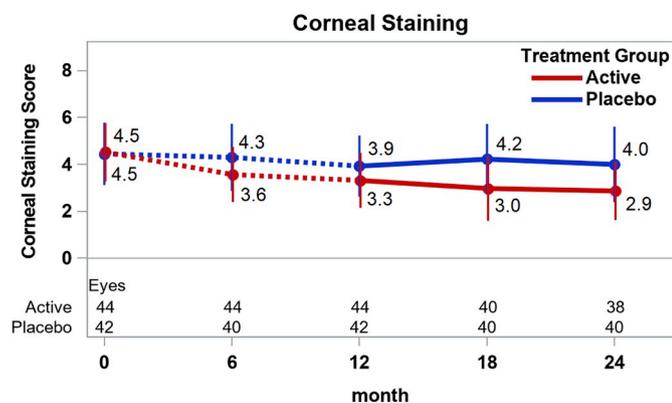


Fig. 3. (continued)

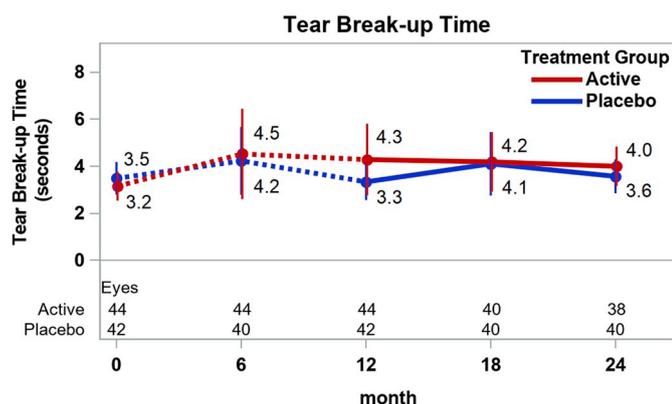


Fig. 3. (continued)

difference for TBUT was -0.8 s ($-2.6, 0.9$); $p = 0.35$) (Fig. 3C) and for Schirmer test was 0.6 mm ($-2.0, 3.2$); $p = 0.65$) (Fig. 3D).

One patient in the placebo group experienced a serious adverse event, hospitalization for dyspnea. There were 19 non-serious adverse events among patients in the active group and 11 among patients in the placebo group ($p = 0.46$; Appendix B; Table A2).

4. Discussion

In this randomized trial of withdrawal of $\omega 3$ supplementation, we evaluated the effects of discontinuing use of $\omega 3$ supplements on the symptoms and signs of DED relative to continuing use. We also evaluated whether there was any added benefit of using $\omega 3$ for 2 years in the active $\omega 3$ group and whether signs and symptoms of DED returned after stopping $\omega 3$ after 1 year in the placebo group.

We found no statistically significant difference in changes in symptoms or signs of DED between patients continuing use of $\omega 3$ supplements and patients discontinuing use. The mean OSDI score increased (worsened) by 3–4 points in each treatment group; however, these mean changes over time were small and not significantly different from zero. The changes in the extension study were different in magnitude from the changes in these patients in the primary trial when the mean improvement at 12 months was approximately 15 points.

Mean conjunctival staining score decreased slightly (improvement) in the active supplement group and Schirmer test results increased (improved) in both groups. No significant worsening of DED signs and symptoms were seen between 12 and 24 months in the placebo group, suggesting that discontinuing the use of $\omega 3$ after 12 months may not have worse outcomes compared to continuing for an additional 12 months.

Strengths of this study include good follow-up and good compliance as judged by the placebo group's decrease in blood EPA and DHA levels. The mean decreases in EPA and DHA in the group that switched to placebo were similar in magnitude to the large mean increases after the patients initiated active supplements in the primary trial, indicating a high level of compliance in both trials. The small sample size of approximately 20 per group limited the precision of the estimation of the mean differences between treatment groups as reflected in their wide confidence intervals. For the difference between treatment groups in mean change in the OSDI score, the 95% confidence interval was $(-10.7, 9.5)$. This interval includes values that we considered clinically meaningful (greater than a 6-point difference in means) when the primary trial was designed [22].

Conduct of a randomized withdrawal trial is not common in ophthalmology, but enables a longitudinal assessment of DED with respect to changes in symptoms and signs in both the placebo and the treatment group. A study duration of 12 months provides information on the sustainability of the treatment effect of $\omega 3$ supplementation and facilitates study of long term safety profile of $\omega 3$ supplementation.

The results from the DREAM extension study are consistent with the results from the DREAM primary trial. In the primary trial, introduction

of ω3 supplementation was associated with a substantial improvement (14 points among all patients) in the mean OSDI score that was similar to the improvement observed in the placebo group. In the extension study, withdrawal of ω3 supplementation was associated with slight worsening (4 points) in the mean OSDI score that was similar to the worsening observed in the ω3 group. Mean changes over time in signs of DED were small and similar between treatment groups in both the primary trial and the extension study. Taken together, the results from the two DREAM clinical trials do not support a beneficial effect of ω3 supplementation on dry eye disease.

Disclosures

Dr. Asbell reports personal fees from Allergan, Bausch& Lomb, Kao, MC2 Therapeutics, Medscape, Miotech, Novartis, Oculus, Rtech,

Santen, Shire, and Valeant; grants from Bausch& Lomb, MC2 Therapeutics, Miotech, Novartis, Rtech, ScientiaCME, and Valeant and non-financial support from Santen, Shire, and Valeant. Dr. Maguire reports personal fees from Genentech/Roche. For the remaining authors, none were declared. The Access Business Group, LLC (Ada, MI) manufactured, packaged and delivered study supplements to the central pharmacy at no cost to the study.

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Appendix A

Table A1
Extension study schedule of procedures

Procedure	Visit (Month)			
	15	18	21	24
OSDI & BODI Questionnaires		Y		Y
Health Economics Questionnaires (SF-36, WPAI, Healthcare Use)		Y		Y
Medical History and Events		Y		Y
Concomitant Medication Query		Y		Y
Adverse Event Query		Y		Y
Tear Osmolarity		Y ¹		Y ¹
Keratograph Break-Up Time, Tear Meniscus Height, Redness, and Meibomian Gland Evaluation		Y ¹		Y ¹
Best Corrected VA (if change in VA ≥ 10 letters, do refraction)		Y		Y
Contrast Sensitivity		Y		Y
Tear Collection for Cytokines		Y ¹		Y ¹
Slit Lamp Evaluation (SLE)		Y		Y
Tear Break-Up Time (TBUT) ³		Y		Y
Corneal Fluorescein Staining ³		Y		Y
Meibomian Gland Examination ³		Y		Y
Lissamine green staining ³		Y		Y
IOP		Y		Y
Schirmer's Tear Test (with anesthetic)		Y		Y
Impression Cytology		Y		Y
Blood Collection (Mon-Thurs) for fatty acid determination		Y		Y
Blood Collection (Mon-Thurs) for antibody determination				Y
Collection of Unused Study Supplements		Y		Y
Reminder Calls (2 weeks before each visit)		Y		Y
“Check-In” Telephone Call	Y		Y	Y ²
Letter to Encourage Compliance (sent 1 month after each visit)		Y		

- 1 Only at centers with required equipment
- 2 Call for final adverse event assessment
- 3 Do all 4 procedures OD, then restart for OS

Appendix B

Table A2
Adverse events between month 12 and 24 in the extension study by system organ class, preferred term, and treatment group

System Organ Class	Preferred Term	Treatment			
		Active 22 people		Placebo 21 people	
		N	Per 100 people	N	Per 100 people
Total		19	86.4	11	52.4
EAR AND LABYRINTH DISORDERS	VERTIGO	1	4.5	–	–
EYE DISORDERS	CONJUNCTIVAL HAEMORRHAGE	1	4.5	–	–
	CONJUNCTIVAL IRRITATION	–	–	1	4.8
	PHOTOPHOBIA	–	–	1	4.8
	PHOTOPSIA	1	4.5	–	–
GASTROINTESTINAL DISORDERS	DYSPEPSIA	1	4.5	–	–
HEPATOBIILIARY DISORDERS	HEPATOMEGALY	1	4.5	–	–
INFECTIONS AND INFESTATIONS	BRONCHITIS	1	4.5	–	–

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Table A2 (continued)

System Organ Class	Preferred Term	Treatment			
		Active 22 people		Placebo 21 people	
		N	Per 100 people	N	Per 100 people
	GINGIVAL INFECTION	–	–	1	4.8
	INFECTION	1	4.5	–	–
	LUNG INFECTION	1	4.5	–	–
	NASAL ABSCESS	1	4.5	–	–
	NASOPHARYNGITIS	1	4.5	–	–
	TOOTH INFECTION	1	4.5	–	–
	URINARY TRACT INFECTION	1	4.5	–	–
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	ARTHROPOD BITE	1	4.5	–	–
	EPICONDYLITIS	–	–	1	4.8
	FRACTURE	1	4.5	–	–
INVESTIGATIONS	BLOOD CALCIUM INCREASED	1	4.5	–	–
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	BACK PAIN	1	4.5	1	4.8
	NECK PAIN	–	–	1	4.8
	TRIGGER FINGER	1	4.5	–	–
NERVOUS SYSTEM DISORDERS	DIZZINESS	–	–	1	4.8
	SCIATICA	–	–	1	4.8
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	ALLERGIC COUGH	1	4.5	–	–
	COUGH	1	4.5	–	–
SURGICAL AND MEDICAL PROCEDURES	CATARACT OPERATION	–	–	2	9.5
VASCULAR DISORDERS	BLOOD PRESSURE FLUCTUATION	–	–	1	4.8

Appendix C. The members of the Dry Eye Assessment and Management (DREAM) Research Group

Certified Roles at Clinical Centers: Clinician (CL); Clinic Coordinator (CC), Data Entry Staff (DE) Principal Investigator (PI), Technician (T).
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Appendix D. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jtos.2019.08.002>.

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