**ORIGINAL CONTRIBUTION**

**ω-3 Fatty Acid Treatment in Multiple Sclerosis (OFAMS Study)**

**A Randomized, Double-Blind, Placebo-Controlled Trial**

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**Objective:** To investigate whether ω-3 fatty acids reduce magnetic resonance imaging (MRI) and clinical disease activity in patients with multiple sclerosis, both as monotherapy and in combination with interferon beta-1a treatment.

**Design:** Multicenter, randomized, double-blind, placebo-controlled clinical trial conducted from 2004 to 2008.

**Setting:** Thirteen public neurology departments in Norway.

**Participants:** Patients aged 18 to 55 years with active relapsing-remitting multiple sclerosis, with a disability score equivalent to 5.0 or less on the Kurtzke Expanded Disability Status Scale. Ninety-two patients were randomized to ω-3 fatty acids (n=46) or placebo capsules (n=46).

**Interventions:** Administration of 1350 mg of eicosapentaenoic acid and 850 mg of docosahexaenoic acid daily for 6 months, all patients in addition received subcutaneously 44 µg of interferon beta-1a 3 times per week for another 18 months.

**Main Outcome Measure:** The primary outcome measure was MRI disease activity as measured by the number of new T1-weighted gadolinium-enhancing lesions during the first 6 months. Secondary outcome measures included MRI disease activity after 9 months and 24 months, relapse rate, disability progression, fatigue, quality of life, and safety.

**Results:** The cumulative number of gadolinium-enhancing MRI lesions during the first 6 months were similar in the ω-3 fatty acids and placebo groups (median difference, 1; 95% CI, 0 to 3; P=.09). No difference in relapse rate was detected after 6 (median difference, 0; 95% CI, 0 to 0; P=.54) or 24 (median difference, 0; 95% CI, 0 to 0; P=.72) months. The proportion of patients without disability progression was 70% in both groups (P > .99). No differences were detected in fatigue or quality-of-life scores, and no safety concerns appeared. Serum analyses of fatty acids showed an increase in ω-3 fatty acids (mean difference, 7.60; 95% CI, 5.57 to 7.91; P < .001) in the patients treated with ω-3 fatty acids compared with the placebo group.

**Conclusion:** No beneficial effects on disease activity were detected from ω-3 fatty acids when compared with placebo as monotherapy or in combination with interferon beta-1a. Magnetic resonance imaging disease activity was reduced as expected by interferon beta-1a.

**Trial Registration:** clinicaltrials.gov Identifier: NCT00360906


**MULTIPLE SCLEROSIS IS A CHRONIC INFLAMMATORY, DEMYELINATING DISEASE OF THE CENTRAL NERVOUS SYSTEM, MAINLY AFFECTING YOUNG ADULTS.** There is currently no curative treatment for multiple sclerosis, but several immunomodulatory agents, including interferon beta, glatiramer acetate, natalizumab, and fingolimod reduce disease activity in the relapsing-remitting course of the disease. Because of the invariable nature of the disease, there is great interest in complementary approaches, both from health care personnel and patients. One such approach is ω-3 fatty acid supplementation. ω-3 Fatty acids belong to the group of essential fatty acids and could, theoretically, have both anti-inflammatory and neuroprotective effects in multiple sclerosis. A number of small, uncontrolled trials have indicated a possible beneficial effect of ω-3 fatty acid supplementation, but controlled clinical trials have not been able to draw definite conclusions. Worldwide,
about 2.5 million people are living with multiple sclerosis, and it has been estimated that about one-third of them are using or have tried supplementation with ω-3 fatty acids to control the disease progress. Since this is the most common form of complementary therapy used by patients with multiple sclerosis, properly designed proof-of-concept studies with magnetic resonance imaging (MRI) end points have been called for. This randomized, double-blind, placebo-controlled trial was conducted to determine whether ω-3 fatty acid supplementation given as monotherapy or in combination with subcutaneous interferon beta-1a could reduce disease activity and disability in patients with multiple sclerosis.

METHODS

STUDY PARTICIPANTS

The OFAMS study was a multicenter, double-blind, randomized, placebo-controlled, parallel-group study designed to compare the effect of daily treatment with concentrated ω-3 fatty acids (Triomega) with the effect of placebo alone or in combination with first-line immunomodulatory treatment with interferon beta-1a in patients with relapsing-remitting multiple sclerosis. Eligible patients fulfilled the McDonald criteria for relapsing-remitting multiple sclerosis, were aged between 18 and 55 years, had a disability score equivalent to 5.0 or less on the Kurtzke Expanded Disability Status Scale (EDSS), and had at least 1 clinical relapse or 1 new T1-weighted gadolinium-enhancing MRI lesion or T2-weighted MRI lesion in the year prior to inclusion. Women with childbearing potential were required to use an adequate contraceptive method throughout the study and not to be pregnant at screening. Exclusion criteria included interferon beta or glatiramer acetate treatment in the year before study entry. Additional detailed exclusion criteria are available in the eAppendix “Methods 1” section (http://www.archneurol.com). Patients provided written informed consent before initiating study procedures. The study protocol was approved by the Regional Committee for Medical and Health Research Ethics in Western Norway and the Norwegian Medicines Agency. The study was undertaken in accordance with the Declaration of Helsinki and the European Medicines Agency Note for Guidance on Good Clinical Practice.

STUDY MEDICINE, RANDOMIZATION, AND MASKING

Eligible patients were recruited from 13 neurology departments in Norway and were randomized for daily treatment with either oral ω-3 fatty acids or placebo. After 6 months, all patients in addition received subcutaneously 44 μg of interferon beta-1a (Rebif) 3 times per week for another 18 months. The study medication was 1-g Triomega capsules ( Pronova Biocare), containing 60% ω-3 fatty acids: 270 mg of eicosapentaenoic acid (EPA) and 170 mg of docosahexaenoic acid per gram. Four international units of α-tocopherol per gram were added for antioxidative protection. The placebo formulation appeared identical, containing corn oil. Labeling and packaging were prepared to meet regulatory requirements. Placebo and ω-3 fatty acids were administered as 5 capsules daily after the morning meal. Patients were randomized by a computer-generated procedure, with an assignment ratio of 1:1, with each patient assigned the lowest randomization number available at the study site. The block size of the randomization was 6 and there was no stratification by centers. We used independent statistical, packaging, and distribution contractors to maintain the blinding for all other personnel. The randomization was conducted by an independent research organization (Smerud Medical Research International AS, Oslo, Norway). The study drug was not suspected to have any clinical or laboratory adverse effects different from placebo that could disturb the double-blind nature of the trial. Therefore, the same neurologist (study neurologist) functioned as both the treating and evaluating physician.

STUDY DESIGN

Information on demographics and medical history was recorded, and the patients were screened and included according to the inclusion and exclusion criteria. All participants underwent a clinical neurological examination, including EDSS scoring, biochemical tests, and a baseline MRI. Monthly T2-weighted and T1-weighted gadolinium-enhanced MRI scans were performed for the first 9 months and thereafter at months 12 and 24. Blinded assessment of the MRI scans was conducted by 2 neuroradiologists (S.B. and B.B.). A detailed description of the MRI procedures is given in the eAppendix “Methods 2” section. Patients underwent clinical examination, laboratory tests, and recording of adverse events at months 1, 3, 6, 7, 9, 12, 18, and 24. Every relapse was recorded throughout the study period; patients were informed to contact the study site by telephone if they experienced symptoms of a relapse. A documented relapse was defined as the appearance of new or worsening old neurological symptoms or signs, in the absence of fever, persisting for more than 48 hours and causing objective changes on neurological examination, preceded by a period of more than 30 days with a stable or improving condition. The EDSS scoring was performed every sixth month (months 0, 6, 12, 18, and 24) during the study. Fatigue (Fatigue Severity Scale), quality of life (Short Form 36), and the Multiple Sclerosis Functional Composite were recorded at the same intervals. Sera samples for neutralizing antibodies against interferon beta were collected after 24 months, and sera samples for total monounsaturated and unsaturated fatty acids, saturated fatty acids, and ω-3 and ω-6 fatty acids were collected at baseline and months 6, 12, and 24. The fatty acid analyses were performed after study termination and thus did not influence the blinding.

OUTCOME MEASURES

The primary outcome measures according to the study protocol were originally the cumulative number of new T1-weighted gadolinium-enhancing lesions during the first 6 months of treatment and the number of new T1-weighted hypointensive lesions after 24 months of treatment. To avoid multiplicity issues, it was decided, prior to database locking and analysis, to keep only 1 primary outcome measure and degrade the number of new T1-weighted hypointensive lesions after 24 months to a secondary outcome measure. Other secondary outcome measures were the combined unique activity, defined as any lesion that was T1 active (T1-weighted enhancing lesion), T2 active (new or enlarging T2-weighted lesion), or both during the first 6 months of treatment and during the whole study period; the number of relapses during the first 6 months of treatment and during the whole study period; the increase in disability as measured by the EDSS during the first 6 months of treatment; the number of relapses during the first 6 months of treatment and during the whole study period; the increase in disability as measured by the EDSS during the first 6 months of treatment; and the number of new T1-weighted hypointensive lesions after 24 months of treatment.
treatment and during the whole study period; changes in the Multiple Sclerosis Functional Composite score during the first 6 months of treatment and during the whole study period; changes in serum levels of total monounsaturated and unsaturated fatty acids, saturated fatty acids, and ω-3 and ω-6 fatty acids at months 6 and 24; the occurrence of adverse events during the first 6 months of treatment and during the whole study period; and the occurrence of neutralizing antibodies against interferon beta-1a during the study. Adverse events were recorded at each clinical visit. A serious adverse event was defined as any adverse event that resulted in death, was life threatening, required hospital admission, prolonged a hospital stay, or resulted in persistent and substantial disability. A relapse was not recorded as an adverse event, irrespective of admission to the hospital. Several tertiary explorative outcome measures were included, such as the time to first relapse; the number of relapse-free patients; the number of patients without progression of disability; the number of patients without MRI disease activity; and change in fatigue (Fatigue Severity Scale) and quality of life (Short Form 36).

**STATISTICAL ANALYSES**

The number of patients necessary in each treatment group was calculated from the assumption that patients with relapsing-remitting multiple sclerosis without immunomodulatory treatment have a mean (SD) of 2.02 (2.19) and a median of 1.33 (range, 0–16) new contrast-enhancing lesions monthly. Based on this assumption and with a significance level of 5%, 40 patients in each group were needed to reach a power of 83% in detecting a 70% reduction in new enhancing lesions on monthly MRI during 3 months (4 scans). Expecting a dropout rate of 10% to 15%, we increased the power of detecting treatment effect by extending the treatment period to 6 months and aimed to include 50 patients in each treatment group. The primary end point was the sum of new T1-weighted gadolinium-enhancing lesions during the first 6 months of treatment, calculated as the sum of lesions evaluated on MRI after 1, 2, 3, 4, 5, and 6 months. Because of the skewed distribution of data, the Mann-Whitney-Wilcoxon nonparametric test was used for the primary analysis, in addition to the Hodges-Lehmann (HL) estimate of median treatment difference.

Each variable was analyzed with respect to (1) treatment groups (unadjusted), (2) treatment groups adjusted for baseline concentrations of ω-3 and ω-6 fatty acids, and (3) treatment group interaction with the baseline concentration of EPA (cutoff at 1.0 in percentage weight of EPA in total serum phospholipid level). The unadjusted analyses were performed using the standard 2-sample t distribution if the normality assumption was not violated and with the Mann-Whitney-Wilcoxon test and HL estimate of median difference if the normality assumption was violated. Survival time was analyzed using the Kaplan-Meier estimator of survival function and categorical variables were analyzed using the χ² test and corresponding estimates of relative risk. Baseline adjusted analyses were performed using analysis of covariance models if the normality assumption was not violated. Counting variables were analyzed using the semiparametric counting process method. We used a robust sandwich estimate of the coefficient estimates to account for the correlation among observations on individual subjects. The counting process method assumes that all events (gadolinium-enhancing lesions) are observed. This assumption did not hold for the 12- and 24-month MRI assessments of new T1-weighted gadolinium-enhancing lesions, because lesions occurring between 9 to 12 and 12 to 24 months may no longer be enhancing at the following assessment. Because of this, the baseline adjusted analysis and the EPA baseline adjusted analyses for the corresponding end points were performed using a Poisson non-linear mixed model. Baseline adjusted survival time was analyzed using the Cox proportional hazard model and baseline adjusted categorical data were analyzed using logistic regression. In the analysis of new T1-weighted hypointensive lesions, the missing MRI assessments were set to zero as a conservative approach, since the dropouts for the first 24 months were predominantly in the placebo group (4 patients in the placebo group and 1 patient in the active group). Differences in the occurrence of adverse events were analyzed using χ² tests or the Fisher exact test if appropriate. SAS software (SAS Institute) was used for all statistical analyses.

**RESULTS**

Eligible patients for the OFAMS study were recruited between December 2004 and July 2006. A total of 102 patients were assessed for eligibility, of whom 92 were allocated to active treatment with ω-3 fatty acids (n=46, 50%) or placebo (n=46, 50%). The participant flowchart is depicted in Figure 1. The 2 groups were similar with regard to baseline demographics and characteristics (Table 1). Eleven patients (3 in the ω-3 fatty acids group and 8 in the placebo group) terminated the study treatment prematurely. One patient was excluded from the intention-to-treat population because of lack of efficacy assessments after the baseline visit; thus, 91 patients remained for the per-protocol analyses. No major protocol violations were reported. Reasons for discontinuation did not differ between the groups (eTable 1). The number of patients with at least 90% compliance to treatment was similar in the 2 groups, with 90% (n=40)
Table 1. Baseline Demographics and Disease Characteristics

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Abbreviations: EDSS, Expanded Disability Status Scale; GdE, gadolinium-enhancing; MRI, magnetic resonance imaging.

in the ω-3 fatty acids group and 76% (n=34) in the placebo group (P=.16).

For the primary outcome, new T1-weighted gadolinium-enhancing lesions during the first 6 months of the study, no effect of ω-3 fatty acid vs placebo treatment was detected (P = .09). The median number of new T1-weighted gadolinium-enhancing lesions was 3 (range, 0-41) in the ω-3 fatty acids group vs 2 (range, 0-44) in the placebo group. The HL location shift estimator of treatment difference was 0.80 (95% CI, 0.40 to 1.56; P = .15). The proportion of patients without MRI disease activity was 95% CI, 0 to 3 in favor of the placebo group. In the robustness analysis, with worst-case imputation of missing data points, the difference between the treatment groups was still not significant (HL = 1; 95% CI, −1 to 2; P = .39). Adjusting for the baseline ω-3:ω-6 fatty acid ratio did not yield significant treatment effects (P = .35) (Figure 2A).

There was no difference in the number of new T1-weighted gadolinium-enhancing lesions between the treatment groups at month 9 (P = .10) or at month 24 (P = .17). The treatment difference in favor of the placebo group after 6 months of treatment was sustained throughout the study, even after adjusting for baseline ω-3:ω-6 fatty acid ratio and EPA levels (eTable 2). The effect of interferon beta-1a treatment was significant, with a lesion rate ratio of 0.32 (95% CI, 0.26 to 0.39; P < .001) compared with the period prior to interferon beta-1a treatment.

There was no difference between the treatment groups regarding new T1-weighted hypointense lesions after 24 months of treatment (HL = 0; 95% CI, 0 to 0; P = .40). When adjusted for baseline serum weight of ω-3:ω-6 fatty acid ratio, there was still no difference between the groups, with a lesion rate ratio of 0.80 (95% CI, 0.40 to 1.56; P = .51) (Figure 2B). No group difference was detected in combined unique activity after 6 (P = .06) or 24 (P = .15) months of treatment (eTable 2). Adjusting for baseline ω-3:ω-6 fatty acid ratio did not influence the result. The proportion of patients without MRI disease activity was 16% in the ω-3 fatty acids group and 14% in the placebo group after 6 months (P = .52). After 24
months, these numbers were reduced to 12% in the ω-3 fatty acids group and 7% in the placebo group (P > .99).

A total of 65 relapses were recorded in 37 patients throughout the study period. There was no difference between the ω-3 fatty acids and placebo groups in number of relapses during the first 6 months of treatment (P = .54) or after 24 months (P = .72). The ω-3:ω-6 fatty acid ratio baseline adjusted analysis did not alter the results (Figure 3).

The proportion of relapse-free patients was 78% in the ω-3 fatty acids group and 82% in the placebo group after 6 months (P = .68) and 57% in the ω-3 fatty acids group vs 58% in the placebo group after 24 months (P = .88).

Mean (SD) EDSS score increased from 1.86 (0.86) to 1.87 (1.0) in the ω-3 fatty acids group and fell from 1.94 (0.78) to 1.88 (0.94) in the placebo group after 6 months. There was no difference between the treatment groups (P = .61) (eTable 2). After 24 months, mean (SD) EDSS score had increased to 2.22 (1.32) in the ω-3 fatty acids group and 2.19 (1.34) in the placebo group, with no difference between the treatment groups (P = .63). Ten patients progressed 1 point on the EDSS score after 6 months, 6 (13%) patients given ω-3 fatty acids vs 4 (10%) given placebo (P = .74). After 24 months, a total of 25 patients had experienced disease progression, 13 (30%) in the ω-3 fatty acids group vs 12 (30%) in the placebo group (P > .99).

No group differences in change of Multiple Sclerosis Functional Composite scores were detected after 6 (P = .53) or 24 (P = .57) months. Similarly, no group difference in fatigue (Fatigue Severity Scale) was detected during the first 6 months (P = .97) or during the whole study period of 24 months (P = .57). Health-related quality of life as measured by the Short Form 36 showed no differences in the Short Form 36 mental score during the first 6 months (P = .53) or during the whole study period of 24 months (P = .85). Similar results were obtained for the Short Form 36 physical score after 6 (P = .66) and 24 (P = .49) months.

As expected, the serum ratio of ω-3 fatty acids:total serum phospholipids increased in the group receiving ω-3 fatty acids compared with the placebo group, both at month 6 (P < .001) and month 24 (P < .001). The ω-3 fatty acids group had a corresponding decrease in the ω-3:ω-6 fatty acid ratio in total serum phospholipid level. There were no significant changes in the levels of ω-3 or ω-6 fatty acids in the placebo group throughout the study period (eTable 2 and eTable 3).

During the study, a total of 169 adverse events were registered, 94 in the ω-3 fatty acids group and 75 in the placebo group. Overall, 34 patients (74%) in the ω-3 fatty acids and 29 (63%) in the placebo group reported any adverse events. The difference between the ω-3 fatty acids and placebo groups was not significant after 6 months (P = .38) or after 24 months (P = .08). A total of 9 serious adverse events were reported for 4 subjects (3 [7%] in the ω-3 fatty acids group and 1 [2%] in the placebo group), none related to the study drug or multiple sclerosis (eTable 4). The most common adverse events were interferon beta–related influenza-like symptoms, which were experienced by 11 (24%) in the ω-3 fatty acids group and 10 (22%) in the placebo group, and injection site reaction, which was experienced by 12 (26%) in the ω-3 fatty acids group and 8 (17%) in the placebo group. Thus, the adverse events were evenly distributed between the ω-3 fatty acids and placebo groups (Table 2). No other noticeable differences between the treatment groups were detected. There were 3 patients who withdrew because of adverse events: 1 (2%) in the ω-3 fatty acids group because of nausea and 2 (4%) in the placebo group because of allergic reactions (1 possible reaction to gadolinium and 1 to carbamazepine, used for neuropathic pain). Neutralizing antibodies (titer ≥20) occurred in 12 patients (26%) in the ω-3 fatty acids group and 15 patients (33%) in the placebo group after 24 months (P = .73).
The results from this study did not show any beneficial effects of ω-3 fatty acid supplementation on disease activity in multiple sclerosis as a monotherapy or in combination with interferon beta. This is in contrast to 2 other studies reporting a possible positive effect of ω-3 fatty acids in multiple sclerosis.20,21 However, these 2 studies were not restricted to ω-3 fatty acid supplementation, possibly influencing the results. Only 2 double-blind, parallel-group studies have been performed on ω-3 fatty acid supplementation in multiple sclerosis, both with largely inconclusive results.8,9 Both groups in these studies were instructed to restrict saturated fatty acid intake, which theoretically could have influenced the outcome. A number of studies have indicated that the intake of saturated fatty acids is an independent predictor of multiple sclerosis mortality.7 Another limitation to these studies was that MRI activity was not implemented as an outcome measure. Disability measures are often sensitive to changes occurring over relatively short intervals. Magnetic resonance imaging end points are more sensitive and have been demonstrated to give an adequate statistical power to detect actual group differences, even with a short study duration and relatively low number of participants.22 Despite inclusion of repeated MRI measures in our study, we found no positive effect of ω-3 fatty acid supplementation on MRI activity and no effect on any of the other predefined secondary end points.

The design of this study allowed us to compare the effect of ω-3 fatty acid supplementation both against placebo alone and in combination with interferon beta. As expected, the MRI disease activity was significantly reduced when interferon beta-1a was introduced. This was in accordance with the previously documented effect of interferon beta in multiple sclerosis.5,6,8,9 Although ω-3 fatty acid supplementation given as monotherapy or in combination with interferon beta had no effect on any of the measured parameters, our data do not suggest that ω-3 fatty acid supplementation was harmful or interfered with the interferon beta treatment. Our study was limited to a total follow-up of 24 months comprising 6 months receiving ω-3 fatty acids only and 18 months receiving a combination treatment with interferon beta. Even though this should allow sufficient time to detect major differences in MRI disease activity, the follow-up time could have been too short to detect actual differences in clinical disease activity related to relapse and disability progression.

An important limitation in this study could be that the sample size did not have sufficient power to detect small and medium treatment effect sizes, both with respect to MRI and clinical disease activity. However, the lack of even a trend in favor of the ω-3 fatty acid treatment arm on MRI or clinical disease activity makes it unlikely that there could be any significant short- or long-term influence of ω-3 fatty acid supplementation in multiple sclerosis.

Treating the patients with ω-3 fatty acids or placebo only, without interferon beta, for 6 months could be considered an ethical problem. In practical terms, the interferon beta treatment delay was not 6 months but rather 2 to 4 months, because ordinary immunomodulatory treatment in Norway needed a formal application for reimbursement at the time when the study was conducted. The interval from when the application was filed until the reimbursement was granted varied from 2 to 6 months, with large regional differences throughout Norway, during the study period. In addition, patients with very active disease were not included in the study and the study protocol included rescue therapy (initiation of interferon beta treatment) for patients with a high disease activity during the first 6 months of the study.

The corn oil capsules used as placebo in this study contained 52% linoleic acid, 33% oleic acid, and 13% saturated acids. This is a standard formula used in most randomized controlled trials of ω-3 fatty acids.23,24 Theoretically, both linoleic and oleic acid could have anti-inflammatory properties that could have caused confounding.7 Earlier studies of polyunsaturated fatty acid supplementation have largely used olive oil as placebo.8,9,22-27 Although olive oil is generally considered to be relatively inert, there is also some evidence that it could inhibit nuclear factor κB activation28 and thus have immunomodulatory properties. A number of clinical trials have assessed the efficacy of supplementing with the ω-6 linoleic and γ-linolenic fatty acids.23,25-27,29,30 Although most of these studies have demonstrated no effect of linoleic acid on relapse rate or disease progression,23,25-27,29,30 1 study found a significant improvement in relapse severity in the group given 17.2 g of linoleic acid per day compared with oleic acid.20 Although linoleic acid seems to have no major effect on disease progression,31 we cannot rule out that high doses of linoleic acid could have a small therapeutic effect in multiple sclerosis. However, in our study, the placebo dosage of linoleic and oleic acid was only minor compared with a usual diet intake and much lower than used in the previous intervention studies with ω-6 fatty acids. A typical western diet has an ω-6:ω-3 fatty acid ratio of 10 to 30:1 and the regular daily intake of both linoleic and oleic acid in Norway is so high that the amount found in the placebo capsules adds insignificant amounts to the total intake. This was also confirmed in the serum measurements of ω-6 serum phospholipid fatty acids, demonstrating that the patients in the placebo group experienced no elevation in serum levels of ω-6 fatty acids at any points (eTable 3). Thus, it seems unlikely that the choice of placebo could interfere with the interpretation of our results.

In conclusion, this randomized, double-blind, placebo-controlled trial provides class I evidence that ω-3 fatty acid supplementation has no beneficial effects on disease activity in relapsing-remitting multiple sclerosis as a monotherapy or in combination with interferon beta-1a.

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Author Contributions: Drs Torkildsen and Wergeland contributed equally to this study. Drs Torkildsen, Wergeland, Olsen, and Myhr had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Dr Myhr, the principal investigator, wrote the protocol and the study was overseen by a steering committee. Dr Torkildsen had full access to all of the data in the study and had the final responsibility for the decision to submit for publication.

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