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Original article

# The effect of phosphatidylserine containing Omega3 fatty-acids on attention-deficit hyperactivity disorder symptoms in children: A double-blind placebo-controlled trial, followed by an open-label extension☆

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ABSTRACT

*Objective:* To study the efficacy and safety of phosphatidylserine (PS) containing Omega3 long-chain polyunsaturated fatty acids attached to its backbone (PS-Omega3) in reducing attention-deficit/hyperactivity disorder (ADHD) symptoms in children.
*Method:* A 15-week, double-blind, placebo-controlled phase followed by an open-label extension of additional 15 weeks. Two hundred ADHD children were randomized to receive either PS-Omega3 or placebo, out of them, 150 children continued into the extension. Efficacy was assessed using Conners' parent and teacher rating scales (CRS-P,T), Strengths and Difficulties Questionnaire (SDQ), and Child Health Questionnaire (CHQ). Safety evaluation included adverse events monitoring.
*Results:* The key finding of the double-blind phase was the significant reduction in the Global:Restless/impulsive subscale of CRS-P and the significant improvement in Parent impact-emotional (PE) subscale of the CHQ, both in the PS-Omega3 group. Exploratory subgroup analysis of children with a more pronounced hyperactive/impulsive behavior, as well as mood and behavior-dysregulation, revealed a significant reduction in the ADHD-Index and hyperactive components. Data from the open-label extension indicated sustained efficacy for children who continued to receive PS-Omega3. Children that switched to PS-Omega3 treatment from placebo showed a significant reduction in subscales scores of both CRS-P and the CRS-T, as compare to baseline scores. The treatment was well tolerated.
*Conclusions:* The results of this 30-week study suggest that PS-Omega3 may reduce ADHD symptoms in children. Preliminary analysis suggests that this treatment may be especially effective in a subgroup of hyperactive-impulsive, emotionally and behaviorally-dysregulated ADHD children.


## 1. Introduction

Attention deficit hyperactivity disorder (ADHD) is a common neurobehavioural disorder affecting 3 to 7% of school-aged children. ADHD can be categorized into three main subtypes according to predominant behavioral features: primarily inattentive, primarily hyperactive-impulsive, and mixed presentation. Although characterized as a childhood disorder, ADHD frequently persists into adolescence in 40 to 70% of cases and into adulthood in 50% of cases [23]. ADHD is a chronic neurological disorder with a complex etiology. Behavioral genetic investigations and twin studies have suggested that it is a highly heritable disorder, and several genes have been linked to its occurrence [14,37]. In addition, various environmental factors such as maternal smoking, excessive alcohol consumption, or preterm birth have been associated with ADHD [1,46].

Phosphatidylserine (PS), an acidic phospholipid (PL) molecule, comprises of a glycerol backbone esterified to the hydroxyl group of the amino acid serine via a phosphate group and to two fatty acids moiety. PS is found mainly in animal innards and in plants, the origin, however, determines the fatty acids composition at position *sn*-1 and 2. Plant-derived PS differs from animal-derived PS mainly in the absence of Omega3 long chain polyunsaturated fatty acids (LC-PUFA). PS has a structural role in maintaining the integrity of cell membranes [30] and was shown to affect multiple neurochemical systems, including the dopaminergic and cholinergic systems [2,8,9,28,44,48]. PS is the most effective acidic PL in

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activating protein kinase C [24] and stimulates sodium-potassium dependent ATPases [39]. In addition, PS supplementation increases brain glucose concentration independent of an increase in blood glucose levels [8]. The precise mechanism of action of PS, however, remains unclear. At the clinical level, PS attenuates both physical [22] and mental stress [3,18], which is suggested to be mediated mainly through a reduction in cortisol secretion. Additionally, administration of PS to elderly with age-associated memory impairment, as well as to patients with mild cognitive impairment, results in a consistent improvement in memory test performance [10,12]. Most of the abovementioned PS scientific evidence is based on PS purified from bovine cortex (BC-PS); however, this source which is relatively highly enriched in Omega3 LC-PUFA is no longer available due to safety concerns of the risk for prion contamination.

Similar to PS, Omega3 LC-PUFA have been linked to brain and central nervous system functioning [25,33–35] and a deficiency in Omega3 fatty acids in rats and monkeys is associated with behavioral, sensory, and neurological dysfunction [13,32,47].

The bioavailability of LC-PUFA has been suggested to vary based on its carrier. Wijendran et al. reported that dietary LC-PUFAs attached to PL rather than to triacylglycerol (TG) backbone are more effective substrates for brain tissues accretion in term baboons [45]. Similar results were shown also in mice [20,21]. Similarly, supplementing middle-aged rats with Omega3, mainly Eicosapentaenoic (EPA, C20:5 Omega3) and Docosahexaenoic acid (DHA, C22:6 Omega3) attached to either TG or PL resulted in increased accretion of DHA in brain tissues in the PL-treated group (17 and 42% as compared with control oil-fed rats, respectively) [42]. Improved bioavailability of LC-PUFA conjugated to PL has also been demonstrated for other tissues including liver, lung, plasma, and erythrocytes [7,29,40,45].

Recently, the effect of administration of PL containing Omega3 (PL-Omega3) LC-PUFA, as compared to fish oil, on the executive functions of school children with ADHD was reported [41]. In this study, children received placebo, fish oil or PL-Omega3 (providing 300 mg PS and 250 mg EPA/DHA daily) for 3 months. Efficacy was evaluated using the Test of Variables of Attention (TOVA). Study findings showed a marked improvement in visual sustained attention performance in the PL-Omega3 group, in comparison to both placebo and fish oil supplementation. Additionally, the group of children receiving PL-Omega3 had the highest proportion of children whose symptoms improved, with 11/18 of the PL-Omega3 children becoming asymptomatic versus 3/21 and 7/21 of the control and fish-oil treated children, respectively.

In the present exploratory study, we evaluated the effect of PS-Omega3 in reducing ADHD symptoms in children in a two-phase study: double-blind, placebo-controlled followed by an open-label extension, each consisting of 15 treatment weeks. Children were monitored for their ADHD symptoms through 30 weeks.

## 2. Subjects and methods

The efficacy and tolerability of PS-Omega3 were initially examined in a 15-week, double-blind, placebo controlled phase (week 0 through week 15) that was subsequently followed by a 15-week open-label extension period (week 15 through week 30).

### 2.1. Participants

Two hundred participants entered the double-blind phase (133 boys and 67 girls), out of them, 150 continued into the open-label extension. Children aged between 6 and 13 with normal weight and height measurements according to the Israeli standard and who regularly attended school were included if they met the following criteria:

a) confirmed DSM-IV-ADHD diagnosis following assessment by the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime (K-SADS-PL) Version 1 [36];
b) a score of at least 1.5 standard deviations above the normal for the patient's age and gender in the Teacher-rated ADHD Rating Scale-IV (RS-IV) School Version;
c) a score of 4 or higher (moderately ill or worse) in the Clinical Global Impression of Severity of Illness (CGI-S) test;
d) willingness of the parent and a teacher who is familiar with the child to participate.

Children were excluded from the study if any of the following conditions existed:

a) girls who reached menarche and presented with three previous regular menstrual cycles;
b) history or current diagnosis of any serious systemic (e.g., diabetes, hyper/hypothyroidism) or neurological condition (e.g., epilepsy, brain tumor);
c) failure to respond to two or more adequate courses of stimulant therapy (among those previously treated children);
d) pervasive developmental disorder (diagnosed according to DSM-IV criteria) or nonverbal learning disability [19,26];
e) diagnosed with psychotic disorders (e.g., schizophrenia) according to the DSM-IV axis;
f) any evidence of suicidal risk or any current psychiatric comorbidity that required psychiatric pharmacotherapy;
g) concomitant use of prescription or nonprescription agents with potent psychotropic properties, including ADHD treatments and dietary supplements, 4-week prior to the study entry;
h) history of alcohol or substance abuse as defined by DSM-IV criteria;
i) consumption of $>$ 250 mg/day of caffeine;
j) history of allergic reactions or sensitivity to marine products, soy, or corn as well as any illness that could jeopardize the participant's health or limit their successful completion of the trial.

Children suffering from ADHD symptoms were recruited using advertisements in newspapers, on the Internet, and in medical centers. The study was conducted according to the principles of the Declaration of Helsinki and good clinical practice and was approved by the Israeli Health Ministry and the institutional review board committee of the Geha Mental Health Center (Petach Tikva, Israel). All parents or legal guardians and children gave their written informed consent prior to participation. Inclusion assessment tools were conducted by a qualified and experienced psychiatrist (K-SADS-PL and CGI-S) or by a psychiatric social worker (K-SADS-PL).

### 2.2. Study design

The design was a single-center, randomized, double-blind, placebo-controlled phase followed by an open-label extension. Participants were randomly assigned to the study groups according to a computerized randomization process based on random block size using a 2:1 ratio (PS-Omega3: placebo) and stratified by gender. A web-based random allocation procedure was used to enhance the concealment and ease of use.

During the double-blind phase participants received four capsules (two capsules twice a day) of PS-Omega3 or an identical-looking capsule filled with cellulose as placebo. The

daily PS-Omega3 dosage provided 300 mg of PS and 120 mg of EPA + DHA (EPA/DHA ratio of 2:1).

Efficacy measures were conducted at each visit-every 5-weeks, (except for CHQ, conducted at baseline and at endpoint). Safety measures were assessed at baseline and at endpoint (except for vital sign measurements, assessed each visit).

Throughout the open-label extension all participants received two capsules of PS-Omega3 daily which provided 150 mg of PS and 60 mg of EPA + DHA. Efficacy and safety measures were assessed at baseline and endpoint (except for vital sign measurements, assessed also at week 22). For treatment adherence monitoring, participants returned all treatment packs at each visit, and adherence was calculated using the number of remaining capsules. PS-Omega3 (Vayarin™) was supplied by Enzymotec Ltd. (Migdal HaEmeq, Israel).

### 2.3. Efficacy measures

The primary efficacy measure of the study was the Conners' Teacher Rating Scale Revised Long-Hebrew Version (CRS-T) [11]. This questionnaire, answered by the child's teacher, assesses symptoms of ADHD in children and adolescents according to the DSM-IV guidelines. Other assessments included the Conners' Parent Rating Scale Revised Long-Hebrew Version (CRS-P), which is answered by the child's parent and the Strength and Difficulties Questionnaire (SDQ) home and school versions which is a brief behavioral screening questionnaire [16,17]. Quality of life was assessed by the Child Health Questionnaire (CHQ-PF50) [27] which assesses physical and psychosocial concepts related to child's well-being; impact of the child's health on their parents' quality of life and the impact on family situations.

### 2.4. Safety measures

Safety measures included assessment of vital signs (resting diastolic and systolic blood pressure and heart rate), physical parameters (weight and height), and physical examination (chest, heart, lungs, abdomen, lymph, ear/nose/throat, limbs, skin, neurological, and electrocardiography). Adverse events assessment included a physician interview with the child and parent (assessed every visit) and a telephone interview conducted by a research associate or a physician (every other week).

### 2.5. Statistical analysis

Results are expressed as mean ± standard deviation (SD). Student's *t*-test was used to evaluate differences in demographic and baseline continuous variables, and in the CHQ between the two study groups. Pearson's $Chi^2$ test was used for the analysis of categorical variables and CGI-S. Intervention effect was tested using an Analysis of Covariance Model (ANCOVA). The main outcomes were change from baseline in CRS-T and CRS-P scores. The covariates submitted to the model were gender, dichotomized (10.5 and 10.5 + ) age, and dichotomized (62 and 62 + ) baseline scores in ADHD and DSM-IV total indexes of the CRS-P. Indicators were added to the ANCOVA along with the group interaction term. The interaction was considered statistically significant when $p < 0.15$. Evaluation of interactions was followed by an exploratory subgroup analysis. Within each treatment arm, the effect was tested using paired Student's *t*-test analysis. All hypotheses were two-sided, and $p < 0.05$ was considered to be significant. Due to the nature of the study, no corrections for multiple testing were applied to the secondary outcomes. All available data was included in the analysis of the intent-to-treat (ITT) population.

Data from the open-label extension was analysed by the participants' randomisation to treatment or placebo in the prior double-blind phase.

Power calculations were based in part on analysis of Conners' parent rating scale reported in a previous trial conducted with PS-Omega3 [41].

Power calculations indicated that group sizes of 104:52 PS-Omega3:Placebo would give at least 80% power at the 0.05 significance level to detect a moderate effect of 3 points reduction in Conners' rating scale. Assuming a 30% attrition rate over the course of the study, a total of 200 participants were targeted for inclusion in the study.

The SPSS (version 18) statistical package was used for all analyses. The statistical analyses were performed by Integristat Biostatistic Services (Tel Aviv, Israel).

## 3. Results

### 3.1. Double-blind phase

A flow chart describing the selection of participants in the double-blind phase is presented in Fig. 1. Of the 247 children screened, 200 met the entry criteria and were randomized to receive PS-Omega3 or placebo. Dropouts were similarly distributed over the PS-Omega3 and placebo groups (20 and 18%, respectively), and the reasons for discontinuation were generally similar across the treatment groups. Out of the 162 participants who completed the double-blind phase, 15 were excluded from the per-protocol (PP) analysis (five from the placebo group and 10 from the PS-Omega3 group); one due to protocol violation and the rest failed to meet the predefined compliance criteria (≥ 65%). The treatment groups were comparable with respect to all the examined demographic and baseline variables (Table 1). The most common comorbid diagnosis was oppositional defiant disorder (8.8%). Among the previously diagnosed children, 25 were not treatment naive (18 in the PS-Omega3 and 7 in the placebo group). Additionally, there were no significant differences between participants who were excluded from the PP analysis and those included in the PP group (data not shown).

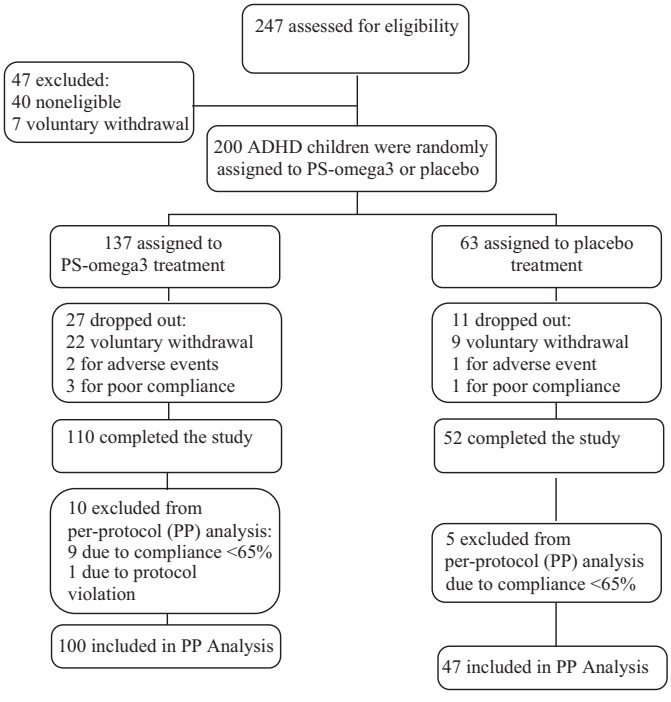


**Fig. 1.** A total of 200 participants were randomized to receive PS-Omega3 or placebo treatment. Study completers ($n = 162$) included participants who completed 15 weeks of treatment. Participants who dropped out or failed to adhere to the study protocol were not included in the efficacy analysis.

**Table 1**
Demographic and clinical baseline characteristics of cohort.

| | PS-Omega3 ($n=100$) | Placebo ($n=47$) | $P$ value |
|---|---|---|---|
| *Demographic Characteristics* | | | |
| Age, $y$ (mean [SD]) | 9.2 [2.0] | 9.2 [1.8] | 0.993 |
| Males, $n$ (%) | 72 (72) | 32 (68) | 0.635 |
| *Clinical Characteristics* | | | |
| Previous ADHD diagnosis, $n$ (%) | 52 (52) | 23 (49) | 0.729 |
| ADHD Subtype, $n$ (%) | | | |
| Hyperactive/Inattentive | 66 (66) | 31 (66) | 0.472 |
| Inattentive | 31 (31) | 16 (34) | |
| Hyperactive | 3 (3) | 0 (0) | |
| CGI-S, $n$ (%) | | | |
| Score of 6 - Extremely seriously ill | 2 (2) | 0 (0) | 0.451 |
| Score of 5 - Seriously ill | 37 (37) | 21 (45) | |
| Score of 4 - Moderately ill | 61 (61) | 26 (55) | |
| Comorbid condition present $n$ (%) | 20 (20) | 8 (17) | 0.668 |
| Oppositional defiant disorder | 11 (11) | 2 (4) | |
| Enuresis | 2 (2) | 1 (2) | |
| Tic disorder | 3 (3) | 1 (2) | |
| Anxiety disorder | 2 (2) | 2 (4) | |
| Social anxiety | 2 (2) | 0 (0) | |
| Specific phobia | 2 (2) | 0 (0) | |
| Conduct disorder | 1 (1) | 0 (0) | |
| Encopresis | 0 (0) | 1 (2) | |
| Obsessive compulsive disorder | 0 (0) | 1 (2) | |

ADHD: Attention Deficit Hyperactivity Disorder; CGI-S: Clinical Global Impression of Severity; $P$ value is based on Student's $t$-test for continuous variables and Pearson's $Chi^2$ for categorical variables.

### 3.1.1. Per-protocol cohort

Efficacy outcomes of the PP cohort are summarized in Table 2. Baseline scores were similar in the PS-Omega3 and placebo groups. Within group analysis showed that scores of two CRS-T subscales, the Global: Emotional lability and DSM-IV: Inattentive, were significantly reduced in the PS-Omega3 group. Nonetheless, there was no significant difference between the PS-Omega3 and placebo group in the mean change from baseline of any of the CRS-T subscales. A reduction in ADHD symptoms was also observed in the parent within group evaluation; the scores of all CRS-P subscales significantly decreased at endpoint in the PS-Omega3 group, as compared to three subscales in the placebo group. Importantly, in the CRS-P, between groups comparison showed a significant reduction in the Conners' Global: Restless/impulsive subscale for the PS-Omega3 treated group, as compared to the placebo group ($p = 0.047$). In addition, the treatment group demonstrated a greater numerical decrease in other CRS-P parameters in comparison to the placebo group, particularly in the ADHD-Index and DSM-IV:Inattentive subscale; however, these reductions failed to reach statistical significance.

In the analysis of quality of life, as assessed by the CHQ, there were significant favorable effects observed in the Family activities and the Parent Impact-emotional subscales in the PS-Omega3 group but not in the placebo group, as compared to baseline. The improvement in the latter subscale was relatively small (20%) but significant as compared to the placebo group ($p = 0.022$). No significant differences between treatment arms were observed for the remaining CHQ subscales or for any of the SDQ subscales (data not shown). Similarly, no significant beneficial effects were observed in the ITT analysis.

### 3.1.2. Subgroup analysis

Based on the PP findings, which suggested a possible treatment effect on restless and impulsive behavior, and since ADHD boys were reported to exhibit increased hyperactive/impulsive behavior as compared to girls [4,5,15], we performed an initial gender based analysis aimed to identify a subgroup of children suspected to be more responsive to treatment based on their specific clinical features. Change from baseline analysis showed that the subgroup of boys preferentially benefited from the treatment as compared to

**Table 2**
Efficacy outcomes of per-protocol cohort at baseline and endpoint (mean ± SD).

| | PS-Omega3 | | | | Placebo | | | | $P$ value |
|---|---|---|---|---|---|---|---|---|---|
| | $N$ | Median | Baseline Mean ± SD | Change Mean ± SD | $N$ | Median | Baseline Mean ± SD | Change Mean ± SD | |
| *CRS-T* | | | | | | | | | |
| Oppositional | 92 | 51 | 58.55 ± 14.34 | −0.02 ± 11.98 | 40 | 56 | 60.53 ± 14.42 | 0.18 ± 12.32 | 0.761[a] |
| Hyperactivity | 92 | 61 | 62.74 ± 13.85 | −1.32 ± 10.13 | 40 | 62 | 63.20 ± 9.53 | −1.73 ± 9.28 | 0.845[a] |
| ADHD-Index | 93 | 66 | 66.37 ± 11.81 | −1.80 ± 9.97 | 42 | 69 | 68.10 ± 10.39 | −2.21 ± 11.29 | 0.674[a] |
| Global:Restless/impulsive | 93 | 64 | 64.70 ± 11.89 | −0.44 ± 10.07 | 40 | 65 | 65.55 ± 8.83 | −1.73 ± 10.54 | 0.849[a] |
| Global:Emotional lability | 93 | 57 | 60.61 ± 14.30 | −2.63 ± 11.37[c] | 41 | 53 | 59.78 ± 14.71 | −0.63 ± 11.33 | 0.276[a] |
| DSM-IV:Inattentive | 94 | 64 | 63.66 ± 10.21 | −1.70 ± 8.07[c] | 41 | 65 | 64.80 ± 9.74 | −2.17 ± 10.23 | 0.947[a] |
| DSM-IV:Hyperactive-impulsive | 93 | 60 | 61.15 ± 13.29 | −0.62 ± 10.52 | 41 | 63 | 60.9 ± 9.55 | −0.46 ± 7.99 | 0.564[a] |
| DSM-IV: Total | 94 | 62 | 63.65 ± 10.84 | −1.00 ± 8.57 | 42 | 65 | 64.43 ± 8.69 | −1.62 ± 8.87 | 0.898[a] |
| *CRS-P* | | | | | | | | | |
| Oppositional | 99 | 60 | 62.10 ± 11.21 | −3.12 ± 10.25[d] | 42 | 61 | 63.05 ± 13.36 | −3.43 ± 12.26 | 0.987[a] |
| Hyperactivity | 99 | 68 | 67.14 ± 12.66 | −4.29 ± 11.39[e] | 42 | 62 | 64.64 ± 10.67 | −2.69 ± 10.90 | 0.368[a] |
| ADHD-Index | 98 | 70 | 69.33 ± 9.87 | −5.36 ± 9.46[e] | 42 | 69 | 69.36 ± 9.23 | −3.10 ± 9.61[c] | 0.110[a] |
| Global:Restless/impulsive | 99 | 69 | 67.21 ± 10.61 | −5.19 ± 9.93[e] | 42 | 62 | 64.24 ± 9.87 | −1.71 ± 11.14 | 0.047[a] |
| Global:Emotional lability | 94 | 57 | 60.39 ± 12.39 | −3.54 ± 10.47[d] | 41 | 57 | 60.76 ± 13.75 | −5.56 ± 11.56[d] | 0.353[a] |
| DSM-IV:Inattentive | 99 | 67 | 67.71 ± 11.17 | −4.97 ± 9.79[e] | 42 | 68 | 68.19 ± 11.07 | −2.74 ± 9.05 | 0.131[a] |
| DSM-IV:Hyperactive-impulsive | 99 | 69 | 67.35 ± 13.02 | −4.23 ± 11.44[e] | 42 | 65 | 65.86 ± 11.04 | −2.62 ± 11.50 | 0.330[a] |
| DSM-IV: Total | 99 | 70 | 68.85 ± 10.88 | −4.86 ± 10.06[e] | 42 | 68 | 68.67 ± 9.79 | −2.95 ± 9.44[c] | 0.198[a] |
| *CHQ* | | | | | | | | | |
| Emotional Impact on Parent | 97 | 50 | 48.8 ± 17.80 | 9.45 ± 21.17[e] | 46 | 50 | 52.9 ± 16.5 | 0.72 ± 20.77 | 0.022[b] |
| Family Activities | 97 | 67 | 68.08 ± 20.86 | 4.59 ± 17.99[c] | 46 | 81 | 75.92 ± 19.68 | −1.01 ± 16.42 | 0.076[b] |
| Physical Summary | 94 | 56 | 54.85 ± 6.45 | 0.93 ± 6.55 | 44 | 55 | 53.66 ± 9.03 | 2.41 ± 10.01 | 0.302[b] |
| Psychosocial Summary | 94 | 40 | 39.99 ± 9.22 | 1.25 ± 9.55 | 44 | 40 | 40.75 ± 8.4 | 1.37 ± 10.26 | 0.944[b] |

CRS-T: Conners' Rating Scale–Teachers version; CRS-P: Conners' Rating Scale–Parents version; CHQ: Child Health Questioner.
[a] Based on analysis of covariance controlled for gender, age, and baseline scores in CRS-P total indexes.
[b] Based on two-sided $t$-test for independent samples.
[c] $p \leq 0.05$ significance based on paired $t$-test.
[d] $p \leq 0.01$ significance based on paired $t$-test.
[e] $p \leq 0.001$ significance based on paired $t$-test

**Table 3**
Demographic and clinical baseline characteristics of children included in the subgroup cohort compared to those excluded.

| | Excluded ($n=69$) | Included ($n=78$) | *P* value |
|---|---|---|---|
| *Demographic Characteristics* | | | |
| Age, *y* (mean [SD]) | 9.1 [1.9] | 9.3 [1.9] | 0.590 |
| Males, *n* (%) | 47 (68) | 57 (73) | 0.509 |
| *Clinical Characteristics* | | | |
| Previous ADHD diagnosis, *n* (%) | 34 (49) | 41 (53) | 0.691 |
| ADHD Subtype, *n* (%) | | | |
| Hyperactive/Inattentive | 38 (55) | 59 (76) | 0.003 |
| Inattentive | 31 (45) | 16 (20) | |
| Hyperactive | 0 (0) | 3 (3.8) | |
| CGI-S, *n* (%) | | | |
| Score of 6 - Extremely seriously ill | 1 (1.4) | 1 (1.3) | 0.108 |
| Score of 5 - Seriously ill | 21 (30) | 37 (47) | |
| Score of 4 - Moderately ill | 47 (68) | 40 (51) | |

ADHD: Attention Deficit Hyperactivity Disorder; CGI-S: Clinical Global Impression of Severity; *P* value is based on Student's *t*-test for continuous variables and Pearson's $Chi^2$ for categorical variables.

the placebo, while there was no significant effect observed in girls. A significant reduction in the Conners' teacher DSM-Inattentive subscale score was observed for the PS-Omega3-treated subgroup of boys as compared to placebo (mean change from baseline ± S.D; $-2.62 \pm 7.59$ and $0.46 \pm 6.54$, respectively; $p = 0.031$), while a favorable treatment associated effect was found in the ADHD-index ($-2.82 \pm 9.38$ and $0.21 \pm 7.87$, respectively) and DSM-Total subscale ($-2.06 \pm 7.82$ and $0.45 \pm 5.97$, respectively); however, these did not reach statistical significance ($p = 0.059$ and $p = 0.052$, respectively).

Based on the possible treatment effect observed on restless and impulsive behavior and the initial gender based analysis, we wished to explore whether children with certain characteristics of the disorder respond differently to treatment. More specifically, we explored whether children rated with an abnormal (> 62) score in at least two of the Conners' subscales: Oppositional, Hyperactivity, ADHD-index, or Global: Emotional lability might show a different treatment response. This group was added as an indicator to the statistical model along with the group interaction term. The interaction was found statistically significant ($p < 0.15$) in four out of the eight CRS-P subscales presented (ADHD-Index $p = 0.05$, Global:Restless/impulsive $p = 0.1$, DSM-IV:Inattentive $p = 0.074$, DSM-IV:Total $p = 0.124$). These interesting interactions encouraged us to conduct an exploratory subgroup analysis of more labile and hyperactive children who tended to suffer from mood and behavior dysregulation.

A total of 78 children (50 in the PS-Omega3 group and 28 in the placebo group) were assigned to this subgroup. Table 3 summarizes the demographic and clinical characteristics of the children included in the subgroup as compared to those who were excluded. As expected, the ADHD subtype of the included children was significantly different from that of the excluded children. No significant differences were observed between the treatment and placebo groups regarding age, gender, and a previous ADHD diagnosis (data not shown). The subgroup efficacy outcomes are summarized in Table 4. PS-Omega3 treatment resulted in a significant reduction in ADHD symptoms as demonstrated by both the parent and teacher Conners' rating scales. Within group analysis revealed a significant reduction in all CRS subscale scores in the PS-Omega3 group except for the Oppositional subscale, while no significant changes were observed in the placebo group. Comparison between study arms revealed a significant treatment effect on the CRS-T. A reduction was observed in the ADHD-index ($p = 0.036$) and DSM-IV:Hyperactivity-impulsivity subscale ($p = 0.039$). Likewise, PS-Omega3 treatment showed statistically significant benefits in the Conners' parent version. The scores in ADHD-index ($p = 0.020$), Global: Restless/impulsive ($p = 0.014$), DSM-IV: inattentive ($p = 0.027$) and DSM-IV: total score ($p = 0.044$) were markedly reduced in the PS-Omega3 group, as compared to those in the placebo group. These results were further supported by the significant benefit observed in the CHQ Parent Impact-emotional subscale ($p = 0.004$). No

**Table 4**
Efficacy outcomes of subgroup cohort at baseline and endpoint (mean ± SD).

| | PS-Omega3 | | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | *N* | Median | Baseline Mean± SD | Change Mean± SD | *N* | Median | Baseline Mean ± SD | Change Mean ± SD | *P* value |
| *CRS-T* | | | | | | | | | |
| Oppositional | 46 | 66 | 68.41 ± 14.18 | −3.52 ± 12.47 | 23 | 65 | 68.70 ± 13.60 | −1.52 ± 14.85 | 0.639[a] |
| Hyperactivity | 47 | 72 | 73.85 ± 9.56 | −5.06 ± 9.77 | 24 | 69 | 68.08 ± 8.34 | −1.63 ± 9.49 | 0.122[a] |
| ADHD-Index | 47 | 76 | 74.68 ± 9.17 | −4.57 ± 8.66 | 25 | 71 | 69.52 ± 9.45 | 0.20 ± 7.97 | 0.036[a] |
| Global:Restless/impulsive | 47 | 74 | 73.26 ± 9.44 | −3.28 ± 8.60 | 25 | 66 | 67.80 ± 7.48 | −0.40 ± 7.63 | 0.192[a] |
| Global:Emotional lability | 47 | 68 | 69.23 ± 13.18 | −5.64 ± 9.78 | 25 | 64 | 66.68 ± 13.35 | −1.24 ± 12.52 | 0.082[a] |
| DSM-IV:Inattentive | 47 | 68 | 67.51 ± 10.41 | −2.85 ± 8.31 | 24 | 67 | 66.08 ± 9.00 | −1.04 ± 8.17 | 0.453[a] |
| DSM-IV:Hyperactive-impulsive | 47 | 71 | 70.96 ± 9.42 | −3.70 ± 11.36 | 25 | 66 | 67.24 ± 7.80 | 0.96 ± 6.86 | 0.039[a] |
| DSM-IV: Total | 46 | 72 | 68.41 ± 14.18 | −3.15 ± 8.49 | 23 | 68 | 68.70 ± 13.60 | −0.52 ± 7.21 | 0.221[a] |
| *CRS-P* | | | | | | | | | |
| Oppositional | 50 | 61 | 62.22 ± 11.24 | −2.62 ± 10.25 | 23 | 58 | 61.04 ± 13.34 | −1.35 ± 12.03 | 0.484[a] |
| Hyperactivity | 50 | 70 | 68.54 ± 13.11 | −5.02 ± 11.85 | 23 | 62 | 65.57 ± 11.25 | −1.09 ± 12.64 | 0.129[a] |
| ADHD-Index | 49 | 71 | 70.14 ± 10.04 | −5.61 ± 9.51 | 23 | 69 | 67.09 ± 9.86 | −0.22 ± 9.34 | 0.020[a] |
| Global:Restless/impulsive | 50 | 70 | 68.50 ± 11.42 | −4.98 ± 10.31 | 23 | 61 | 62.52 ± 10.15 | 1.30 ± 12.07 | 0.014[a] |
| Global:Emotional lability | 48 | 57 | 59.67 ± 12.10 | −4.28 ± 10.62 | 23 | 56 | 58.04 ± 13.00 | −4.73 ± 13.13 | 0.861[a] |
| DSM-IV:Inattentive | 50 | 67 | 67.62 ± 11.42 | −5.20 ± 9.73 | 23 | 66 | 65.00 ± 11.06 | −0.09 ± 9.29 | 0.027[a] |
| DSM-IV:Hyperactive-impulsive | 50 | 71 | 68.90 ± 13.29 | −5.26 ± 10.87 | 23 | 67 | 67.26 ± 11.92 | −1.30 ± 13.67 | 0.107[a] |
| DSM-IV: Total | 50 | 70 | 69.68 ± 11.01 | −5.66 ± 9.74 | 23 | 68 | 67.57 ± 10.40 | −1.13 ± 10.78 | 0.044[a] |
| *CHQ* | | | | | | | | | |
| Emotional Impact on Parent | 49 | 50 | 48.3 ± 19.62 | 10.88 ± 23.15 | 28 | 50 | 55.06 ± 17.47 | −4.46 ± 19.31 | 0.004[b] |
| Family Activities | 49 | 75 | 71.7 ± 20.56 | 3.78 ± 18.56 | 28 | 81 | 78.3 ± 15.84 | −2.86 ± 16.9 | 0.124[b] |
| Physical Summary | 48 | 56 | 55.32 ± 5.88 | 1.25 ± 5.54 | 26 | 55 | 55.17 ± 5.31 | 2.29 ± 5.29 | 0.435[b] |
| Psychosocial Summary | 48 | 39 | 40.64 ± 10.2 | 1.08 ± 9.47 | 26 | 42 | 42.49 ± 7.73 | −0.21 ± 9.88 | 0.585[b] |

CRS-T: Conners' Rating Scale–Teachers version, CRS-P: Conners' Rating Scale–Parents version, CHQ: Child Health Questioner.
[a] Based on analysis of covariance controlled for gender and age.
[b] Based on two-sided *t*-test for independent samples.

significant differences between treatment arms were observed for any of the SDQ subscales (data not shown). No treatment associated effect was observed in the group of children not included in the selected subgroup (data not shown).

### 3.2. Open-label extension

Out of the 162 participants who completed the double-blind phase, 150 children enrolled into the open-label extension, 102 continued to receive PS-Omega3 from the double-blind phase, (hereafter referred to as PS-Omega3-continuous) and 48 were switched to PS-Omega3 after receiving placebo during the double-blind phase (hereafter referred to as PS-Omega3-naive). A total of 140 children completed the study, 127 of whom were included in the PP efficacy analysis. Twelve children were excluded due to failure to meet the mean compliance criteria ($\geq$ 65%) and one due to protocol violation.

#### 3.2.1. Phosphatidylserine-Omega3-continuous

For the group of participants that continued to receive PS-Omega3, a significant improvement in the CHQ Family Activities and Psychosocial Summary score was observed (mean change from baseline $\pm$ SD; $3.90 \pm 15.62$ and $1.88 \pm 7.99$, respectively) (Table 5).

#### 3.2.2. Phosphatidylserine-Omega3-naive

In the group of participants switching to PS-Omega3 after receiving placebo during the double-blind phase, a significant treatment effect was observed in both CRS-T and -P subscales in the open-label extension (Table 5). Specifically, two subscales of the CRS-T, demonstrated a significant reduction in mean change from baseline. The score of the Oppositional subscale declined by $4.21 \pm 7.38$ points ($p = 0.023$) and the Hyperactivity subscale score by $2.94 \pm 5.15$ ($p = 0.032$). All other subscales of the CRS-T resulted in lower scores at the endpoint compared to baseline, but the differences were not statistically significant.

In the CRS-P, a statistically significant mean reduction of approximately four points was observed in the Hyperactivity ($p = 0.032$), DSM-IV:Inattentive ($p = 0.013$), DSM-IV:Hyperactivity-impulsivity ($p = 0.021$), and in the DSM-IV:Total subscale score ($p = 0.007$), compared to baseline scores (Table 5). In addition, the scores of the Oppositional, ADHD-Index, and the Global Index:-Restless-impulsivity subscales tended to be reduced as well ($p = 0.077$, $p = 0.051$, and $p = 0.064$, respectively). No significant differences were observed in the CHQ.

## 4. Tolerability

The treatment was generally well tolerated; no major adverse events were noted by the study physicians and children maintained good health throughout the 30 treatment weeks. During the double-blind phase, 13 adverse events (in 12 participants) were classified as possibly or probably treatment-related in the PS-Omega3 group. These included six cases of gastrointestinal discomfort, one case each of atopic dermatitis, hyperactivity, tics, nausea, elevated serum glutamic oxaloacetic transaminase (SGOT) and two cases of tantrum episodes. In the placebo group, five adverse events (in five participants) were classified as possibly or probably treatment related. These included four cases of gastrointestinal discomfort and one case of headache. No significant findings were observed during physical examination or in vital signs or weight measurements. During the open-label extension, seven adverse events (in five participants) that were classified by the study physicians as possibly or probably treatment-related were recorded. These included three cases of gastrointestinal discomfort, one case each of headache, insomnia, high triacylglyceride level, and soft stools.

## 5. Discussion

This study aimed to evaluate, using both school and home rating scales, whether administration of PS-Omega3 may reduce ADHD symptoms in children. The study spanned over 30 weeks and consisted of a double-blind placebo-controlled phase followed by an open-label extension. In the double-blind phase, teachers failed to detect significant treatment effect, while a different

**Table 5**
PS-Omega3 continuous and naive groups: Baseline (week 15) and mean change from baseline efficacy outcomes (mean $\pm$ SD).

| | Open-label extension continuous group | | | | Open-label extension naive group | | | |
|---|---|---|---|---|---|---|---|---|
| | *N* | Baseline Mean $\pm$ SD | Change Mean $\pm$ SD | *P* value | *N* | Baseline Mean $\pm$ SD | Change Mean $\pm$ SD | *P* value |
| *CRS-T* | | | | | | | | |
| Oppositional | 45 | $57.51 \pm 12.95$ | $-1.38 \pm 10.39$ | 0.379 | 19 | $60.58 \pm 15.71$ | $-4.21 \pm 7.38$ | 0.023 |
| Hyperactivity | 40 | $58.68 \pm 12.21$ | $0.5 \pm 7.46$ | 0.674 | 17 | $61.35 \pm 10.34$ | $-2.94 \pm 5.15$ | 0.032 |
| ADHD-Index | 40 | $62.35 \pm 10.64$ | $0 \pm 8.62$ | 1.000 | 18 | $64.44 \pm 10.07$ | $-1.72 \pm 6.19$ | 0.254 |
| Global:Restless/impulsive | 39 | $61.97 \pm 10.98$ | $-0.59 \pm 8.99$ | 0.684 | 18 | $62.83 \pm 9.31$ | $-1.33 \pm 7.69$ | 0.472 |
| Global:Emotional lability | 43 | $58.05 \pm 13.11$ | $-1.33 \pm 9.62$ | 0.371 | 19 | $59.37 \pm 13.79$ | $-2.89 \pm 8.77$ | 0.168 |
| DSM-IV:Inattentive | 41 | $61.54 \pm 10.37$ | $-0.32 \pm 8.1$ | 0.803 | 17 | $60.94 \pm 8.38$ | $-1.35 \pm 8.57$ | 0.524 |
| DSM-IV:Hyperactive-impulsive | 41 | $57.68 \pm 12.13$ | $1.1 \pm 8.62$ | 0.420 | 18 | $60.67 \pm 9.71$ | $-1.83 \pm 9.08$ | 0.404 |
| DSM-IV: Total | 40 | $61.45 \pm 11.07$ | $0.4 \pm 7.64$ | 0.742 | 17 | $61.59 \pm 7.83$ | $-2.65 \pm 6.86$ | 0.131 |
| *CRS-P* | | | | | | | | |
| Oppositional | 87 | $58.85 \pm 12.21$ | $-1.41 \pm 9.43$ | 0.166 | 36 | $58.92 \pm 12.63$ | $-2.33 \pm 7.68$ | 0.077 |
| Hyperactivity | 87 | $62.45 \pm 12.57$ | $-1.15 \pm 9.88$ | 0.281 | 36 | $61.67 \pm 13.02$ | $-4.06 \pm 10.88$ | 0.032 |
| ADHD-Index | 87 | $64.05 \pm 10.21$ | $-0.95 \pm 7.91$ | 0.264 | 36 | $65.67 \pm 12.79$ | $-2.86 \pm 8.51$ | 0.051 |
| Global:Restless/impulsive | 87 | $61.77 \pm 10.25$ | $-0.09 \pm 7.35$ | 0.907 | 36 | $62.31 \pm 13.26$ | $-3.39 \pm 10.62$ | 0.064 |
| Global:Emotional lability | 81 | $56.44 \pm 12.07$ | $-0.57 \pm 10.67$ | 0.633 | 35 | $54 \pm 12.54$ | $-0.63 \pm 8.45$ | 0.663 |
| DSM-IV:Inattentive | 87 | $62.47 \pm 11.75$ | $-0.44 \pm 8.6$ | 0.637 | 36 | $64.83 \pm 12.89$ | $-3.75 \pm 8.58$ | 0.013 |
| DSM-IV:Hyperactive-impulsive | 87 | $62.85 \pm 12.28$ | $-1.41 \pm 9.4$ | 0.164 | 36 | $62.94 \pm 13.14$ | $-4.47 \pm 11.07$ | 0.021 |
| DSM-IV: Total | 87 | $63.69 \pm 11.59$ | $-1.1 \pm 8.83$ | 0.247 | 36 | $65.22 \pm 12.87$ | $-4.42 \pm 9.29$ | 0.007 |
| *CHQ* | | | | | | | | |
| Emotional Impact on Parent | 87 | $58.52 \pm 20.57$ | $-0.19 \pm 22.27$ | 0.936 | 38 | $55.7 \pm 20.24$ | $3.95 \pm 21.02$ | 0.254 |
| Family Activities | 87 | $72.25 \pm 20.1$ | $3.90 \pm 15.62$ | 0.022 | 38 | $77.41 \pm 18.67$ | $3.51 \pm 17.32$ | 0.219 |
| Physical Summary | 86 | $56.03 \pm 4.92$ | $-0.54 \pm 5.11$ | 0.328 | 38 | $55.4 \pm 5.74$ | $1 \pm 6.06$ | 0.316 |
| Psychosocial Summary | 86 | $41.44 \pm 10.1$ | $1.88 \pm 7.99$ | 0.032 | 38 | $98.39 \pm 5.91$ | $0.58 \pm 6.43$ | 0.578 |

CRS-T: Conners' Rating Scale–Teachers version; CRS-P: Conners' Rating Scale–Parents version; CHQ: Child Health Questioner; *P* values are based on Student's paired *t*-test.

pattern was observed in the parents' rating scales. A significant greater reduction was observed in the PS-Omega3 group in the restless/impulsive subscale of the Conners' parent scale, compared to the placebo group. In addition, a significant superiority was observed in the Parent impact-emotional subscale of CHQ. This subscale reflects the distress of the parents regarding their child's physical health, emotional well being, attention or learning abilities, ability to get along with others, and general behavior [27]. The significant effect in this subscale together with the greater improvement in the frequency of disruption in the family activity subscale might suggest an improvement in the child's quality of life following PS-Omega3 treatment. Another interesting preliminary finding is the identification of a subgroup of children who responded differently to the PS-Omega3 treatment. This subgroup included children with a more pronounced hyperactive and impulsive behavior. The corresponding CRS subscales related to this type of behavior were used to identify this subgroup: Oppositional subscale, which indicates that the child breaks rules, is easily annoyed, and has problems with authority; Hyperactive subscale, which indicates that the child has difficulties sitting still, has trouble focusing on a task, and is generally restless and impulsive; ADHD-index, which identifies children at risk for ADHD; and Conners' Global Index: emotional lability which indicates that the child is prone to emotional responses such as crying and anger. Interestingly, in this subgroup, a significant greater attenuation in ADHD symptoms was observed in both Conners' parent and teacher scales, especially in the ADHD-index and the hyperactive components. In addition, similar to the PP cohort a greater improvement in quality of life related parameters was observed in the PS-Omega3.

Efficacy results of the PS-Omega3-continuous group demonstrated sustained efficacy observed for all of the CRS-T,-P subscales. Interestingly, in this extension additional improvement in CHQ was observed, suggesting that improvements in the child and family quality of life were gradually and consistently obtained.

Preliminary indications on the efficacy of a reduced dose of PS-Omega3 consumption were obtained from the PS-Omega3 naive group. Following 15 weeks of PS-Omega3 consumption, the naive group demonstrated a significant reduction in subscales scores of both CRS-P and the CRS-T, as compare to baseline scores.

While the findings obtained throughout this 30-week study are encouraging, we acknowledge certain limitations. Specifically to the double-blind phase, no superiority was obtained in the primary outcome measure CRS-T. This rating scale is a widely accepted and validated measure of efficacy. Several factors might have influenced the sensitivity of this scale to assess the effects of treatment. Such factors include the relatively high number of children per classroom in Israel (up to 42 children) and the lack of training of the Israeli teachers in identifying and managing ADHD. Another factor previously reported to influence the sensitivity of this scale is related to the extent of teacher involvement in the study [38]. In the current study, the teacher was not actively involved; moreover, there was unexpected replacement of the reporting teachers during the study. Altogether, the above-mentioned factors suggest that the teachers in this study were probably unable to pay profound attention to each child and accurately perceive the child's state. Indeed, the insensitivity of the teachers to the child's behavior is reflected by the CRS-T baseline scores. Although all of the children in the study were diagnosed with ADHD according to the DSM-IV criteria, most of the CRS-T subscale median values were within the normal range ($< 63$) (Table 2). In contrast, the baseline median values of most subscales in the parental scale were above 62 (indicating abnormality), reflecting the parents' higher sensitivity to the child's disorder. This observation is in accordance with previous reports describing different perception of children's behavior by parents and teachers [6]. Another limitation is that the subgroup analysis was not planned prior to study initiation rather it was conducted following significant interactions found. Limitations concerning the open-label extension include the lack of a corresponding placebo controlled group and the relatively high percentage of missing data in the CRS-T, due mainly to summer vacation during which teachers could not rate the participants' behavior.

Lastly, because of the exploratory nature of this study, we chose not to correct for multiple testing. Due to the above-mentioned limitations, in order to confirm the results, the corresponding hypotheses needs to be tested in an independent confirmatory study.

Altogether, the findings of the present study join the accumulating data which support the positive effect of PS containing Omega3 fatty acids in improving executive functions of schoolchildren [41] and in ameliorating other neurological disorders [31,43].

To conclude, the current report suggest that administration of PS-Omega3 to children may reduce ADHD symptoms specifically in a subgroup of hyperactive-impulsive, emotionally and behaviorally dysregulated ADHD children. Preliminary data suggest that the beneficial effects of PS-Omega3 might be achieved and preserved by a reduced PS-Omega3 dose. These observations are encouraging and could assist in planning future large-scale, placebo-controlled trials evaluating the efficacy of PS-Omega3 in ADHD children.

## Disclosure of interest

I.M., A.M., D.K., S.R., H.T., A.W. declare that they have no conflicts of interest concerning this article.

T.C., Y.R., D.Z.-R., Y.M.: are employees of Enzymotec Ltd.

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