

Appendix 11

Summary of Clinical Studies Using DHA-rich Oil from *Schizochytrium* sp. Microalgae in Adults

Appendix 11

Appendix 11.1 - DHA Supplementation and the Prevention of Premature Labor in Pregnant Women Using a Functional Food Source of DHA (McGregor *et al.*, 1999)

Protocol No./ Principal Investigator/ Location/ Publication(s)	Study Dates (mm/dd/yy) Number of Sites	Study Design & Population	Dose/ Duration	Sample Size (N)	Age (years) Range/ (Mean)	Male/ Female White/ Non-white	Safety Results		
COMIRB99-490 McGregor <i>et al.</i> US Martek sponsored study	Study Start NR Study End 12/2003 # Sites: 3	Randomized, double-blind, placebo-controlled parallel study Population: Pregnant women at 16-18 weeks of gestation	DHA-S Nutritional Bar × wk 20 of gestation until delivery 0.3 g/DHA/d 0.6 g/DHA/d Control 0.016 g/DHA/d	221 221 221	NR	0/663 Race: NR	Preliminary results: W/D: 291 (92 from Control; 105 from 0.3 g DHA group; 94 from 0.6 g DHA group) Lost to follow up: 4 (from the DHA supplemented groups) The overall incidence of non-serious adverse events was 24.4%, 36.7%, and 35.3% for the control, 300-mg and 600-mg groups, respectively. There were 35 treatment-emergent serious adverse events (SAEs) report in all subjects. All of these SAEs were considered unrelated to the clinical trial material.		
				Preliminary Data Final Report Pending					

NR= not reported

AE= adverse experience

SAE= serious adverse experience

DHA-S= Martek's DHA-rich oil produced by the microalgae *Schizochytrium* sp

DHA= docosahexaenoic acid

W/D= withdrawal

Appendix 11

Appendix 11.2 - Memory Improvement with Docosahexaenoic Acid Study (MIDAS) - A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Effects of DHA on Cognitive Functions in the Elderly (Yurko-Mauro, 2007)

Protocol No./ Principal Investigator/ Location/ Publication(s)	Study Dates (mm/dd/yy) Number of Sites	Study Design & Population	Dose/ Duration	Sample Size (N)	Age (years) Range/ (Mean)	Male/ Female White/ Non-white	Safety Results		
2005.1002 (MIDAS) Yurko-Mauro. US http://www.clinicaltrials.gov/ct/show/NCT00278135?order=4 Martek sponsored study	Study Start: 2005 Study End: 2008 # Sites: 16	Randomized, double-blind, placebo-controlled, parallel group study Population: Healthy elderly adults with mild memory complaint	DHA-S 0.9 g/DHA/d × 6 mo Placebo (corn/soy oil) × 6 mo 1:1 allocation per group	As of 10/09/07 N=320/465 have been recruited (160 estimated per protocol) (160 estimated per protocol)	≥ 55 yr	NR	Study is ongoing and treatment blinded All AEs and SAEs are treatment blinded at this time As of 10/09/07, SAEs: 5 (1 of which resulted in death from Chronic Obstructive Pulmonary Disease)		

NR= not reported

AE= adverse experience

SAE= serious adverse experience

DHA-S= Martek's DHA-rich oil produced by the microalgae *Schizochytrium* sp

DHA= docosahexaenoic acid

W/D= withdrawal

W/D AE= withdrawal due to adverse experience

Appendix 11

Appendix 11.3 - Effect of Supplemental DHA on HDL and LDL Subclasses in Patients with Low HDL and High Non-HDL Cholesterol (Barringer *et al.*, 2003)

Protocol No./ Principal Investigator/ Location/ Publication(s)	Study Dates (mm/dd/yy) Number of Sites	Study Design & Population	Dose/ Duration	Sample Size (N)	Age (years) Range/ (Mean)	Male/ Female White/ Non-white	Safety Results		
QA-FP-9-OTHR-NS-02-023 Barringer <i>et al.</i> US Investigator study	Study Start : NR Study Stop : NR #Sites: 1	Randomized, double-blind, placebo-controlled Population: Mildly overweight men and women with low HDL (high density lipoprotein) dyslipidemia	Orange Drink containing DHA-S 1.5 g/DHA/d × 12 wk Orange Drink without DHA × 12 wk	N=20 N=21	45.7±1.8 48.3±13.2	12/7 Race: NR 17/2 Race: NR	“DHA is ... extremely well tolerated when taken as a supplement in the 1-1.5 gm/day range.” W/D: 3 (2 due to AE;1 lost to follow-up) W/D AE: 2 (gastrointestinal intolerance – 1 in each group) SAEs: None		

NR= not reported

AE= adverse experience

SAE= serious adverse experience

DHA-S= Martek's DHA-rich oil produced by the microalgae *Schizochytrium* sp

DHA= docosahexaenoic acid

W/D= withdrawal

W/D AE= withdrawal due to adverse experience

Appendix 11

Appendix 11.4 - Evaluation of the Effects of DHASCO-S on the Minimal Erythema Dose Under Static Conditions (Berg *et al.*, 2006)

Protocol No./ Principal Investigator/ Location/ Publication(s)	Study Dates (mm/dd/yy) Number of Sites	Study Design & Population	Dose/ Duration	Sample Size (N)	Age (years) Range/ (Mean)	Male/ Female White/ Non-white	Safety Results		
2006-1009 Berg US (Hilltop) Martek sponsored study	Study Start 2-11-06 Study End 3-12-06 # Sites: 1	Randomized, double-blind, placebo-controlled parallel study Population: Health adults	DHA-S 1.2 g/DHA/d × 28 d Placebo × 28 d	N=23 N=23	36.17 34.87	3/20 4/19 Race: 37/0	“The product was generally well tolerated” W/D=2 (1 from each group) W/D AE: 0 AEs: 16 (11 AEs in 7 subjects from DHA group; 5 AEs in 5 subjects from Placebo group. 3 were considered related to DHA supplement and included burping, diarrhea and stomach cramps) SAEs: 0		

NR= not reported

AE= adverse experience

SAE= serious adverse experience

DHA-S= Martek's DHA-rich oil produced by the microalgae *Schizochytrium* sp

DHA= docosahexaenoic acid

W/D= withdrawal

W/D AE= withdrawal due to adverse experience

Appendix 11

Appendix 11.5 - ABCD-E Trial; Attention and Behavior in Children on a Dietary Supplement (ABCD-Efficacy) - A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effects of DHA on Cognitive Functions in Preschool (Blue *et al.*, 2007)

Protocol No./ Principal Investigator/ Location/ Publication(s)	Study Dates (mm/dd/yy) Number of Sites	Study Design & Population	Dose/ Duration	Sample Size (N)	Age (years) Range/ (Mean)	Male/ Female White/ Non-white	Safety Results		
2006-1008 (ABCD-E) Blue, Goswami, Howard, <i>et al.</i> US http://www.clinicaltrials.gov/ct/show/NCT00351624?order=1 Martek sponsored study	Study Start: 05/12/06 Study Stop: 03/05/07 # Sites: 11	Multicenter, randomized, double-blind, placebo-controlled, parallel study Population: Healthy children	DHA-S 0.4 g/DHA/d × 4 mo Placebo (High oleic sunflower oil) × 4 mo	N=102 N=100	4 yr 0 mo to 4 yr 8 mo	45/40 78/7 47/43 72/18	Docosahexaenoic acid provided from chewable softgel capsules containing bubblegum flavored microalgal oil demonstrated a favorable safety profile. The overall AE profiles for the DHA and placebo treatment groups were similar. No deaths or SAEs were reported during the study, and no subject in the DHA treatment group discontinued the study prematurely due to an AE. W/D: 10 - Parent's Request (4 DHA; 3 Placebo) - Non-compliance (2 DHA; 1 Placebo) Lost to follow-up: 11 DHA; 9 Placebo W/D AEs: 1 Placebo (Ocular Icterus) SAEs: 0		

NR= not reported

AE= adverse experience

SAE= serious adverse experience

DHA-S= Martek's DHA-rich oil produced by the microalgae *Schizochytrium* sp

DHA= docosahexaenoic acid

W/D= withdrawal

W/D AE= withdrawal due to adverse experience

Appendix 11

Appendix 11.6 - Nutritional Intervention to Prevent Diabetes , Pilot Study (Chase and Clare-Salzler, 2007)

Protocol No./ Principal Investigator/ Location/ Publication(s)	Study Dates (mm/dd/yy) Number of Sites	Study Design & Population	Dose/ Duration	Sample Size (N)	Age (years) Range/ (Mean)	Male/ Female White/ Non-white	Safety Results		
2005.1003 Chase US http://www.clinicaltrials.gov/ct/show/NCT00333554?order=1 NIDDK sponsored study	Study Start: 09/2006 Study End: ongoing # Sites: 9	Two-arm, multicenter, randomized, double-masked, controlled study Population: Pregnant & nursing mothers and their infants Note: Either mother, or infant or both have an increased risk for Type 1 Diabetes	Pregnant /Nursing Women: DHA-S 0.8 g/DHA/d until they weaned infants Placebo Infants: DHA-S 0.15 g/DHA/d × post-weaning until they became toddlers Toddlers: 0.4 g/DHA/d until final follow-up (~ 2 yr)	As of 10/01/07 N=44/90 have been enrolled 0 0	≥ 18 yr (Women) <6 mo (Infants)	Women 0/90 Race: NR Infants & Toddlers Sex & Race: NR	Study is ongoing and treatment blinded. All AEs and SAEs are treatment blinded at this time W/D: 0 W/D AE: 0 SAEs: 7 as of 10/01/07		

NR= not reported

AE= adverse experience

SAE= serious adverse experience

DHA-S= Martek's DHA-rich oil produced by the microalgae *Schizochytrium* sp

DHA= docosahexaenoic acid

W/D= withdrawal

W/D AE= withdrawal due to adverse experience

Appendix 11

Appendix 11.7 - Supplementation of Orange Juice with Docosahexaenoic Acid (DHA) Improves Plasma Phospholipid DHA Content of Children (Hawthorne *et al.*, 2007)

Protocol No./ Principal Investigator/ Location/ Publication(s)	Study Dates (mm/dd/yy) Number of Sites	Study Design & Population	Dose/ Duration	Sample Size (N)	Age (years) Range/ (Mean)	Male/ Female White/ Non-white	Safety Results		
Hawthorne, Abrams, Heird US <i>Poster: PAS 2007 and ADA FNCE 2007</i> Non Martek study	Study Start: NR Study End: NR # Sites: 1	Randomized, open-label Population: Healthy children	DHA-S 0.05g DHA/d × 6 wk or 0.10g DHA/d × 6 wk in orange juice	16 15	4-6 7-12	8/8 Race: 5/11 7/8 Race: 4/11	“In both age groups, orange juice (180 mL/d) supplemented with 50 or 100 mg DHA was well-tolerated”		

NR= not reported

AE= adverse experience

SAE= serious adverse experience

DHA-S= Martek's DHA-rich oil produced by the microalgae *Schizochytrium* sp

DHA= docosahexaenoic acid

W/D= withdrawal

W/D AE= withdrawal due to adverse experience

Appendix 11

Appendix 11.8 - OmegaSoy Study - Combined Benefits of Soy Isoflavones and DHA-rich Algal Oil (Howe *et al.*, 2002)

Protocol No./ Principal Investigator/ Location/ Publication(s)	Study Dates (mm/dd/yy) Number of Sites	Study Design & Population	Dose/ Duration	Sample Size (N)	Age (years) Range/ (Mean)	Male/ Female White/ Non-white	Safety Results		
QA-FP-5-CARD-NS-01-008 Howe <i>et al.</i> Australia Investigator study	Study Start: NR Study Stop: NR # Sites: 1	Randomized, placebo-controlled, cross-over study Population: Men and women with LDL (low density lipoprotein) cholesterol >3.5 mmol/L, triglycerides >1.6 mmol/L and preferably, mildly elevated blood pressure (>135/85) Cross-over design	DHA-S 2.7 g/DHA/d × 12 wk Placebo (olive oil) × 12 wk	40 (All subjects received DHA in the crossover design)	>40	NR	Investigator did not report any serious adverse events during the study. Two subjects voluntarily withdrew from the study stating that they did not like “the taste” of the dietary supplements. W/D: 2		

NR= not reported

AE= adverse experience

SAE= serious adverse experience

DHA-S= Martek's DHA-rich oil produced by the microalgae *Schizochytrium* sp

DHA= docosahexaenoic acid

W/D= withdrawal

W/D AE= withdrawal due to adverse experience

Appendix 11

Appendix 11.9 - ABCD Pilot Trial Attention and Behavior in Children on a Dietary Supplement: A Pilot Study (Jensen and Heird, 2005)

Protocol No./ Principal Investigator/ Location/ Publication(s)	Study Dates (mm/dd/yy) Number of Sites	Study Design & Population	Dose/ Duration	Sample Size (N) Total Withdrawals, Withdrawals Due to AEs	Age (years) Range/ (Mean)	Male/ Female White/ Non-white	Safety Results		
NEUR-SP-04-007; Version 2 11/4/05 Jensen US (ABCD) Martek sponsored study	Study Start: NR Study Stop: NR # Sites: 1	Unblinded, randomized, dose-comparison, pilot study Population: Healthy Children age 4-6 years	DHA-S 0.2 g/DHA/d X 27-33 d 0.4 g/DHA/d x 27-33 d No placebo control	N=21 N=22	(5.13) (5.13)	10/11 Race: NR 11/11 Race: NR	<p>“There were no significant or serious adverse events and the product was well tolerated.”</p> <p>W/D: 1 (0.2 g DHA/d — Subject moved) W/D AE: 0</p> <p>AEs: 29 (in 16 children, 10 from the 0.2 g DHA group; 6 from the 0.4 g DHA group. 2 possibly related to treatment, 1 from each group)</p> <p>SAEs: 0</p>		

NR= not reported

AE= adverse experience

SAE= serious adverse experience

DHA-S= Martek's DHA-rich oil produced by the microalgae *Schizochytrium* sp

DHA= docosahexaenoic acid

W/D= withdrawal

W/D AE= withdrawal due to adverse experience

Appendix 11

Appendix 11.10 - A Pilot Study Assessing the Cognitive and Mood Effects of 8 weeks of supplementation with 400mg or 1000mg of DHASCO-S in Healthy Children Aged 10 to 12 years (Kennedy, 2007)

Protocol No./ Principal Investigator/ Location/ Publication(s)	Study Dates (mm/dd/yy) Number of Sites	Study Design & Population	Dose/ Duration	Sample Size (N)	Age (years) Range/ (Mean)	Male/ Female White/ Non-white	Safety Results		
2006.1010 Kennedy UK (Northumbria) Investigator study	Study Start 6/10/06 Study End 12/17/06 # Sites: 1	Randomized, double-blind, placebo-controlled parallel study Population: Healthy Children	DHA-S 0.4 g/DHA/d × 8 wk 1.0 g/DHA/d × 8 wk Placebo × 8 wk	N=30 N=30 N=30	10-12 (11.11) (10.10) (10.87)	17/9 Race: NR 15/15 Race: NR 12/18 Race: NR	“There were no serious adverse events related to taking the active treatments. No participant withdrew from the study due to intolerance of their treatment, and in general the study treatments were well tolerated.” W/D=2 (both from 0.4 g DHA/d; 1 for non-compliance and 1 was not study related) W/D AE: 0		

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SAE= serious adverse experience

DHA-S= Martek's DHA-rich oil produced by the microalgae *Schizochytrium* sp

DHA= docosahexaenoic acid

W/D= withdrawal

W/D AE= withdrawal due to adverse experience

Appendix 11

Appendix 11.11 - A Double-Blind, Randomized, Parallel, Controlled Clinical Trial to Evaluate the Effects of a Docosahexaenoic Acid (DHA)-Containing Capsules on Serum Lipids in Men and Women with Below-Average High Density Lipoprotein (HDL) Cholesterol Levels (Maki *et al.*, 2005)

Protocol No./ Principal Investigator/ Location/ Publication(s)	Study Dates (mm/dd/yy) Number of Sites	Study Design & Population	Dose/ Duration	Sample Size (N)	Age (years) Range/ (Mean)	Male/ Female White/ Non-white	Safety Results		
OMT-2001-01 Maki <i>et al.</i> US <i>J Amer Coll Nutr</i> 2005 Martek sponsored study	Study Start: NR Study Stop: NR # Sites: 1	Randomized, double-blind, placebo-controlled study Population: Individuals with below average levels of fasting HDL (high density lipoprotein) cholesterol Men: ≥35mg/dL - ≤44mg/dL Women: ≥35mg/dL - ≤54mg/dL	DHA-S 1.52 g/DHA/d × 6 wk Placebo (olive oil) × 6 wk	N=31 N=30	(55.8± 2.3) (51.4± 2.6) 21-80 range	17/10 19/8 14/16 24/6	“There were no statistically or clinically important differences in the incidence of abnormal clinical chemistry values or vital signs from baseline to the end of treatment (data not shown). In addition, there were no differences between groups in the incidence of treatment-emergent adverse events overall or for any body system.” W/D=4 (DHA Group: 1 lost to follow up; 1 abnormal lab work at Week 1; 2 failed to complete study) W/D AE: 3 DHA SAEs: 0		

NR= not reported

AE= adverse experience

SAE= serious adverse experience

DHA-S= Martek’s DHA-rich oil produced by the microalgae *Schizochytrium* sp

DHA= docosahexaenoic acid

W/D= withdrawal

W/D AE= withdrawal due to adverse experience

Appendix 11

Appendix 11.12 - A Bioequivalence Study Testing Blood Levels of DHA Following Supplementation with DHASCO or DHA-rich Algal Oil Capsules or Nutrition Bars (Arterburn *et al.*, 2007)

Protocol No./ Principal Investigator/ Location/ Publication(s)	Study Dates (mm/dd/yy) Number of Sites	Study Design & Population	Dose/ Duration	Sample Size (N)	Age (years) Range/ (Mean)	Male/ Female White/ Non-white	Safety Results		
BIOA-SP-02-005 (DHA BIO-4) Arterburn <i>et al.</i> US <i>Lipids</i> 2007[E-pub] Martek sponsored study	Study Start: 09/30/2002 Study Stop: 11/14/2002 # Site: 1	An 8-arm, prospective, randomized, parallel group, bioequivalence study Population: Healthy adults Note: Only data on the DHA-S are presented in this table	DHA-S capsules 0.2 g/DHA/d × 4 wk DHA-S food bar 0.465 g/DHA /d × 4 wk DHA-S capsules 0.6 g/DHA/d × 4 wk DHA-S capsules 1 g/DHA/d × 4 wk Placebo capsules (corn/soy oil) × 4 wk	N=12 N=12 N=12 N=12	35.9 (11.34) 37.4 (10.44) 36.9 (11.48) 41.0 (11.40) 40.2 (14.65)	3/9 9/3 5/7 11/1 3/9 11/1 6/6 10/2 4/8 11/1	There were no deaths, serious or clinically significant adverse events (AEs) reported for any subject during the supplementation period. No subject discontinued supplementation due to an AE. All AEs were evaluated by the Investigator as being "Mild" to "Moderate" in severity. Only eructation was significantly associated with supplementation. W/D: 0 W/D AE: 0 SAEs: 0		

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SAE= serious adverse experience

DHA-S= Martek's DHA-rich oil produced by the microalgae *Schizochytrium* sp

DHA= docosahexaenoic acid

W/D= withdrawal

W/D AE= withdrawal due to adverse experience

Appendix 11

Appendix 11.13 - Assessment of the Safety of DHA -S oil (*i.e.*, DHA-rich algal oil), an Algal Source of Docosahexaenoic Acid in Human Subjects (Sanders *et al.*, 2006)

Protocol No./ Principal Investigator/ Location/ Publication(s)	Study Dates (mm/dd/yy) Number of Sites	Study Design & Population	Dose/ Duration	Sample Size (N)	Age (years) Range/ (Mean)	Male/ Female White/ Non-white	Safety Results		
Sanders <i>et al.</i> UK <i>Sanders et al.</i> , 2006 Martek sponsored study	Study Start : NR Study Stop : NR # Sites: 1	Randomized, double-blind, placebo-controlled, parallel-design trial Population: Healthy men & women	DHA- S 1.5 g/DHA/d × 4 wk Placebo (olive oil) × 4 wk	N=40 N=40	Female 31.6 (13.2) Male 29.8 (11.5) Female 35.2 (14.5) Male 33.4 (14.7)	20/20 Race: NR 19/20 Race: NR	“There were no significant differences between treatments in LDL size, blood pressure, plasma glucose, serum C-reactive protein, plasma FVII antigen, FVII activated, fibrinogen, von Willebrand factor, tocopherol or carotenoids concentrations, plasminogen activator inhibitor-1, creatine kinase or troponin-I activities, haematology or liver function tests or self-reported adverse effects. Overall, the oil was well tolerated and did not adversely affect cardiovascular risk.” W/D: 1 (Placebo) W/D AE: 0 SAEs: 0		

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DHA= docosahexaenoic acid

W/D= withdrawal

W/D AE= withdrawal due to adverse experience

Appendix 11

Appendix 11.14 - The Triglyceride Lowering Effects of a Modest Dose of DHA Alone versus in Combination with Low Dose EPA in Patients with Coronary Artery Disease and Elevated Triglycerides (Schwellenbach *et al.*, 2006)

Protocol No./ Principal Investigator/ Location/ Publication(s)	Study Dates (mm/dd/yy) Number of Sites	Study Design & Population	Dose/ Duration	Sample Size (N)	Age (years) Range/ (Mean)	Male/ Female White/ Non-white	Safety Results		
Schwellenbach <i>et al.</i> US <i>Schwellenbach et al.</i> 2006 Investigator study	Study Start: NR Study Stop: NR # Sites: 1	Prospective, randomized, double-blind study Population: Patients with coronary artery disease and triglycerides TG >200 mg/dL	DHA-S * 1 g/DHA/d × 8 wk 1 g/DHA/d + 0.252 g EPA/d (commercial fish oil) × 8 wk *Verified by manufacturer Not reported in pub	N=57 N=59	70.3 (8.4) 68.6 (9.7)	37/20 Race: NR 45/14 Race: NR	“Overall the omega-3 fatty acid supplements were well tolerated” “A greater proportion of subjects in the [fish oil] group reported fishy taste as a problem with their treatment” WD: 2, one in each group due to gastrointestinal disturbance AEs: none SAEs: none		

NR= not reported

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SAE= serious adverse experience

DHA-S= Martek's DHA-rich oil produced by the microalgae *Schizochytrium* sp

DHA= docosahexaenoic acid

W/D= withdrawal

W/D AE= withdrawal due to adverse experience

Appendix 11

Appendix 11.15 - The Influence of Docosahexaenoic Acid Supplementation on Vascular Function: A Randomized Controlled Trial (Abstract publication-ISSFAL)-Study currently ongoing, interim report (Singhal *et al.*, 2006)

Protocol No./ Principal Investigator/ Location/ Publication(s)	Study Dates (mm/dd/yy) Number of Sites	Study Design & Population	Dose/ Duration	Sample Size (N)	Age (years) Range/ (Mean)	Male/ Female White/ Non-white	Safety Results		
NEUR-NS-04-006 Singhal <i>et al.</i> UK <i>Abstract presented at ISSFAL 2006</i> Investigator study	Study Start: 11/15/04 Study End: ongoing # Sites: 1	Randomized, open-label Population: Healthy young adult volunteers	DHA-S 1.65g DHA/d × 16 wk Placebo (Olive oil) × 16 wk 1:1 allocation per group	128/256 (64 estimated per protocol) (64 estimated per protocol)	18-36	Sex: NR Race: NR	Study is ongoing This was an interim analysis at the half-way point of data collection. No safety issues were noted by investigator		

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DHA= docosahexaenoic acid

W/D= withdrawal

W/D AE= withdrawal due to adverse experience