Effects of Icosapent Ethyl, a Highly Purified Eicosapentaenoic Acid Ethyl Ester, on the Fatty Acid Profile in Plasma and Red Blood Cells in Statin-Treated Patients With Persistent High Triglycerides (Results From the ANCHOR Study)

Rebecca A. Juliano, PhD[1]; Rene A. Braeckman, PhD[2]; Mehar S. Manku, PhD[3]; Christie M. Ballantyne, MD[4]; Ralph T. Doyle, Jr., BA[1]; Paresh N. Soni, MD, PhD[5]; William G. Stirtan, PhD[6]

[1]Amarin Pharma Inc., Bedminster, NJ, USA; [2]Doylestown, PA, USA; [3]Birmingham, UK; [4]Baylor College of Medicine and the Houston Methodist DeBakey Heart and Vascular Center, Houston, TX, USA; [5]Mystic, CT, USA; [6]East Lyme, CT, USA

ABSTRACT

Icosapent ethyl (Vascepa®; Amarin Pharma Inc., Bedminster, NJ) is a high-purity prescription form of EPA ethyl ester approved at 4 g/day as an adjunct to diet to reduce TG levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia. This subanalysis of the ANCHOR study evaluated the effects of icosapent ethyl on fatty acid profiles and the relationships between icosapent ethyl and TG lowering in plasma and RBCs. ANCHOR was a phase 3, double-blind, 12-week clinical study in high-risk statin-treated patients with residually high TG levels (≥200 and <500 mg/dL) despite control of LDL-C (≥40 and <100 mg/dL). Patients (N=702) on stable diet were randomized to icosapent ethyl 4 g/day, 2 g/day, or placebo. Twenty eight fatty acids were measured in plasma and RBCs for 153 patients using a GC/FID method. Mean baseline plasma EPA levels were 20, 27, and 24 µg/g for icosapent ethyl 4 g/day, 2 g/day, and placebo, respectively; mean EPA levels increased by 635% ($P<0.0001$) and 270% ($P<0.0001$) with icosapent ethyl 4 g/day and 2 g/day by week 12 compared with placebo. Mean baseline plasma EPA expressed as percentage of total fatty acids (mol%) was 0.4%, 0.6%, and 0.5% for icosapent ethyl 4 g/day, 2 g/day, and placebo, respectively. Mean plasma EPA (mol%) at week 12 was 3.6%, 1.9%, and 0.5% for icosapent ethyl 4 g/day, 2 g/day, and placebo, respectively. Levels of the EPA metabolite DPAn-3 also increased with both doses of icosapent ethyl ($P<0.0001$). Compared with placebo, the mean AA/EPA plasma ratio (suggested to be useful as a biomarker for arteriosclerotic disease) decreased from baseline by 91% ($P<0.0001$) and 76% ($P<0.0001$) with icosapent ethyl 4 g/day and 2 g/day, respectively. Total n-3 fatty acids increased and total n-6 fatty acids decreased with both doses of icosapent ethyl ($P<0.0001$) and significant reductions were observed with icosapent ethyl 4 g/day in the FADI compared with placebo. Similar results were observed in RBCs. Increased doses of icosapent ethyl resulted in increased EPA levels and corresponded with reductions in TG. The TG-lowering effect of icosapent ethyl was due to the increase in EPA, as there were no statistically significant changes in plasma DHA concentrations. Overall, icosapent ethyl significantly increased EPA in plasma and RBCs in a linear, dose-dependent fashion consistent with its TG-lowering effect and caused other shifts in fatty acid concentrations and RBC membrane content that may have clinical benefit.

INTRODUCTION

- Icosapent ethyl (Vascepa®; Amarin Pharma Inc., Bedminster, NJ) is a high-purity prescription form of EPA ethyl ester approved by the US FDA as an adjunct to diet to reduce TG levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia
- In the ANCHOR study, icosapent ethyl significantly improved TG levels along with other lipid, lipoprotein, and inflammatory parameters in patients at high risk for CVD with persistent high fasting TG levels (≥200 and <500 mg/dL) despite LDL-C control (≥40 and <100 mg/dL) with statin treatment[1]
- SCD catalyzes the biosynthesis of MUFAs from saturated fatty acids (rate-limiting enzyme)[2]
  - MUFAs produced via SCD activity are the most abundant MUFAs used as substrates for TG synthesis; therefore, increased SCD activity leads to an increase in TG levels[2]
  - Accordingly, SCD has been shown to play an important role in atherosclerosis as well as obesity, diabetes, inflammation, and cancer[3,4]
  - The FADI (ratio of palmitoleic acid [C16:1]/palmitic acid [C16:0] or stearic acid [C18:0]/oleic acid [C18:1n-9] in plasma) can be used as a biomarker to assess SCD activity[2]
- In this analysis, the effects of icosapent ethyl on fatty acid profiles were evaluated and the relationship between changes in fatty acid profiles to fasting TG reduction were explored in patients from the ANCHOR study

METHODS

Study Design

- ANCHOR was a phase 3, 12-week, multicenter, double-blind, randomized, placebo-controlled study with a 4–6 week lead-in period of diet and lifestyle stabilization and washout of prohibited non-statin lipid-altering medications
- Patients aged >18 years with qualifying lipid levels (TG ≥200 and <500 mg/dL and LDL-C ≥40 and <100 mg/dL) at high risk for CVD on stable diet and statin dose (atorvastatin, rosuvastatin, or simvastatin with or without ezetimibe) were eligible for inclusion
- Patients were randomized to receive either icosapent ethyl 4 g/day, icosapent ethyl 2 g/day, or matched placebo and entered a 12-week double-blind treatment period

Assessments and Measurements

- Exploratory efficacy end points included percent change from baseline to week 12 in plasma concentration and RBC membrane content of fatty acids compared with placebo
- Lipids were extracted from plasma and RBC suspensions and converted into fatty acid methyl esters for analysis using a validated GC/FID method
  - GC/FID measures total fatty acid concentrations, including unesterified fatty acids and fatty acids incorporated (esterified) in circulating phospholipids, triacylglycerols, and cholesteryl esters

Statistical Analysis

- All end points were exploratory, with significance defined as $P<0.05$
- Analyses included the ITT population (all randomized patients who had a baseline TG primary efficacy end point measurement, received ≥1 dose of study drug, and had ≥1 postrandomization efficacy measurement); patients with missing baseline or week 12 measurements were excluded; outliers were detected for each parameter and were excluded
- Fatty acid parameters were compared between icosapent ethyl and placebo using an ANCOVA model with treatment, gender, type of statin therapy, and presence of diabetes as factors and the baseline parameter value as a covariate; LSMs, SEs, and 2-tailed 95% CIs for each treatment group and for each comparison were reported

RESULTS

Patients

- Twenty-eight fatty acids were measured in plasma and RBCs for 153 patients
  - Some patients had missing fatty acid data at baseline and/or week 12 and therefore are not included (as reflected in the n values)
- Baseline characteristics were comparable between treatment groups: 61.4% male, 96.3% white, mean age 61.4 years, weight 95.7 kg, BMI 32.9 kg/m²

Fatty Acid Concentrations in Plasma (Figures 1 and 2A, Table 1)

- At baseline, the mean molar EPA plasma concentrations (mol%) were 0.4%, 0.6%, and 0.5% for icosapent ethyl 4 g/day, 2 g/day, and placebo, respectively; at week 12, they were 3.6%, 1.9%, and 0.5%, respectively (data not shown)
- Both doses of icosapent ethyl significantly increased mean concentrations of EPA and DPAn-3, as well as the ratio of total n-3 to total n-6 in plasma compared with placebo
- Both doses of icosapent ethyl significantly decreased mean plasma AA to EPA ratio compared with placebo
- Neither dose of icosapent ethyl produced a significant change in mean concentration of DHA in plasma compared with placebo

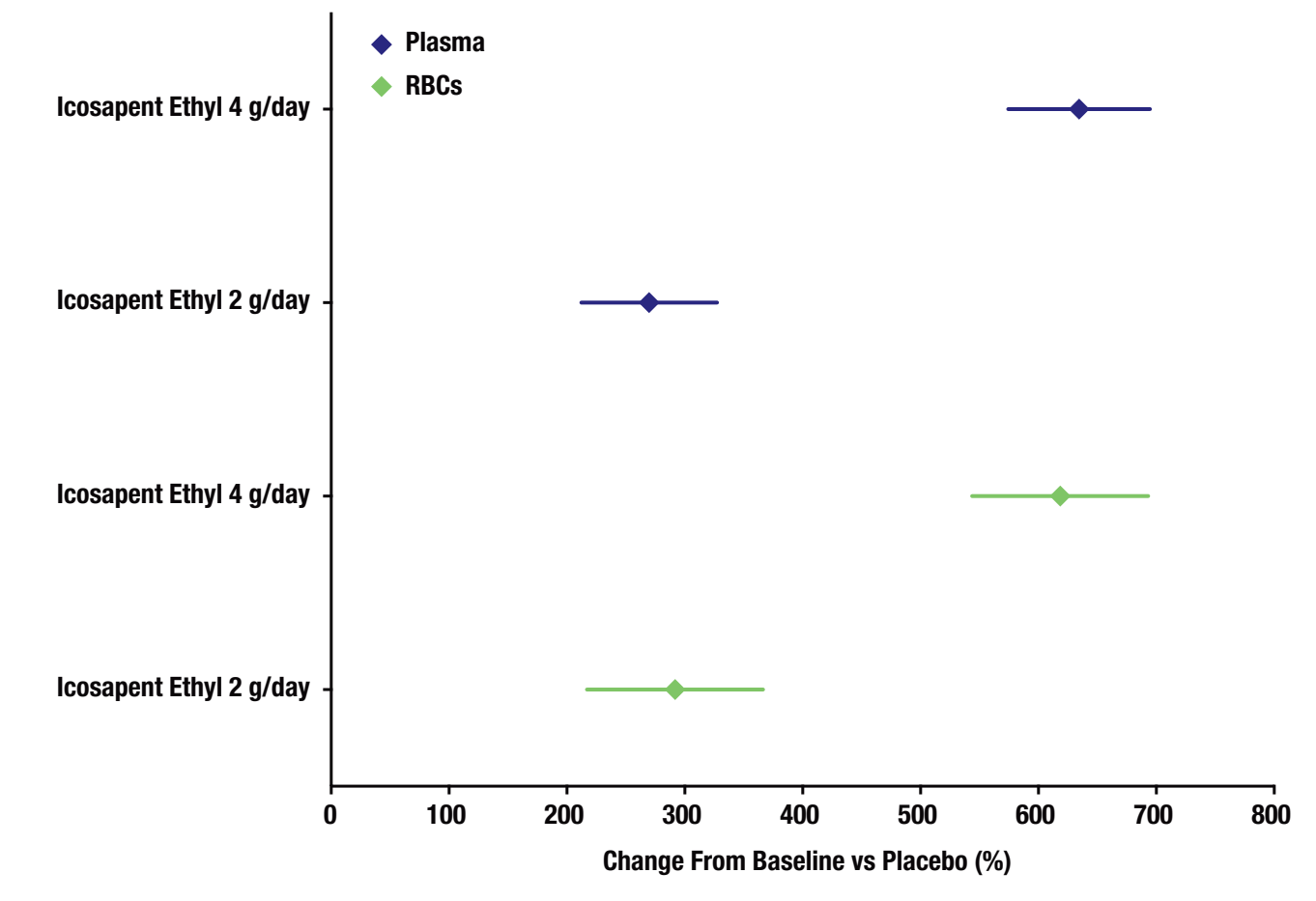
Fatty Acid Concentrations in RBCs (Figures 1 and 2A, Table 2)

- Both doses of icosapent ethyl significantly increased mean concentrations of EPA and DPAn-3, as well as the ratio of total n-3 to total n-6 in RBCs compared with placebo
- Both doses of icosapent ethyl significantly decreased mean RBC AA to EPA ratio compared with placebo
- Both doses of icosapent ethyl significantly reduced mean concentration of DHA in RBCs compared with placebo

Fatty Acid Desaturation Index (Figure 2B)

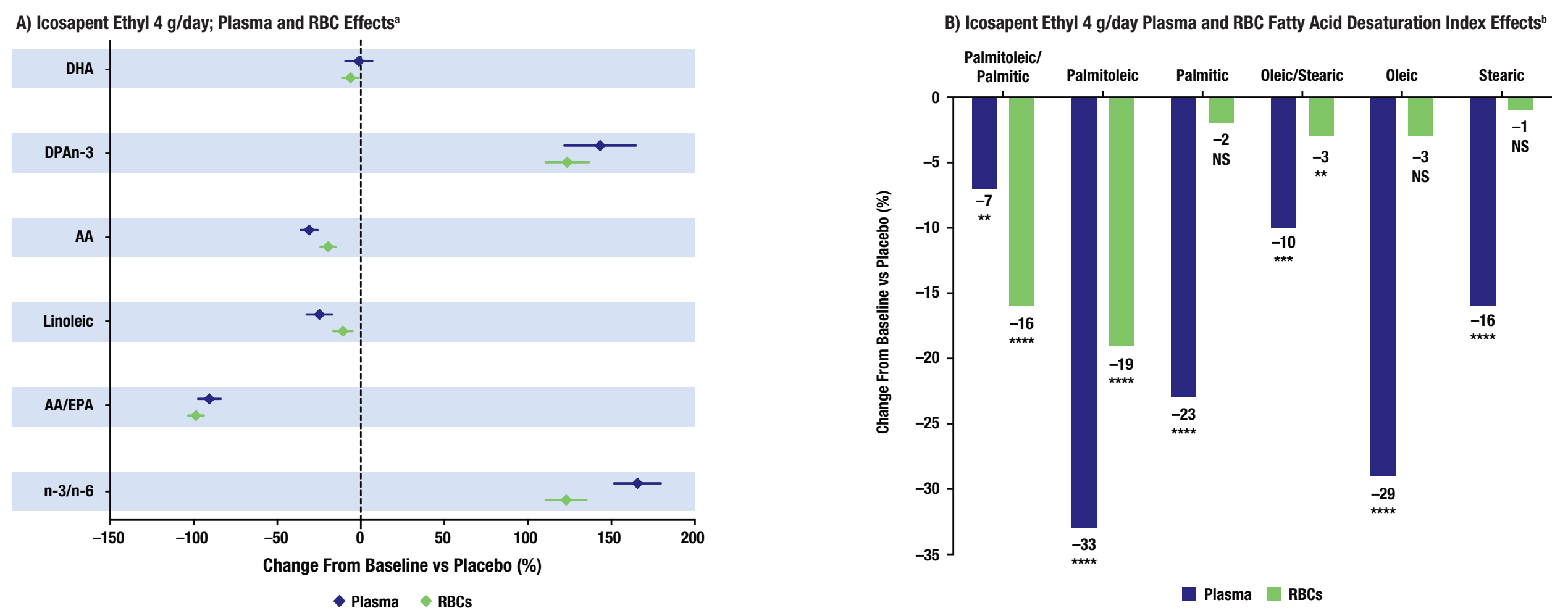
- Icosapent ethyl 4 g/day significantly reduced the ratios of palmitoleic acid (C16:1)/palmitic acid (C16:0) and oleic acid (C18:1n-9)/stearic acid (C18:0) in both plasma and RBCs
- In plasma, icosapent ethyl 4 g/day significantly reduced each of the FADI fatty acids: palmitoleic (C16:1), palmitic (C16:0), oleic (C18:1n-9), and stearic (C18:0)
- In RBCs, icosapent ethyl 4 g/day significantly reduced palmitoleic acid (C16:1), but reductions in the other FADI fatty acids were not significant

Figure 1. Change From Baseline to Week 12 in Plasma and RBC EPA Concentrations Compared With Placebo



All $P<0.0001$; data are presented as LS mean changes from baseline vs placebo; error bars represent 95% CI.

Figure 2. Percent Change in Plasma and RBC Fatty Acid Concentrations and Ratios Compared With Placebo


A) Icosapent Ethyl 4 g/day; Plasma and RBC Effects[a]

B) Icosapent Ethyl 4 g/day Plasma and RBC Fatty Acid Desaturation Index Effects[b]

[a]Data are presented as LS mean changes from baseline vs placebo; error bars represent 95% CI. See Tables 1 and 2 for P values.
[b]Data are presented as LS mean changes from baseline vs placebo. ****$P<0.0001$; ***$P<0.001$; **$P<0.01$; *$P<0.05$; NS=not significant.

Table 1. Change From Baseline to Week 12 in Plasma Fatty Acid Concentrations and Ratios

	Icosapent Ethyl 4 g/day			Icosapent Ethyl 2 g/day			Placebo			% Change From Baseline vs Placebo (LSM)	
Plasma Fatty Acid[a]	Baseline Mean (SD)	Week 12 Mean (SD)	Change LSM (SE)	Baseline Mean (SD)	Week 12 Mean (SD)	Change LSM (SE)	Baseline Mean (SD)	Week 12 Mean (SD)	Change LSM (SE)	Icosapent Ethyl 4 g/day	Icosapent Ethyl 2 g/day
Concentration (µg/g)										%, P	%, P
EPA (C20:5n-3) n=43, 50, 51	19.57 (6.410)	144.68 (56.464)	135.98 (5.998)	26.58 (13.081)	89.26 (39.682)	71.82 (5.397)	24.29 (29.025)	24.39 (25.073)	10.43 (5.457)	634.50 <0.0001	269.83 <0.0001
DHA (C22:6n-3) n=48, 51, 52	51.80 (15.369)	54.02 (13.842)	2.84 (1.852)	58.90 (18.850)	62.68 (18.569)	5.18 (1.729)	58.54 (34.274)	61.59 (32.907)	4.44 (1.743)	–1.12 0.7820	0.72 0.8566
DPA (C22:5n-3) n=49, 51, 52	20.19 (5.573)	50.45 (14.172)	31.79 (1.794)	23.35 (6.627)	44.26 (13.536)	22.44 (1.711)	21.41 (7.999)	23.83 (9.403)	3.91 (1.714)	143.27 <0.0001	89.21 <0.0001
AA (C20:4n-6) n=50, 51, 52	282.84 (71.080)	223.26 (65.530)	–60.69 (6.295)	301.19 (73.446)	266.70 (61.205)	–31.13 (5.965)	306.96 (74.556)	328.17 (67.119)	26.25 (6.124)	–30.87 <0.0001	–19.19 <0.0001
Palmitic (C16:0) n=48, 49, 51	974.49 (223.707)	846.22 (213.932)	–162.1 (44.906)	1066.3 (291.555)	1004.4 (321.157)	–49.05 (42.879)	1038.7 (299.038)	1100.2 (352.507)	56.28 (42.832)	–22.87 <0.0001	–11.64 0.0170
Palmitoleic (C16:1) n=48, 48, 52	128.11 (41.653)	102.64 (36.488)	–28.98 (8.043)	141.85 (53.564)	129.91 (55.681)	–9.95 (7.743)	141.97 (62.221)	154.72 (73.802)	14.03 (7.703)	-33.15 <0.0001	–18.78 0.0029
Stearic (C18:0) n=50, 46, 50	278.90 (55.757)	254.07 (48.217)	–30.83 (8.149)	302.46 (61.838)	276.18 (52.769)	–19.50 (8.154)	291.88 (61.887)	304.54 (62.494)	13.52 (7.995)	–16.16 <0.0001	–12.35 0.0004
Oleic (C18:1n-9) n=47, 49, 51	979.09 (261.606)	784.41 (208.940)	–220.0 (49.146)	1029.0 (271.253)	972.10 (328.891)	–59.99 (46.758)	1011.0 (296.705)	1091.5 (403.343)	66.70 (46.802)	–29.48 <0.0001	–13.59 0.0121
Linoleic (C18:2n-6) n=50, 49, 52	1069.4 (262.259)	922.28 (200.324)	–152.5 (38.151)	1124.8 (253.026)	1082.2 (284.980)	–34.06 (36.992)	1093.0 (258.966)	1221.8 (350.910)	127.42 (36.433)	–24.75 <0.0001	–14.39 0.0003
Ratio										%, P	%, P
AA/EPA n=47, 50, 50	16.23 (6.665)	1.61 (0.795)	–14.17 (0.556)	13.19 (4.156)	3.35 (1.727)	–11.21 (0.538)	16.97 (6.785)	16.63 (6.638)	0.60 (0.532)	–90.64 <0.0001	–75.70 <0.0001
Total n-3/n-6 n=47, 51, 51	0.09 (0.014)	0.23 (0.060)	0.15 (0.006)	0.10 (0.020)	0.15 (0.037)	0.07 (0.005)	0.09 (0.040)	0.09 (0.038)	0.01 (0.005)	165.65 <0.0001	64.51 <0.0001
Oleic/Stearic n=47, 52, 52	3.5186 (0.4372)	3.1572 (0.5703)	–0.3976 (0.0818)	3.4239 (0.4943)	3.4014 (0.5492)	–0.0860 (0.0766)	3.4780 (0.5323)	3.4626 (0.6427)	–0.0647 (0.0778)	–9.5415 0.0009	–0.0889 0.9743
Palmitoleic/Palmitic n=49, 51, 49	0.1328 (0.0278)	0.1225 (0.0268)	–0.0098 (0.0025)	0.1327 (0.0243)	0.1296 (0.0253)	–0.0026 (0.0024)	0.1363 (0.0296)	0.1343 (0.0279)	–0.0008 (0.0025)	–6.8178 0.0043	–1.3428 0.5649

[a]Patient numbers (n) are reported for icosapent ethyl 4 g/day, icosapent ethyl 2 g/day, and placebo, respectively.

Table 2. Change From Baseline to Week 12 in Red Blood Cell Fatty Acid Concentrations and Ratios

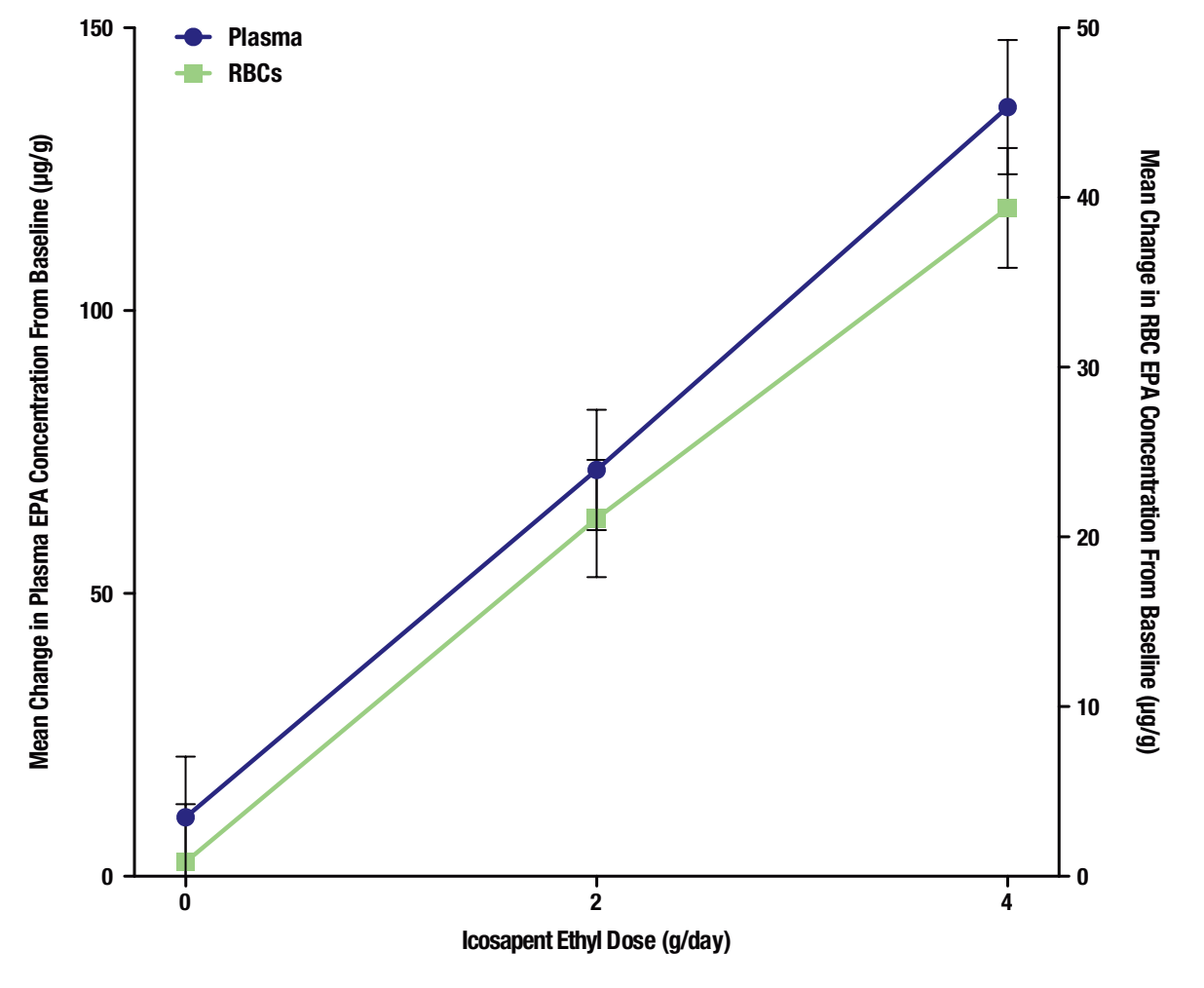
	Icosapent Ethyl 4 g/day			Icosapent Ethyl 2 g/day			Placebo			% Change From Baseline vs Placebo (LSM)	
RBC Fatty Acid[a]	Baseline Mean (SD)	Week 12 Mean (SD)	Change LSM (SE)	Baseline Mean (SD)	Week 12 Mean (SD)	Change LSM (SE)	Baseline Mean (SD)	Week 12 Mean (SD)	Change LSM (SE)	Icosapent Ethyl 4 g/day	Icosapent Ethyl 2 g/day
Concentration (µg/g)										%, P	%, P
EPA (C20:5n-3) n=49, 49, 48	6.09 (2.248)	43.28 (17.957)	39.38 (1.791)	8.19 (2.741)	28.38 (8.467)	21.08 (1.748)	7.09 (3.320)	6.40 (3.313)	0.84 (1.730)	618.46 <0.0001	291.74 <0.0001
DHA (C22:6n-3) n=44, 48, 47	44.10 (11.708)	39.14 (8.328)	–6.29 (0.983)	50.53 (13.163)	44.72 (11.403)	–5.49 (0.935)	47.35 (11.696)	45.12 (11.861)	–2.70 (0.919)	–6.12 0.0178	–4.93 0.0491
DPA (C22:5n-3) n=46, 50, 46	28.54 (5.757)	62.14 (12.564)	33.67 (1.417)	31.59 (4.973)	52.24 (8.931)	21.24 (1.328)	29.69 (5.496)	28.60 (5.146)	–0.85 (1.380)	123.56 <0.0001	75.84 <0.0001
AA (C20:4n-6) n=44, 48, 47	185.38 (37.044)	153.50 (28.599)	–37.08 (3.596)	190.87 (28.621)	173.05 (25.684)	–19.77 (3.314)	189.44 (25.769)	193.57 (27.707)	0.98 (3.417)	–19.48 <0.0001	–10.92 <0.0001
Palmitic (C16:0) n=46, 49, 50	304.13 (36.930)	301.24 (36.607)	–5.77 (4.438)	317.29 (37.234)	321.13 (41.409)	5.14 (4.120)	313.71 (39.421)	313.52 (32.643)	0.04 (4.151)	–2.24 0.1895	0.89 0.5946
Palmitoleic (C16:1) n=47, 51, 51	9.32 (4.184)	7.67 (2.370)	–1.40 (0.379)	8.80 (2.858)	9.26 (3.423)	0.48 (0.351)	9.24 (3.353)	9.45 (3.225)	0.42 (0.358)	–19.37 <0.0001	–1.59 0.7139
Stearic (C18:0) n=45, 50, 46	170.95 (18.926)	170.73 (18.752)	–1.15 (2.550)	174.94 (22.438)	178.73 (22.873)	4.00 (2.367)	173.93 (15.024)	174.73 (18.323)	0.74 (2.466)	–0.71 0.7048	2.13 0.2445
Oleic (C18:1n-9) n=45, 50, 45	194.52 (27.259)	188.77 (23.798)	–7.74 (3.060)	201.65 (30.007)	204.73 (31.588)	3.26 (2.821)	198.70 (24.650)	198.42 (24.609)	–1.00 (2.997)	–3.15 0.0943	2.13 0.2424
Linoleic (C18:2n-6) n=48, 49, 48	146.81 (31.853)	132.49 (26.003)	–15.77 (3.752)	154.32 (33.436)	153.06 (37.572)	–1.12 (3.521)	151.38 (24.241)	153.50 (32.521)	1.53 (3.612)	–10.65 0.0004	–1.71 0.5610
Ratio										%, P	%, P
AA/EPA n=46, 50, 50	31.86 (10.373)	3.61 (1.700)	–26.95 (0.801)	26.12 (8.202)	6.39 (1.965)	–21.98 (0.771)	31.44 (11.465)	33.26 (9.955)	3.10 (0.767)	–98.64 <0.0001	–87.14 <0.0001
Total n-3/n-6 n=48, 52, 50	0.18 (0.034)	0.40 (0.107)	0.23 (0.009)	0.20 (0.047)	0.30 (0.061)	0.11 (0.009)	0.19 (0.042)	0.18 (0.041)	–0.00 (0.009)	122.92 <0.0001	60.38 <0.0001
Oleic/Stearic n=48, 50, 51	1.1496 (0.1127)	1.1263 (0.1080)	–0.0258 (0.0112)	1.1465 (0.0980)	1.1602 (0.1135)	0.0115 (0.0106)	1.1488 (0.1235)	1.1614 (0.1284)	0.0106 (0.0107)	–3.1585 0.0066	0.0095 0.9933
Palmitoleic/Palmitic n=48, 50, 49	0.0296 (0.0090)	0.0257 (0.0064)	–0.0032 (0.0009)	0.0281 (0.0068)	0.0288 (0.0077)	0.0008 (0.0008)	0.0296 (0.0081)	0.0306 (0.0080)	0.0016 (0.0008)	–15.6756 <0.0001	2.7463 0.4163

[a]Patient numbers (n) are reported for icosapent ethyl 4 g/day, icosapent ethyl 2 g/day, and placebo, respectively.

Icosapent Ethyl: Dose, Plasma EPA Levels, and TG-Lowering Relationships

- Increasing doses of icosapent ethyl increased both plasma and RBC EPA concentrations (**Figure 3**)
- Increasing EPA concentrations in plasma and RBCs were accompanied by greater reductions in plasma TG levels (**Figure 4**)

Figure 3. Dose Dependence of EPA Concentrations in Plasma and RBCs

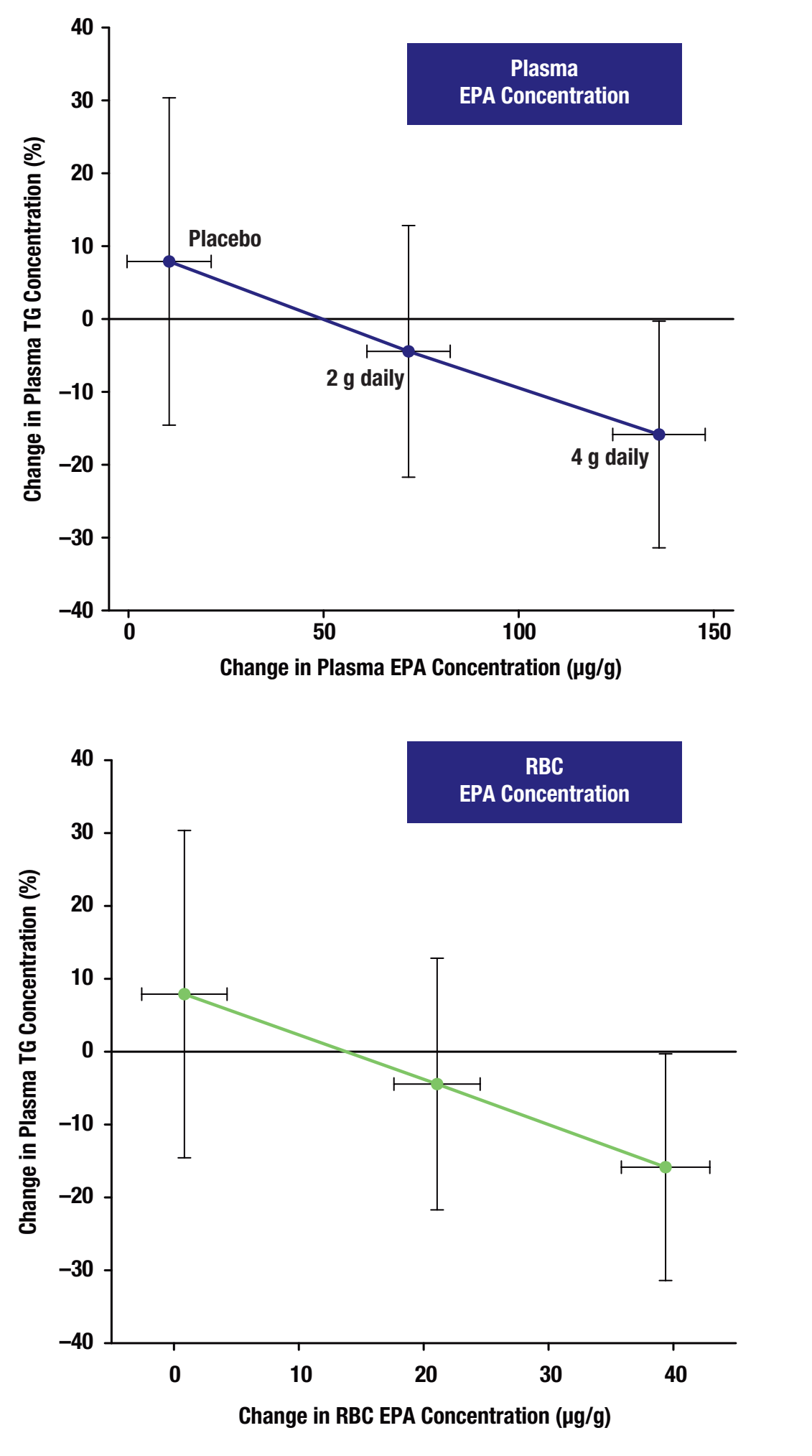


EPA data are presented as mean concentrations based on baseline-subtracted trough concentrations of total EPA (change from baseline) at steady state; error bars are 95% CI.

Change in Proportion (mol%) of Fatty Acid Classes (Table 3)

- Treatment with icosapent ethyl resulted in significant changes as follows:
  - Increased proportion of n-3 fatty acids in plasma and RBCs
  - Decreased proportion of n-6 fatty acids in plasma and RBCs
  - Decreased proportion of MUFAs in plasma and RBCs (4 g/day)

Figure 4. Relationship Between Plasma TG Lowering and EPA Concentrations in Plasma and RBCs (PK/PD Relationship)



TG concentrations are presented as median percent change from baseline; vertical error bars = Q1, Q3 of IQR; EPA data are presented as mean concentrations based on baseline-subtracted trough concentrations of total EPA (change from baseline) at steady state; horizontal error bars = 95% CI.

Table 3. Percent Change in the Proportion of Fatty Acid Classes to Total[a] Fatty Acids

	Icosapent Ethyl 4 g/day			Icosapent Ethyl 2 g/day			Placebo			% Change From Baseline vs Placebo (LSM)	
Fatty Acid Class[b]	Baseline Mean (SD)	Week 12 Mean (SD)	Change LSM (SE)	Baseline Mean (SD)	Week 12 Mean (SD)	Change LSM (SE)	Baseline Mean (SD)	Week 12 Mean (SD)	Change LSM (SE)	Icosapent Ethyl 4 g/day	Icosapent Ethyl 2 g/day
Plasma Proportion of Total (%)[b]										%, P	%, P
Saturated n=50, 52, 53	33.79 (2.543)	33.59 (2.389)	–0.54 (0.312)	34.28 (2.188)	33.62 (2.244)	–0.71 (0.294)	34.20 (2.488)	33.63 (2.357)	–0.69 (0.297)	0.48 0.6611	–0.19 0.8643
Monounsaturated n=50, 52, 53	28.63 (2.770)	26.72 (2.976)	–2.04 (0.442)	28.48 (2.240)	27.96 (2.811)	–0.72 (0.418)	28.67 (2.586)	28.40 (3.301)	–0.38 (0.421)	–5.58 0.0038	–1.09 0.5623
Total n-6 n=50, 52, 53	34.63 (3.910)	32.54 (3.429)	–1.85 (0.520)	34.01 (2.688)	33.30 (3.425)	–0.77 (0.490)	34.02 (3.350)	34.85 (3.840)	0.79 (0.494)	–7.66 <0.0001	–4.81 0.0115
Total n-3 n=50, 52, 53	2.95 (0.479)	7.16 (1.978)	4.45 (0.194)	3.23 (0.679)	5.13 (1.168)	2.12 (0.185)	3.11 (1.297)	3.12 (1.136)	0.25 (0.185)	142.22 <0.0001	60.25 <0.0001
RBCs Proportion of Total (%)[b]										%, P	%, P
Saturated n=50, 51, 53	43.35 (2.165)	44.15 (3.010)	0.47 (0.342)	43.76 (3.052)	43.50 (2.110)	–0.31 (0.328)	43.82 (2.594)	42.98 (1.724)	–0.88 (0.326)	3.13 0.0011	1.24 0.1852
Monounsaturated n=50, 51, 53	20.43 (2.199)	19.79 (1.688)	–0.46 (0.227)	19.96 (1.142)	19.94 (1.142)	–0.03 (0.216)	19.89 (1.587)	20.03 (1.848)	0.05 (0.215)	–2.65 0.0401	–0.52 0.6790
Total n-6 n=50, 51, 53	30.75 (1.967)	25.84 (3.165)	–4.91 (0.365)	30.23 (3.085)	28.10 (2.103)	–2.45 (0.351)	30.58 (3.051)	31.47 (2.178)	0.81 (0.348)	–19.60 <0.0001	–11.40 <0.0001
Total n-3 n=50, 51, 53	5.46 (1.130)	10.22 (2.484)	4.93 (0.242)	6.05 (1.314)	8.46 (1.482)	2.65 (0.236)	5.72 (1.185)	5.52 (1.116)	–0.01 (0.231)	89.38 <0.0001	50.07 <0.0001

[a]Total = mole sum of omega-3, omega-6, monounsaturated, and saturated fatty acids.
[b]Patient numbers (n) are reported for icosapent ethyl 4 g/day, icosapent ethyl 2 g/day, and placebo, respectively.
Saturated fatty acids = sum of myristic, palmitic, stearic, arachidic, behenic, and lignoceric acids.
MUFAs = myristoleic, palmitoleic, cis-vaccenic, oleic, gondoic/gadoleic, erucic, and nervonic acids.
n-6 fatty acids = sum of linoleic, γ-linolenic, eicosadienoic, dihomo-γ-linolenic, n-6 arachidonic, adrenic, and n-6 docosapentaenoic acids.
n-3 fatty acids = sum of α-linolenic, stearidonic, eicosatrienoic, n-3 arachidonic, eicosapentaenoic, n-3 docosapentaenoic, and docosahexaenoic acids.

SUMMARY

- In the ANCHOR study, icosapent ethyl significantly increased the concentrations of EPA and its metabolite, DPAn-3, in plasma and RBCs
  - Icosapent ethyl significantly reduced the AA/EPA ratio in plasma and RBCs; the AA/EPA ratio has been suggested to be useful as a biomarker for arteriosclerotic disease[5]
- Icosapent ethyl 4 g/day significantly reduced the FADI ratios in both plasma and RBCs
  - These reductions in FADI are consistent with the robust TG lowering observed in ANCHOR[1]
  - This may be clinically meaningful, as reductions in the FADI might be expected to have beneficial effects on CVD and other diseases[4,6]
- Icosapent ethyl increased the proportion of n-3 fatty acids and decreased the proportions of n-6 and in plasma and RBCs
  - n-3 fatty acids generally exert anti-inflammatory effects while n-6 fatty acids may exert pro-inflammatory effects[5,7]
- Icosapent ethyl did not significantly increase the concentration of DHA in plasma or RBCs, indicating that its metabolic effects (including TG lowering) are not due to increases in DHA levels

CONCLUSIONS

- Overall, icosapent ethyl significantly increased EPA concentrations in a linear, dose-dependent fashion consistent with its TG-lowering effect, caused beneficial shifts in the fatty acid profile, significantly decreased the AA/EPA ratio in plasma and RBCs, and produced potentially beneficial reductions in FADI in statin-treated patients at high CHD risk

REFERENCES

1. Ballantyne CM, et al. *Am J Cardiol*. 2012;110:984-92.
2. Sampath H, Ntambi JM. *Future Lipidol*. 2008;3:163-73.
3. Sampath H, Ntambi JM. *Ann N Y Acad Sci*. 2011;1243:47-53.
4. Paton CM, Ntambi JM. *Am J Physiol Endocrinol Metab*. 2009;297:E28-E37.
5. Itakura H, et al. *J Atheroscler Thromb*. 2011;18:99-107.
6. Liu X, et al. *Adv Nutr*. 2011;2:15-22.
7. James MJ, et al. *Am J Clin Nutr*. 2000;71(1 Suppl):343S-8.

ABBREVIATIONS

AA = arachidonic acid; ANCOVA = analysis of covariance; BMI = body mass index; CHD = coronary heart disease; CI = confidence interval; CVD = cardiovascular disease; DHA = docosahexaenoic acid; DPAn-3 = docosapentaenoic acid n-3; EPA = eicosapentaenoic acid; FADI = fatty acid desaturation index; GC/FID = gas chromatograph assay with flame ionization detector; IQR = interquartile range; ITT = intent-to-treat; LDL-C = low-density lipoprotein cholesterol; LSM = least-squares mean; MUFAs = monounsaturated fatty acids; PD = pharmacodynamics; PK = pharmacokinetics; RBC = red blood cell; SCD = stearoyl-coenzyme A desaturase; SD = standard deviation; SE = standard error; TG = triglycerides; US FDA = United States Food and Drug Administration

ANCHOR was designed and sponsored by Amarin Pharma Inc., Bedminster, NJ, USA.

Presented at the Kern Lipid Conference, August 3–5, 2015, Vail, CO.

Previous Presentation: American Heart Association Annual Scientific Session, November 3–7, 2012, Los Angeles, CA.