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Pharmacokinetic and Triglyceride-lowering Pharmacodynamic Effects of Icosapent Ethyl (Eicosapentaenoic Acid Ethyl Ester) Across Clinical Studies

William G. Stirtan, PhD,[1] Rene A. Braeckman, PhD,[2] Harold E. Bays, MD,[3] Christie M. Ballantyne, MD,[4] Paresh N. Soni, MD, PhD,[5] Rebecca A. Juliano, PhD[1]

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ABSTRACT

Synopsis: Icosapent ethyl is a high-purity prescription form of eicosapentaenoic acid (EPA) ethyl ester approved to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia.

Objective: To examine the effects of icosapent ethyl on EPA concentrations in plasma and red blood cells (RBCs) in response to dose and the relationship to TG lowering across 3 clinical studies.

Methods: MARINE and ANCHOR were 12-week, phase 3, double-blind studies that randomized adult patients to icosapent ethyl 4 g/day, icosapent ethyl 2 g/day, or placebo. MARINE randomized 229 patients with TG ≥500 and ≤2000 mg/dL while ANCHOR randomized 702 high-risk patients with TG ≥200 and <500 mg/dL despite low-density lipoprotein cholesterol (LDL-C) control while on statin therapy. Icosapent ethyl 4 g/day and 2 g/day was also investigated in 48 healthy adult subjects for 4 weeks in a phase 1 pharmacokinetics (PK) study.

Results: In all studies, a greater increase in EPA concentrations in both plasma and RBCs was observed with icosapent ethyl 4 g/day than with 2 g/day, indicating a dose-dependent increase in EPA exposure. EPA concentration data from healthy volunteers and in patients with hypertriglyceridemia indicate that the PK of EPA are linear with dose. Following treatment with icosapent ethyl 4 g/day, mean±SD plasma EPA levels increased from 61.2±67.4 µg/mL at baseline to 326.7±205.7 µg/mL at 12 weeks in MARINE and from 28.1±18.8 µg/mL at baseline to 182.6±71.7 µg/mL at 12 weeks in ANCHOR. In MARINE and ANCHOR, median percent reductions in TG from baseline were higher with icosapent ethyl 4 g/day than with 2 g/day and demonstrated a dose-proportional relationship. In plasma and RBCs, a linear pharmacodynamic (PD) relationship between EPA levels and TG reduction was also observed, demonstrating a linear concentration-response relationship.

Conclusions: Taken together, the linear-dose-PK and dose-concentration-response PD relationships indicate that the PK/PD of icosapent ethyl are predictable as the results demonstrate a trend of increasing TG-lowering efficacy with respect to both the icosapent ethyl dose and EPA concentration in plasma and RBCs.

INTRODUCTION

- Icosapent ethyl (Vascepa® [formerly AMR101]; 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
- A phase 1 PK study conducted in healthy volunteers demonstrated that the PK profile of icosapent ethyl was that of a slowly cleared and extensively distributed molecule with dose-linearity
- The MARINE and ANCHOR pivotal studies demonstrated collectively that icosapent ethyl significantly reduced TG levels in patients with very high (MARINE) or high (ANCHOR) TG levels and on statin therapy without raising LDL-C[1,2]
- The present analysis evaluated data from 2 studies conducted in patients with elevated TG levels and 1 study conducted in healthy volunteers for a PK/PD dose-response relationship with respect to icosapent ethyl dose, EPA concentration in plasma and RBCs, and reduction in TG levels

METHODS

Study Design

- Phase 1 PK study
  - Open-label, randomized, multidose study with a 14-day screening period followed by a 4-week treatment period
  - Healthy, nonsmoking volunteers aged >18 and ≤55 years not receiving any lipid-altering medications or supplements within 6 weeks before the study were randomized to 4 icosapent ethyl dose regimens (groups 1 and 2 are included in this analysis):
    - Group 1: icosapent ethyl 2 g/day (one 1000-mg capsule BID)
    - Group 2: icosapent ethyl 4 g/day (two 1000-mg capsules BID)
    - Group 3: icosapent ethyl 2 g/day (two 1000-mg capsules QD)
    - Group 4: icosapent ethyl 2 g/day (two 500-mg capsules BID)
  - After dosing, subjects entered an 18-day post-treatment PK sampling period
- MARINE and ANCHOR[1,2]
  - Phase 3, placebo-controlled, randomized, double-blind, multicenter studies with a 4- to 6-week lead-in period of diet, lifestyle, and medication stabilization with washout of prohibited lipid-altering medications
  - In both studies, patients aged >18 years with qualifying lipid levels (MARINE: TG ≥500 mg/dL and ≤2000 mg/dL; ANCHOR: TG ≥200 and <500 mg/dL and LDL-C ≥40 and ≤115 mg/dL) entered a 12-week, double-blind treatment period and were randomized to receive either icosapent ethyl 4 g/day, icosapent ethyl 2 g/day, or matched placebo
  - In the MARINE study, stable statin therapy with or without ezetimibe was permitted but not required
  - In the ANCHOR study, patients were required to be at high risk for cardiovascular disease as defined by the NCEP ATP III guidelines[3] and on stable statin dose (atorvastatin, rosuvastatin, or simvastatin with or without ezetimibe)

Assessments and Measurements

- In the MARINE and ANCHOR studies, the trough EPA concentrations were measured after 12 weeks of dosing with icosapent ethyl 4 g/day, icosapent ethyl 2 g/day, or placebo
- In the Phase 1 PK study, the trough EPA concentrations were measured after 28 days of dosing with icosapent ethyl 4 or 2 g/day (there was no placebo group; a value of zero is used in plots as a point of reference)
- EPA concentrations were measured with a validated LC-MS/MS method in plasma and in RBCs in all 3 studies
  - Total plasma EPA included all EPA forms (unesterified EPA and that incorporated in phospholipids, triacylglycerols, and cholesteryl esters); in RBCs, EPA was from cell membranes, where it is mainly incorporated in phospholipids
  - Total EPA in plasma and RBCs: lipids were isolated by acid/methanol/chloroform extraction followed by centrifugation and purified by isohexane and solid-phase extraction after confirmed complete lipid hydrolysis and transmethylation (acid/methanol, 50°C overnight)
  - Quantitation utilized linolenic acid as an internal standard and EPA as the standard for the calibration curve; for total plasma EPA and total RBC EPA, the lower limits of quantitation were 10 µg/mL and 5 µg/mL, respectively
- TG levels were evaluated in the MARINE and ANCHOR studies as previously reported[1,2]
  - Serum TG levels were measured with enzymatic colorimetric tests with calibration directly traceable to US CDC reference procedures

RESULTS

Subjects

- Baseline characteristics are summarized in **Table 1** and were comparable among treatment groups within each study

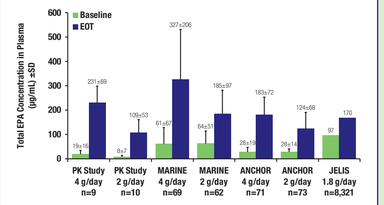
Table 1. Demographics and Baseline Characteristics

	Phase 1 PK Study		MARINE			ANCHOR		
Characteristic	Icosapent Ethyl 4 g/day (n=12)	Icosapent Ethyl 2 g/day (n=12)	Icosapent Ethyl 4 g/day (n=77)	Icosapent Ethyl 2 g/day (n=76)	Placebo (n=76)	Icosapent Ethyl 4 g/day (n=233)	Icosapent Ethyl 2 g/day (n=236)	Placebo (n=233)
Age, mean (SD), y	37.9 (12.9)	36.9 (13.5)	51.9 (10.3)	53.4 (9.3)	53.4 (8.3)	61.1 (10.0)	61.8 (9.4)	61.2 (10.1)
Male, *n* (%)	6 (50.0)	6 (50.0)	59 (76.6)	58 (76.3)	58 (76.3)	142 (60.9)	144 (61.0)	145 (62.2)
Weight, mean (SD), kg	75.5 (13.4)	74.5 (14.1)	93.2 (18.3)	92.1 (15.6)	93.0 (16.9)	94.5 (18.3)	95.5 (18.3)	97.0 (19.1)
BMI, mean (SD), kg/m^2	27.2 (2.6)	26.2 (2.6)	30.4 (4.3)	30.8 (4.2)	31.0 (4.3)	32.7 (5.0)	32.9 (5.0)	33.0 (5.0)
Diabetes, n (%)	NA	NA	22 (28.6)	20 (26.3)	21 (27.6)	171 (73.4)	172 (72.9)	171 (73.4)
TG, median (IQR), mg/dL	NA	NA	679.5 (265.3) n=76	656.5 (303.5) n=73	703.0 (426.5) n=75	264.8 (93.0) n=226	254.0 (92.5) n=234	259.0 (81.0) n=227
Total plasma EPA, mean (SD), µg/mL	19.3 (16.1) n=9	7.9 (7.0) n=10	61.2 (67.4) n=69	63.6 (51.4) n=62	57.7 (42.7) n=61	28.1 (18.8) n=71	28.1 (13.7) n=73	28.1 (28.0) n=81
RBC EPA, mean (SD), µg/mL	12.1 (15.7) n=9	5.7 (4.3) n=10	16.0 (9.2) n=66	15.7 (9.9) n=61	14.7 (9.3) n=64	11.6 (5.6) n=69	10.9 (5.2) n=71	11.2 (6.6) n=79

EPA Dose Response

- Healthy subjects and patients with hypertriglyceridemia experienced dose-dependent increases in plasma EPA concentrations following treatment with icosapent ethyl (**Figure 1**)
- Similar plasma EPA increases were observed in the JELIS study, which investigated pure EPA ethyl ester, the same active ingredient as in icosapent ethyl, in a cardiovascular outcomes study with a planned 5-year follow-up[4]

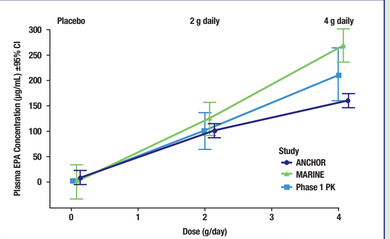
Figure 1. Mean Trough Total EPA Concentrations (±SD) in Plasma at Baseline and EOT in the Phase 1 PK, MARINE, ANCHOR, and JELIS Studies



EOT=4 weeks for the phase 1 PK study; 12 weeks in the MARINE and ANCHOR studies. JELIS was an outcomes study with a planned follow-up of 5 years. Baseline values were not subtracted from EOT values.

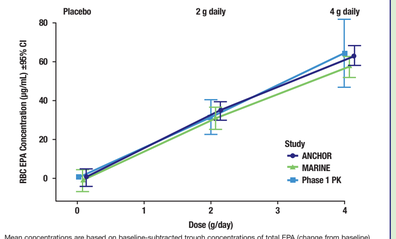
- Increasing doses of icosapent ethyl led to greater increases in EPA concentrations in both plasma and RBCs in all 3 studies (**Figures 2** and **3**)

Figure 2. Icosapent Ethyl Dose Dependence of Plasma EPA Concentrations* in the Phase 1 PK, MARINE, and ANCHOR Studies



*Mean concentrations are based on baseline-subtracted trough concentrations of total EPA (change from baseline) at steady state.

Figure 3. Icosapent Ethyl Dose Dependence of RBC EPA Concentrations in the Phase 1 PK, MARINE, and ANCHOR Studies

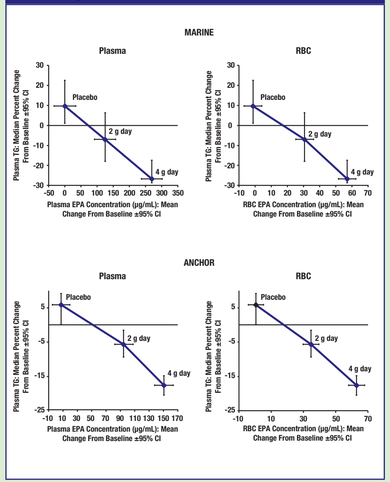


Mean concentrations are based on baseline-subtracted trough concentrations of total EPA (change from baseline) at steady state.

Relationship Between EPA Concentration and TG-lowering Response

- Patients in the MARINE and ANCHOR studies treated with icosapent ethyl experienced a dose-dependent reduction in TG levels that was also linearly associated with an increase in EPA levels (**Figure 4**)

Figure 4. Icosapent Ethyl: Relationship Between Plasma TG-lowering and EPA Concentrations in Plasma and RBCs



Factors Potentially Affecting Icosapent Ethyl PK

- Data from both the MARINE and ANCHOR studies demonstrate that gender, age, baseline TG levels, body weight, and BMI have no effect on EPA concentrations in plasma and RBCs
- Treatment with concomitant medications including statins, antihypertensive medications, and antiplatelet medications did not affect increases in plasma EPA concentrations in both the MARINE and ANCHOR studies
- Analysis of patients in ANCHOR indicated that patients with and without diabetes mellitus had on average the same plasma and RBC EPA increases
- Icosapent ethyl was administered with or following a meal (or snack) and therefore exposure measurements of EPA were studied in the fed state

SUMMARY AND CONCLUSIONS

- Plasma and RBC EPA levels were increased compared with baseline in both the icosapent ethyl 4 g/day and 2 g/day groups in all 3 studies, and were linear with dose, indicating that icosapent ethyl has predictable PK
  - In patients with very high TG levels, the end-of-treatment plasma EPA level was 327 µg/mL with icosapent ethyl 4 g/day in the MARINE study; in the separate EVOLVE study, plasma EPA and DHA levels were 170 µg/mL and 169 µg/mL, respectively, following treatment with omega-3-carboxylic acids 4 g/day[4]
  - In patients with high TG levels, the end-of-treatment plasma EPA level was 183 µg/mL with icosapent ethyl 4 g/day in the ANCHOR study; in the separate ESPRIT study, plasma EPA and DHA levels were 105 µg/mL and 100 µg/mL, respectively, following treatment with omega-3-carboxylic acids 4 g/day[5]
  - In the JELIS study, which investigated EPA ethyl ester, the same active ingredient as icosapent ethyl, the on-treatment plasma EPA level was 170 µg/mL[6]
- The relationships between icosapent ethyl dose and TG-lowering response and between EPA concentration and TG-lowering response were similar and linear, indicating that icosapent ethyl has predictable PD and PK/PD characteristics
- Demographic factors (age, gender, body weight, BMI, and presence of diabetes mellitus), baseline TG levels, and concomitant medications (statins, antihypertensives, and antiplatelets) did not appear to affect the increase in EPA concentrations in plasma and RBCs after treatment with icosapent ethyl
- The PK results were similar among all 3 studies; the PK/PD results were similar between the 2 studies investigated, MARINE and ANCHOR

ABBREVIATIONS

BID=twice daily; BMI=body mass index; BW=body weight; CDC=Centers for Disease Control and Prevention; CI=confidence interval; EOT=end of treatment; EPA=eicosapentaenoic acid; ESPRIT=Epanova Combined With a Statin in Patients With Hypertriglyceridemia to Reduce Non-HDL Cholesterol; EVOLVE=Epanova for Lowering Very High Triglycerides trial; IQR=interquartile range; ITT=intent to treat; JELIS=Japan EPA Lipid Intervention Study; LC-MS/MS=liquid chromatography with tandem mass spectrometry; LDL-C=low-density lipoprotein cholesterol; LSM=least-squares means; MARINE=Multi-Center, Placebo Controlled, Randomized, Double-Blind, 12-week study with an open-label Extension; NA=not applicable; NCEP ATP III=National Cholesterol Education Program Adult Treatment Panel III; PD=pharmacodynamic; PK=pharmacokinetic; QD=once daily; RBC=red blood cell; SD=standard deviation; TG=triglyceride; US FDA=United States Food and Drug Administration

AUTHOR DISCLOSURES

Drs. Braeckman and Soni are former employees of Amarin Pharma Inc.

Dr. Bays' research site has received research grants from Amarin Pharma Inc., Amgen, Ardea, Arena, Boehringer Ingelheim, Cargill Inc., California Raisin Board, Eisai, Elcelyx, Esperion, Essentialis, Forest Laboratories, Gilead Sciences Inc., Given, GlaxoSmithKline, High Point Pharmaceuticals, Hoffman LaRoche, Home Access, Merck & Co., Micrognathus, Nektar, Novartis, Novo Nordisk, Omthera, Orexigen, Pfizer Inc., Pozen, Regeneron, Shionogi, Stratum Nutrition, Takeda Pharmaceuticals, TIMI, TransTech Pharma, Trygg Pharmaceuticals, TWI Bio, Vivus, WPU, and Xoma. Dr. Bays has received consulting fees or speaking honoraria from Amarin Pharma Inc., Amgen, AstraZeneca, Bristol-Myers Squibb, Catabasis, Daiichi Sankyo, Eisai, Merck & Co., Vivus, WPU, and Zeomedex.

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Dr. Stirtan is an employee and stock shareholder of Amarin Pharma Inc.

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ABSTRACT

Synopsis: Icosapent ethyl is a high-purity prescription form of eicosapentaenoic acid (EPA) ethyl ester approved to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia.

Objective: To examine the effects of icosapent ethyl on EPA concentrations in plasma and red blood cells (RBCs) in response to dose and the relationship to TG lowering across 3 clinical studies.

Methods: MARINE and ANCHOR were 12-week, phase 3, double-blind studies that randomized adult patients to icosapent ethyl 4 g/day, icosapent ethyl 2 g/day, or placebo. MARINE randomized 229 patients with TG ≥500 and ≤2000 mg/dL while ANCHOR randomized 702 high-risk patients with TG ≥200 and <500 mg/dL despite low-density lipoprotein cholesterol (LDL-C) control while on statin therapy. Icosapent ethyl 4 g/day and 2 g/day was also investigated in 48 healthy adult subjects for 4 weeks in a phase 1 pharmacokinetics (PK) study.

Results: In all studies, a greater increase in EPA concentrations in both plasma and RBCs was observed with icosapent ethyl 4 g/day than with 2 g/day, indicating a dose-dependent increase in EPA exposure. EPA concentration data from healthy volunteers and in patients with hypertriglyceridemia indicate that the PK of EPA are linear with dose. Following treatment with icosapent ethyl 4 g/day, mean±SD plasma EPA levels increased from 61.2±67.4 µg/mL at baseline to 326.7±205.7 µg/mL at 12 weeks in MARINE and from 28.1±18.8 µg/mL at baseline to 182.6±71.7 µg/mL at 12 weeks in ANCHOR. In MARINE and ANCHOR, median percent reductions in TG from baseline were higher with icosapent ethyl 4 g/day than with 2 g/day and demonstrated a dose-proportional relationship. In plasma and RBCs, a linear pharmacodynamic (PD) relationship between EPA levels and TG reduction was also observed, demonstrating a linear concentration-response relationship.

Conclusions: Taken together, the linear-dose-PK and dose-concentration-response PD relationships indicate that the PK/PD of icosapent ethyl are predictable as the results demonstrate a trend of increasing TG-lowering efficacy with respect to both the icosapent ethyl dose and EPA concentration in plasma and RBCs.

INTRODUCTION

- Icosapent ethyl (Vascepa® [formerly AMR101]; 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
- A phase 1 PK study conducted in healthy volunteers demonstrated that the PK profile of icosapent ethyl was that of a slowly cleared and extensively distributed molecule with dose-linearity
- The MARINE and ANCHOR pivotal studies demonstrated collectively that icosapent ethyl significantly reduced TG levels in patients with very high (MARINE) or high (ANCHOR) TG levels and on statin therapy without raising LDL-C[1,2]
- The present analysis evaluated data from 2 studies conducted in patients with elevated TG levels and 1 study conducted in healthy volunteers for a PK/PD dose-response relationship with respect to icosapent ethyl dose, EPA concentration in plasma and RBCs, and reduction in TG levels

METHODS

Study Design

- Phase 1 PK study
  - Open-label, randomized, multidose study with a 14-day screening period followed by a 4-week treatment period
  - Healthy, nonsmoking volunteers aged >18 and ≤55 years not receiving any lipid-altering medications or supplements within 6 weeks before the study were randomized to 4 icosapent ethyl dose regimens (groups 1 and 2 are included in this analysis):
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  - After dosing, subjects entered an 18-day post-treatment PK sampling period
- MARINE and ANCHOR[1,2]
  - Phase 3, placebo-controlled, randomized, double-blind, multicenter studies with a 4- to 6-week lead-in period of diet, lifestyle, and medication stabilization with washout of prohibited lipid-altering medications
  - In both studies, patients aged >18 years with qualifying lipid levels (MARINE: TG ≥500 mg/dL and ≤2000 mg/dL; ANCHOR: TG ≥200 and <500 mg/dL and LDL-C ≥40 and ≤115 mg/dL) entered a 12-week, double-blind treatment period and were randomized to receive either icosapent ethyl 4 g/day, icosapent ethyl 2 g/day, or matched placebo
  - In the MARINE study, stable statin therapy with or without ezetimibe was permitted but not required
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Assessments and Measurements

- In the MARINE and ANCHOR studies, the trough EPA concentrations were measured after 12 weeks of dosing with icosapent ethyl 4 g/day, icosapent ethyl 2 g/day, or placebo
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  - Total EPA in plasma and RBCs: lipids were isolated by acid/methanol/chloroform extraction followed by centrifugation and purified by isohexane and solid-phase extraction after confirmed complete lipid hydrolysis and transmethylation (acid/methanol, 50°C overnight)
  - Quantitation utilized linolenic acid as an internal standard and EPA as the standard for the calibration curve; for total plasma EPA and total RBC EPA, the lower limits of quantitation were 10 µg/mL and 5 µg/mL, respectively
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  - Serum TG levels were measured with enzymatic colorimetric tests with calibration directly traceable to US CDC reference procedures

RESULTS

Subjects

- Baseline characteristics are summarized in **Table 1** and were comparable among treatment groups within each study

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	Icosapent Ethyl 4 g/day (n=12)	Icosapent Ethyl 2 g/day (n=12)	Icosapent Ethyl 4 g/day (n=77)	Icosapent Ethyl 2 g/day (n=76)	Placebo (n=76)	Icosapent Ethyl 4 g/day (n=233)	Icosapent Ethyl 2 g/day (n=236)	Placebo (n=233)
Age, mean (SD), y	37.9 (12.9)	36.9 (13.5)	51.9 (10.3)	53.4 (9.3)	53.4 (8.3)	61.1 (10.0)	61.8 (9.4)	61.2 (10.1)
Male, n (%)	6 (50.0)	6 (50.0)	59 (76.6)	58 (76.3)	58 (76.3)	142 (60.9)	144 (61.0)	145 (62.2)
Weight, mean (SD), kg	75.5 (13.4)	74.5 (14.1)	93.2 (18.3)	92.1 (15.6)	93.0 (16.9)	94.5 (18.3)	95.5 (18.3)	97.0 (19.1)
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Diabetes, n (%)	NA	NA	22 (28.6)	20 (26.3)	21 (27.6)	171 (73.4)	172 (72.9)	171 (73.4)
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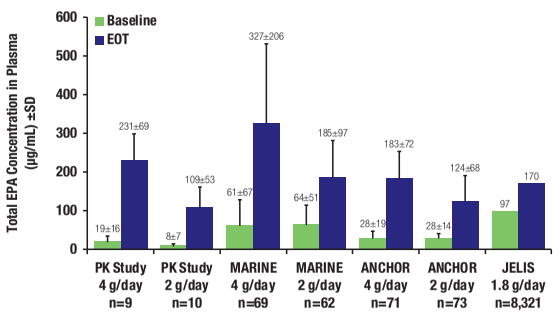
Total plasma EPA, mean (SD), µg/mL	19.3 (16.1) n=9	7.9 (7.0) n=10	61.2 (67.4) n=69	63.6 (51.4) n=62	57.7 (42.7) n=61	28.1 (18.8) n=71	28.1 (13.7) n=73	28.1 (28.0) n=81
RBC EPA, mean (SD), µg/mL	12.1 (15.7) n=9	5.7 (4.3) n=10	16.0 (9.2) n=66	15.7 (9.9) n=61	14.7 (9.3) n=64	11.6 (5.6) n=69	10.9 (5.2) n=71	11.2 (6.6) n=79

EPA Dose Response

- Healthy subjects and patients with hypertriglyceridemia experienced dose-dependent increases in plasma EPA concentrations following treatment with icosapent ethyl (**Figure 1**)
- Similar plasma EPA increases were observed in the JELIS study, which investigated pure EPA ethyl ester, the same active ingredient as in icosapent ethyl, in a cardiovascular outcomes study with a planned 5-year follow-up[4]

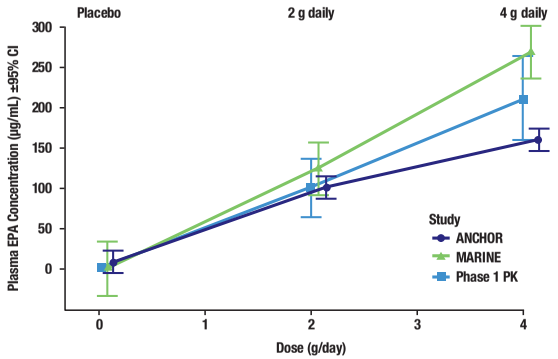
Figure 1. Mean Trough Total EPA Concentrations (±SD) in Plasma at Baseline and EOT in the Phase 1 PK, MARINE, ANCHOR, and JELIS Studies



EOT=4 weeks for the phase 1 PK study; 12 weeks in the MARINE and ANCHOR studies. JELIS was an outcomes study with a planned follow-up of 5 years. Baseline values were not subtracted from EOT values.

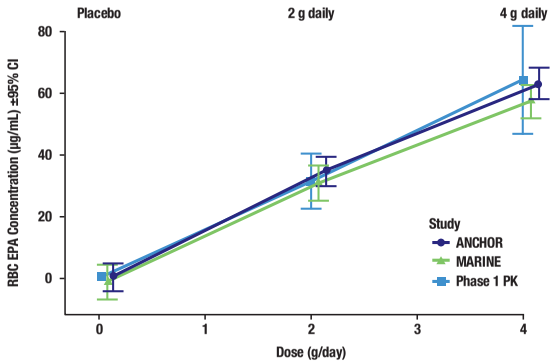
- Increasing doses of icosapent ethyl led to greater increases in EPA concentrations in both plasma and RBCs in all 3 studies (**Figures 2** and **3**)

Figure 2. Icosapent Ethyl Dose Dependence of Plasma EPA Concentrations* in the Phase 1 PK, MARINE, and ANCHOR Studies



*Mean concentrations are based on baseline-subtracted trough concentrations of total EPA (change from baseline) at steady state.

Figure 3. Icosapent Ethyl Dose Dependence of RBC EPA Concentrations in the Phase 1 PK, MARINE, and ANCHOR Studies

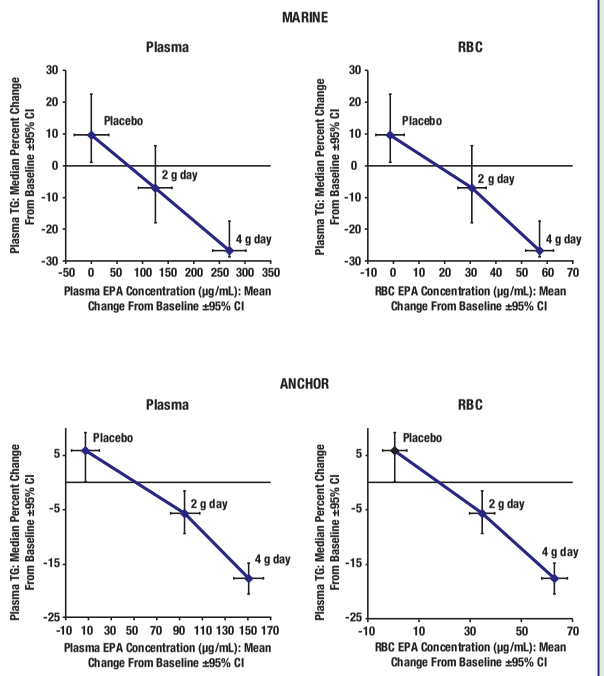


Mean concentrations are based on baseline-subtracted trough concentrations of total EPA (change from baseline) at steady state.

Relationship Between EPA Concentration and TG-lowering Response

- Patients in the MARINE and ANCHOR studies treated with icosapent ethyl experienced a dose-dependent reduction in TG levels that was also linearly associated with an increase in EPA levels (**Figure 4**)

Figure 4. Icosapent Ethyl: Relationship Between Plasma TG-lowering and EPA Concentrations in Plasma and RBCs



Factors Potentially Affecting Icosapent Ethyl PK

- Data from both the MARINE and ANCHOR studies demonstrate that gender, age, baseline TG levels, body weight, and BMI have no effect on EPA concentrations in plasma and RBCs
- Treatment with concomitant medications including statins, antihypertensive medications, and antiplatelet medications did not affect increases in plasma EPA concentrations in both the MARINE and ANCHOR studies
- Analysis of patients in ANCHOR indicated that patients with and without diabetes mellitus had on average the same plasma and RBC EPA increases
- Icosapent ethyl was administered with or following a meal (or snack) and therefore exposure measurements of EPA were studied in the fed state

SUMMARY AND CONCLUSIONS

- Plasma and RBC EPA levels were increased compared with baseline in both the icosapent ethyl 4 g/day and 2 g/day groups in all 3 studies, and were linear with dose, indicating that icosapent ethyl has predictable PK
  - In patients with very high TG levels, the end-of-treatment plasma EPA level was 327 µg/mL with icosapent ethyl 4 g/day in the MARINE study; in the separate EVOLVE study, plasma EPA and DHA levels were 170 µg/mL and 169 µg/mL, respectively, following treatment with omega-3-carboxylic acids 4 g/day[4]
  - In patients with high TG levels, the end-of-treatment plasma EPA level was 183 µg/mL with icosapent ethyl 4 g/day in the ANCHOR study; in the separate ESPRIT study, plasma EPA and DHA levels were 105 µg/mL and 100 µg/mL, respectively, following treatment with omega-3-carboxylic acids 4 g/day[5]
  - In the JELIS study, which investigated EPA ethyl ester, the same active ingredient as icosapent ethyl, the on-treatment plasma EPA level was 170 µg/mL[6]
- The relationships between icosapent ethyl dose and TG-lowering response and between EPA concentration and TG-lowering response were similar and linear, indicating that icosapent ethyl has predictable PD and PK/PD characteristics
- Demographic factors (age, gender, body weight, BMI, and presence of diabetes mellitus), baseline TG levels, and concomitant medications (statins, antihypertensives, and antiplatelets) did not appear to affect the increase in EPA concentrations in plasma and RBCs after treatment with icosapent ethyl
- The PK results were similar among all 3 studies; the PK/PD results were similar between the 2 studies investigated, MARINE and ANCHOR

ABBREVIATIONS

BID=twice daily; BMI=body mass index; BW=body weight; CDC=Centers for Disease Control and Prevention; CI=confidence interval; EOT=end of treatment; EPA=eicosapentaenoic acid; ESPRIT=Epanova Combined With a Statin in Patients With Hypertriglyceridemia to Reduce Non-HDL Cholesterol; EVOLVE=Epanova for Lowering Very High Triglycerides trial; IQR=interquartile range; ITT=intent to treat; JELIS=Japan EPA Lipid Intervention Study; LC-MS/MS=liquid chromatography with tandem mass spectrometry; LDL-C=low-density lipoprotein cholesterol; LSM=least-squares means; MARINE=**M**ulti-Center, Pl**A**cebo Controlled, **R**andomized, Double-Bl**I**N**d**, 12-week study with an open-label **E**xtension; NA=not applicable; NCEP ATP III=National Cholesterol Education Program Adult Treatment Panel III; PD=pharmacodynamic; PK=pharmacokinetic; QD=once daily; RBC=red blood cell; SD=standard deviation; TG=triglyceride; US FDA=United States Food and Drug Administration

AUTHOR DISCLOSURES

Drs. Braeckman and Soni are former employees of Amarin Pharma Inc.

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Dr. Stirtan is an employee and stock shareholder of Amarin Pharma Inc.

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