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Icosapent Ethyl (Eicosapentaenoic Acid Ethyl Ester): Effects on Remnant-like Particle Cholesterol From the MARINE and ANCHOR Studies

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ABSTRACT

Synopsis: Remnant-like particle cholesterol (RLP-C) represents the cholesterol carried by partially catabolized triglyceride (TG)-rich lipoproteins such as very-low-density lipoproteins (VLDL) in the fasted state and chylomicron remnants in the post-prandial state. Increased RLP-C levels are atherogenic and may increase the risk of atherosclerotic cardiovascular disease. Long-chain polyunsaturated omega-3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid reduce RLP-C levels. Icosapent ethyl is a high-purity prescription form of EPA ethyl ester approved to reduce TG levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia.

Objective: To evaluate the effects of icosapent ethyl on RLP-C levels in patients from the MARINE and ANCHOR studies.

Methods: MARINE (TG ≥500 and ≤2000 mg/dL; N=229) and ANCHOR (TG ≥200 and <500 mg/dL despite statin control of low-density lipoprotein cholesterol; N=702) were both 12-week, phase 3, double-blind studies that randomized adult patients to icosapent ethyl 4 g/day, 2 g/day, or placebo. This analysis assessed the median percentage change from baseline to study end in RLP-C levels compared with placebo. Serum RLP-C was measured with an immunoseparation assay (Polymedco).

Results: In both the MARINE (n=218 with RLP-C data) and ANCHOR (n=252 with RLP-C data) studies, compared with placebo, icosapent ethyl 4 g/day (see Table 2) and 2 g/day reduced RLP-C levels. Compared with placebo, the approved icosapent ethyl dose of 4 g/day also reduced RLP-C to a greater extent in subgroups with higher baseline TG levels, reduced RLP-C in statin-treated patients in the MARINE study, and reduced RLP-C in patients receiving moderate- to high-intensity statins in the ANCHOR study.

Conclusion: Compared with placebo, icosapent ethyl reduced RLP-C levels in adult patients in the MARINE and ANCHOR studies, including significant reductions in RLP-C in hypertriglyceridemic patients with TG ≥200 mg/dL and ≥500 mg/dL receiving statin therapy.

INTRODUCTION

- RLP-C is the cholesterol content of TG-rich lipoproteins such as chylomicron remnants (in the nonfasting state) and VLDL and IDL (in the fasting and nonfasting states)[1]
- Increased TG levels are associated with increased RLP-C levels, which are associated with increased risk for cardiovascular events[1-4]
- Long-chain polyunsaturated omega-3 fatty acids such as EPA and DHA reduce RLP-C levels[5,6]
- Icosapent ethyl (Vascepa®; Amarin Pharma Inc., Bedminster, NJ, USA) 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[7]
- The MARINE and ANCHOR studies demonstrated that icosapent ethyl 4 g/day significantly reduced TG levels and non-HDL-C and improved other lipid parameters without raising LDL-C in patients with very high (MARINE) or high (ANCHOR) TG levels compared with placebo[8,9]
- These analyses evaluated the effects of icosapent ethyl on RLP-C in patients from the MARINE and ANCHOR studies

METHODS

Study Design

- MARINE and ANCHOR were 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[8,9]
- In both studies, patients aged >18 years with qualifying lipid levels (MARINE: TG ≥500 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 CVD as defined by the NCEP ATP III guidelines and on a stable statin dose (atorvastatin, rosuvastatin, or simvastatin with or without ezetimibe)[9,10]

Assessments and Measurements

- Per prespecified exploratory endpoints of the MARINE and ANCHOR studies, serum RLP-C was measured with an immunoseparation assay by Polymedco (Cortlandt Manor, NY, USA) on the Daytona chemistry analyzer (Randox, Crumlin, United Kingdom)
- Lipid levels were measured as previously reported[8]
- Median differences in percent change from baseline between the icosapent ethyl and placebo treatment groups were estimated with the Hodges-Lehmann method; *P* values are from the Wilcoxon rank-sum test
- A *P* value of 0.05 was the prespecified alpha for significance for exploratory end points in the MARINE and ANCHOR studies and was used in these analyses

RESULTS

Patients

- Baseline demographics and lipid parameters appeared comparable among treatment groups within each study (**Table 1**)
- Total RLP-C levels were assessed in 218 and 252 patients from the MARINE and ANCHOR studies, respectively
- In MARINE, 25% of patients were on statin therapy; in ANCHOR, all patients were on statins, 93.2% of whom were on medium- or higher-intensity statin regimens

Table 1. Baseline Characteristics (Randomized Populations) and Baseline Lipid Parameters (Patients From ITT Populations With RLP-C Measurements)

	Icosapent Ethyl 4 g/day	Icosapent Ethyl 2 g/day	Placebo
Baseline Characteristics			
MARINE	**n=77**	**n=76**	**n=76**
Age, mean (SD), y	51.9 (10.27)	53.4 (9.34)	53.4 (8.34)
Male, n (%)	59 (77)	58 (76)	58 (76)
Weight, mean (SD), kg	93.2 (18.27)	92.1 (15.57)	93.0 (16.92)
BMI, mean (SD), kg/m^2	30.4 (4.29)	30.8 (4.24)	31.0 (4.25)
Diabetes, n (%)	22 (29)	20 (26)	21 (28)
ANCHOR	**n=233**	**n=236**	**n=233**
Age, mean (SD), y	61.1 (10.03)	61.8 (9.42)	61.2 (10.05)
Male, n (%)	142 (61)	144 (61)	145 (62)
Weight, mean (SD), kg	94.5 (18.30)	95.5 (18.29)	97.0 (19.14)
BMI, mean (SD), kg/m^2	32.7 (4.99)	32.9 (4.98)	33.0 (5.04)
Diabetes, n (%)	171 (73)	172 (73)	171 (73)
Baseline Lipid Parameters[a]			
MARINE			
TG (mg/dL)	679.5 (268.0) n=75	660.5 (304.0) n=70	706.0 (413.0) n=73
LDL-C (mg/dL)	90.0 (45.0) n=75	81.0 (61.0) n=70	81.0 (56.0) n=73
Non-HDL-C (mg/dL)	225.0 (93.0) n=75	211.5 (77.0) n=70	230.0 (85.0) n=73
VLDL-C (mg/dL)	122.0 (101.0) n=75	121.5 (59.0) n=70	130.0 (81.0) n=73
VLDL-TG (mg/dL)	521.0 (352.0) n=75	506.0 (447.0) n=70	549.0 (453.0) n=73
Apo B (mg/dL)	121.0 (34.0) n=75	117.5 (35.0) n=70	118.0 (39.0) n=73
ANCHOR			
TG (mg/dL)	255.8 (90.0) n=82	262.5 (83.25) n=84	264.3 (77.5) n=86
LDL-C (mg/dL)	78.0 (22.0) n=82	83.0 (22.0) n=83	80.0 (29.0) n=85
Non-HDL-C (mg/dL)	122.0 (32.0) n=82	124.5 (31.5) n=84	124.0 (29.0) n=86
VLDL-C (mg/dL)	43.5 (19.0) n=82	41.0 (20.0) n=83	41.0 (16.0) n=85
VLDL-TG (mg/dL)	195.5 (102.0) n=82	192.0 (86.0) n=83	197.0 (89.0) n=85
Apo B (mg/dL)	88.5 (24.0) n=82	91.0 (19.0) n=84	92.0 (22.0) n=86

[a]Data are presented as medians (IQR) for baseline lipid parameter values. Baseline RLP-C levels are shown in Table 2.

MARINE

- Compared with placebo, at the approved dose of 4 g/day, icosapent ethyl significantly reduced RLP-C levels by 29.8% (*P*=0.0041) (**Figure 1, Table 2**)
- Compared with placebo, following treatment with icosapent ethyl 4 g/day, significant reductions in RLP-C levels were observed in patients not receiving statins (21.4%; *P*=0.0456; n=56) as well as in patients receiving statins (56.8%; *P*=0.0198; n=19) (**Figure 2, Table 2**)
- Compared with placebo, following treatment with icosapent ethyl 4 g/day, significant reductions in RLP-C levels were observed in patients with baseline TG >750 mg/dL (37.5%; *P*=0.0196; n=28); in patients with baseline TG ≤750 mg/dL, RLP-C levels were reduced, although statistical significance was not reached (26.1%; *P*=0.0570; n=47) (**Table 2**)

ANCHOR

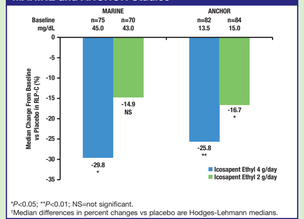
- Compared with placebo, icosapent ethyl 4 g/day significantly reduced RLP-C levels by 25.8% (*P*=0.0001) (**Figure 1, Table 2**)
- RLP-C levels were also evaluated in subgroups based on statin regimen intensity (**Figure 3, Table 2**)
- Compared with placebo, following treatment with icosapent ethyl 4 g/day, significant reductions in RLP-C levels were observed in patients below the median baseline TG level (<259 mg/dL; 22.2%; *P*=0.0263; n=42), as well as above (≥259 mg/dL; 30.6%; *P*=0.0010; n=40) (**Table 2**)

Table 2. Change From Baseline to Week 12 in RLP-C in Patients From the MARINE and ANCHOR Studies

	RLP-C Concentration[a]									Median Change From Baseline in RLP-C Concentration vs Placebo[b]	
	Icosapent Ethyl 4 g/day			Icosapent Ethyl 2 g/day			Placebo			Icosapent Ethyl 4 g/day	Icosapent Ethyl 2 g/day
	Baseline, mg/dL	End of Treatment, mg/dL	Change, %	Baseline, mg/dL	End of Treatment, mg/dL	Change, %	Baseline, mg/dL	End of Treatment, mg/dL	Change, %	%, *P*	%, *P*
MARINE		n=76			n=73			n=75			
ITT[c]	45.0 (53.0)	n=75 38.0 (45.0)	−16.1 (86.5)	43.0 (37.0)	n=70 44.5 (38.0)	5.8 (85.5)	47.0 (58.0)	n=73 58.0 (90.0)	14.2 (105.4)	−29.8 0.0041	−14.9 0.1528
Current Statin Use											
No	45.0 (55.5)	n=56 39.5 (48.5)	−16.6 (85.9)	45.0 (34.5)	n=52 44.5 (36.0)	3.0 (67.6)	50.5 (61.0)	n=56 54.5 (77.5)	7.0 (107.0)	−21.4 0.0456	−8.5 0.4421
Yes	37.0 (45.0)	n=19 33.0 (27.0)	−16.1 (136.4)	31.5 (47.0)	n=18 46.5 (50.0)	29.2 (108.0)	40.0 (38.0)	n=17 65.0 (124.0)	54.3 (116.9)	−56.8 0.0198	−41.6 0.1511
Baseline TG cut at 750 mg/dL											
≤750 mg/dL	34.0 (30.0)	n=47 29.0 (28.0)	−8.8 (100.0)	27.5 (23.0)	n=42 32.5 (23.0)	18.2 (85.8)	30.0 (21.0)	n=41 33.0 (31.0)	19.0 (95.5)	−26.1 0.0570	−7.3 0.6554
>750 mg/dL	89.5 (109.0)	n=28 68.5 (73.0)	−25.4 (59.7)	66.0 (51.5)	n=28 65.0 (35.5)	−10.7 (72.5)	90.5 (75.5)	n=32 100.5 (89.5)	5.7 (111.1)	−37.5 0.0196	−25.4 0.1016
ANCHOR		n=226			n=234			n=227			
ITT[c]	13.5 (6.0)	n=82 10.0 (6.0)	−24.0 (45.5)	15.0 (7.0)	n=84 11.0 (7.0)	−11.1 (40.0)	14.0 (7.0)	n=86 13.0 (9.0)	8.0 (66.9)	−25.8 0.0001	−16.7 0.0153
Statin Intensity[d]											
Lower	16.0 (3.0)	n=5 15.0 (5.0)	−29.2 (33.3)	15.0 (6.0)	n=7 11.0 (9.0)	−11.1 (21.1)	15.0 (6.0)	n=6 11.0 (24.0)	−19.4 (105.1)	−11.9 0.5228	2.7 0.8303
Medium and higher	13.0 (6.0)	n=77 10.0 (6.0)	−23.1 (45.5)	15.0 (7.0)	n=77 11.0 (7.0)	−11.1 (42.3)	14.0 (7.0)	n=80 13.0 (8.5)	8.7 (66.5)	−26.7 0.0002	−17.3 0.0135
Study-Wide Median[e] TG (259 mg/dL)											
<259	11.0 (4.0)	n=42 9.0 (5.0)	−16.0 (47.6)	11.5 (5.0)	n=40 11.0 (3.5)	−8.1 (37.4)	11.0 (5.0)	n=37 12.0 (7.0)	9.1 (58.2)	−22.2 0.0263	−16.4 0.1092
≥259	17.0 (5.5)	n=40 11.0 (6.5)	−31.3 (37.6)	18.0 (8.0)	n=44 13.5 (7.0)	−17.4 (37.2)	16.0 (4.0)	n=49 16.0 (11.0)	7.7 (64.1)	−30.6 0.0010	−18.0 0.0658

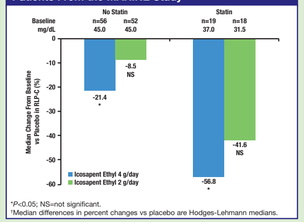
[a]Data are presented as median (IQR) for end point values.
[b]Median differences in percent changes vs placebo are Hodges-Lehmann medians.
[c]Patients from ITT populations with RLP-C measurements.
[d]Statin intensity definitions are in the Definitions and Abbreviations section.
[e]Study-wide median represents the median of patients assessed in the 4 g/day, 2 g/day, and placebo groups.

Figure 1. Median Percent Change From Baseline to Week 12 vs Placebo in RLP-C in Patients From the MARINE and ANCHOR Studies†



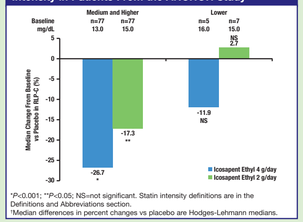
*P<0.05; **P<0.01; NS=not significant.
†Median differences in percent changes vs placebo are Hodges-Lehmann medians.

Figure 2. Median Percent Change From Baseline to Week 12 vs Placebo in RLP-C by Statin Use in Patients From the MARINE Study†



*P<0.05; NS=not significant.
†Median differences in percent changes vs placebo are Hodges-Lehmann medians.

Figure 3. Median Percent Change From Baseline to Week 12 vs Placebo in RLP-C by Statin Regimen Intensity in Patients From the ANCHOR Study†



*P<0.001; **P<0.05; NS=not significant. Statin intensity definitions are in the Definitions and Abbreviations section.
†Median differences in percent changes vs placebo are Hodges-Lehmann medians.

SUMMARY AND CONCLUSIONS

- These analyses examined the effects of icosapent ethyl on RLP-C levels in patients from the MARINE (TG ≥500 and ≤2000 mg/dL) and ANCHOR (TG ≥200 and <500 mg/dL) studies
- In addition to previously reported TG- and non-HDL-C–lowering effects, which were observed without increases in LDL-C,[8,9] icosapent ethyl significantly lowered RLP-C levels in patients from the MARINE and ANCHOR studies compared with placebo
- When patients were stratified by baseline TG levels, reductions in RLP-C with the approved dose of icosapent ethyl 4 g/day compared with placebo were greatest among patients with higher baseline TG levels from both the MARINE and ANCHOR studies
- Compared with placebo, icosapent ethyl 4 g/day reduced RLP-C in statin-treated patients in the MARINE and ANCHOR studies
- Reductions in RLP-C with icosapent ethyl 4 g/day may be greater in patients receiving moderate- to higher-intensity statin regimens as demonstrated in the ANCHOR study, although small sample size may be a limiting factor in the subgroup analyses of patients receiving lower-intensity statin regimens in the ANCHOR study, and of patients receiving statin therapy in the MARINE study
- These analyses extend the findings to date of the potentially beneficial lipid effects of icosapent ethyl in patients with elevated TG levels including effects on top of statin therapy

DEFINITIONS AND ABBREVIATIONS

Lower-intensity statin regimens=simvastatin 5 to 10 mg; Medium-intensity statin regimens=rosuvastatin 5 to 10 mg, atorvastatin 10 to 20 mg, simvastatin 20 to 40 mg, simvastatin 10 to 20 mg plus ezetimibe 5 to 10 mg; Higher-intensity statin regimens=rosuvastatin 20 to 40 mg, atorvastatin 40 to 80 mg, simvastatin 80 mg, simvastatin 40 to 80 mg plus ezetimibe 5 to 10 mg; Apo B=apolipoprotein B; BMI=body mass index; CVD=cardiovascular disease; DHA=docosahexaenoic acid; EPA=eicosapentaenoic acid; IDL=intermediate-density lipoprotein; IQR=interquartile range; ITT=intent to treat; LDL-C=low-density lipoprotein cholesterol; MARINE=**M**ulti-Center, Pl**A**cebo Controlled, **R**andomized, Double-Bl**IN**d, 12-week study with an open-label **E**xtension; NCEP ATP III=National Cholesterol Education Program Adult Treatment Panel III; Non-HDL-C=non-high-density lipoprotein cholesterol; RLP-C=remnant-like particle cholesterol; SD=standard deviation; TG=triglyceride; US FDA=United States Food and Drug Administration; VLDL=very-low-density lipoprotein; VLDL-C=very-low-density lipoprotein cholesterol; VLDL-TG=very-low-density lipoprotein triglycerides

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DISCLOSURES

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Drs. Stirtan, Philip and Juliano and Mr. Doyle are employees and stock shareholders of Amarin Pharma Inc. Dr. Philip is also affiliated with Chilton Medical Center.

Rene A. Braeckman and Paresh N. Soni are former employees of Amarin Pharma Inc.

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ABSTRACT

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Assessments and Measurements

- Per prespecified exploratory endpoints of the MARINE and ANCHOR studies, serum RLP-C was measured with an immunoseparation assay by Polymedco (Cortlandt Manor, NY, USA) on the Daytona chemistry analyzer (Randox, Crumlin, United Kingdom)
- Lipid levels were measured as previously reported[8]
- Median differences in percent change from baseline between the icosapent ethyl and placebo treatment groups were estimated with the Hodges-Lehmann method; *P* values are from the Wilcoxon rank-sum test
- A *P* value of 0.05 was the prespecified alpha for significance for exploratory end points in the MARINE and ANCHOR studies and was used in these analyses

RESULTS

Patients

- Baseline demographics and lipid parameters appeared comparable among treatment groups within each study (**Table 1**)
- Total RLP-C levels were assessed in 218 and 252 patients from the MARINE and ANCHOR studies, respectively
- In MARINE, 25% of patients were on statin therapy; in ANCHOR, all patients were on statins, 93.2% of whom were on medium- or higher-intensity statin regimens

Table 1. Baseline Characteristics (Randomized Populations) and Baseline Lipid Parameters (Patients From ITT Populations With RLP-C Measurements)

	Icosapent Ethyl 4 g/day	Icosapent Ethyl 2 g/day	Placebo
Baseline Characteristics			
MARINE	**n=77**	**n=76**	**n=76**
Age, mean (SD), y	51.9 (10.27)	53.4 (9.34)	53.4 (8.34)
Male, n (%)	59 (77)	58 (76)	58 (76)
Weight, mean (SD), kg	93.2 (18.27)	92.1 (15.57)	93.0 (16.92)
BMI, mean (SD), kg/m^2	30.4 (4.29)	30.8 (4.24)	31.0 (4.25)
Diabetes, n (%)	22 (29)	20 (26)	21 (28)
ANCHOR	**n=233**	**n=236**	**n=233**
Age, mean (SD), y	61.1 (10.03)	61.8 (9.42)	61.2 (10.05)
Male, n (%)	142 (61)	144 (61)	145 (62)
Weight, mean (SD), kg	94.5 (18.30)	95.5 (18.29)	97.0 (19.14)
BMI, mean (SD), kg/m^2	32.7 (4.99)	32.9 (4.98)	33.0 (5.04)
Diabetes, n (%)	171 (73)	172 (73)	171 (73)
Baseline Lipid Parameters[a]			
MARINE			
TG (mg/dL)	679.5 (268.0) n=75	660.5 (304.0) n=70	706.0 (413.0) n=73
LDL-C (mg/dL)	90.0 (45.0) n=75	81.0 (61.0) n=70	81.0 (56.0) n=73
Non-HDL-C (mg/dL)	225.0 (93.0) n=75	211.5 (77.0) n=70	230.0 (85.0) n=73
VLDL-C (mg/dL)	122.0 (101.0) n=75	121.5 (59.0) n=70	130.0 (81.0) n=73
VLDL-TG (mg/dL)	521.0 (352.0) n=75	506.0 (447.0) n=70	549.0 (453.0) n=73
Apo B (mg/dL)	121.0 (34.0) n=75	117.5 (35.0) n=70	118.0 (39.0) n=73
ANCHOR			
TG (mg/dL)	255.8 (90.0) n=82	262.5 (83.25) n=84	264.3 (77.5) n=86
LDL-C (mg/dL)	78.0 (22.0) n=82	83.0 (22.0) n=83	80.0 (29.0) n=85
Non-HDL-C (mg/dL)	122.0 (32.0) n=82	124.5 (31.5) n=84	124.0 (29.0) n=86
VLDL-C (mg/dL)	43.5 (19.0) n=82	41.0 (20.0) n=83	41.0 (16.0) n=85
VLDL-TG (mg/dL)	195.5 (102.0) n=82	192.0 (86.0) n=83	197.0 (89.0) n=85
Apo B (mg/dL)	88.5 (24.0) n=82	91.0 (19.0) n=84	92.0 (22.0) n=86

[a]Data are presented as medians (IQR) for baseline lipid parameter values.
Baseline RLP-C levels are shown in Table 2.

MARINE

- Compared with placebo, at the approved dose of 4 g/day, icosapent ethyl significantly reduced RLP-C levels by 29.8% (*P*=0.0041) (**Figure 1, Table 2**)
- Compared with placebo, following treatment with icosapent ethyl 4 g/day, significant reductions in RLP-C levels were observed in patients not receiving statins (21.4%; *P*=0.0456; n=56) as well as in patients receiving statins (56.8%; *P*=0.0198; n=19) (**Figure 2, Table 2**)
- Compared with placebo, following treatment with icosapent ethyl 4 g/day, significant reductions in RLP-C levels were observed in patients with baseline TG >750 mg/dL (37.5%; *P*=0.0196; n=28); in patients with baseline TG ≤750 mg/dL, RLP-C levels were reduced, although statistical significance was not reached (26.1%; *P*=0.0570; n=47) (**Table 2**)

ANCHOR

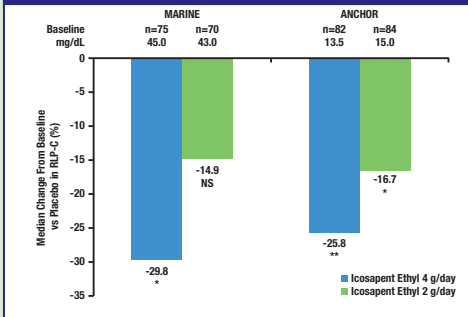
- Compared with placebo, icosapent ethyl 4 g/day significantly reduced RLP-C levels by 25.8% (*P*=0.0001) (**Figure 1, Table 2**)
- RLP-C levels were also evaluated in subgroups based on statin regimen intensity (**Figure 3, Table 2**)
- Compared with placebo, following treatment with icosapent ethyl 4 g/day, significant reductions in RLP-C levels were observed in patients below the median baseline TG level (<259 mg/dL; 22.2%; *P*=0.0263; n=42), as well as above (≥259 mg/dL; 30.6%; *P*=0.0010; n=40) (**Table 2**)

Table 2. Change From Baseline to Week 12 in RLP-C in Patients From the MARINE and ANCHOR Studies

	RLP-C Concentration[a]									Median Change From Baseline in RLP-C Concentration vs Placebo[b]	
	Icosapent Ethyl 4 g/day			Icosapent Ethyl 2 g/day			Placebo			Icosapent Ethyl 4 g/day	Icosapent Ethyl 2 g/day
	Baseline, mg/dL	End of Treatment, mg/dL	Change, %	Baseline, mg/dL	End of Treatment, mg/dL	Change, %	Baseline, mg/dL	End of Treatment, mg/dL	Change, %	%, *P*	%, *P*
MARINE		n=76			n=73			n=75			
ITT[c]		n=75			n=70			n=73		−29.8	−14.9
	45.0 (53.0)	38.0 (45.0)	−16.1 (86.5)	43.0 (37.0)	44.5 (38.0)	5.8 (85.5)	47.0 (58.0)	58.0 (90.0)	14.2 (105.4)	0.0041	0.1528
Current Statin Use											
No		n=56			n=52			n=56		−21.4	−8.5
	45.0 (55.5)	39.5 (48.5)	−16.6 (85.9)	45.0 (34.5)	44.5 (36.0)	3.0 (67.6)	50.5 (61.0)	54.5 (77.5)	7.0 (107.0)	0.0456	0.4421
Yes		n=19			n=18			n=17		−56.8	−41.6
	37.0 (45.0)	33.0 (27.0)	−16.1 (136.4)	31.5 (47.0)	46.5 (50.0)	29.2 (108.0)	40.0 (38.0)	65.0 (124.0)	54.3 (116.9)	0.0198	0.1511
Baseline TG cut at 750 mg/dL											
≤750 mg/dL		n=47			n=42			n=41		−26.1	−7.3
	34.0 (30.0)	29.0 (28.0)	−8.8 (100.0)	27.5 (23.0)	32.5 (23.0)	18.2 (85.8)	30.0 (21.0)	33.0 (31.0)	19.0 (95.5)	0.0570	0.6554
>750 mg/dL		n=28			n=28			n=32		−37.5	−25.4
	89.5 (109.0)	68.5 (73.0)	−25.4 (59.7)	66.0 (51.5)	65.0 (35.5)	−10.7 (72.5)	90.5 (75.5)	100.5 (89.5)	5.7 (111.1)	0.0196	0.1016
ANCHOR		n=226			n=234			n=227			
ITT[c]		n=82			n=84			n=86		−25.8	−16.7
	13.5 (6.0)	10.0 (6.0)	−24.0 (45.5)	15.0 (7.0)	11.0 (7.0)	−11.1 (40.0)	14.0 (7.0)	13.0 (9.0)	8.0 (66.9)	0.0001	0.0153
Statin Intensity[d]											
Lower		n=5			n=7			n=6		−11.9	2.7
	16.0 (3.0)	15.0 (5.0)	−29.2 (33.3)	15.0 (6.0)	11.0 (9.0)	−11.1 (21.1)	15.0 (6.0)	11.0 (24.0)	−19.4 (105.1)	0.5228	0.8303
Medium and higher		n=77			n=77			n=80		−26.7	−17.3
	13.0 (6.0)	10.0 (6.0)	−23.1 (45.5)	15.0 (7.0)	11.0 (7.0)	−11.1 (42.3)	14.0 (7.0)	13.0 (8.5)	8.7 (66.5)	0.0002	0.0135
Study-Wide Median[e] TG (259 mg/dL)											
<259		n=42			n=40			n=37		−22.2	−16.4
	11.0 (4.0)	9.0 (5.0)	−16.0 (47.6)	11.5 (5.0)	11.0 (3.5)	−8.1 (37.4)	11.0 (5.0)	12.0 (7.0)	9.1 (58.2)	0.0263	0.1092
≥259		n=40			n=44			n=49		−30.6	−18.0
	17.0 (5.5)	11.0 (6.5)	−31.3 (37.6)	18.0 (8.0)	13.5 (7.0)	−17.4 (37.2)	16.0 (4.0)	16.0 (11.0)	7.7 (64.1)	0.0010	0.0658

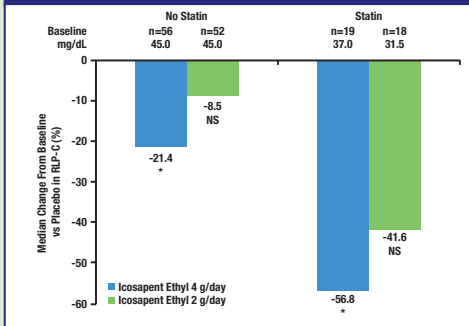
[a]Data are presented as median (IQR) for end point values.
[b]Median differences in percent changes vs placebo are Hodges-Lehmann medians.
[c]Patients from ITT populations with RLP-C measurements.
[d]Statin intensity definitions are in the Definitions and Abbreviations section.
[e]Study-wide median represents the median of patients assessed in the 4 g/day, 2 g/day, and placebo groups.

Figure 1. Median Percent Change From Baseline to Week 12 vs Placebo in RLP-C in Patients From the MARINE and ANCHOR Studies†



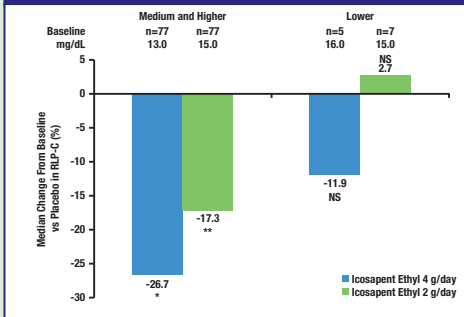
*P<0.05; **P<0.01; NS=not significant.
†Median differences in percent changes vs placebo are Hodges-Lehmann medians.

Figure 2. Median Percent Change From Baseline to Week 12 vs Placebo in RLP-C by Statin Use in Patients From the MARINE Study†



*P<0.05; NS=not significant.
†Median differences in percent changes vs placebo are Hodges-Lehmann medians.

Figure 3. Median Percent Change From Baseline to Week 12 vs Placebo in RLP-C by Statin Regimen Intensity in Patients From the ANCHOR Study†



*P<0.001; **P<0.05; NS=not significant. Statin intensity definitions are in the Definitions and Abbreviations section.
†Median differences in percent changes vs placebo are Hodges-Lehmann medians.

SUMMARY AND CONCLUSIONS

- These analyses examined the effects of icosapent ethyl on RLP-C levels in patients from the MARINE (TG ≥500 and ≤2000 mg/dL) and ANCHOR (TG ≥200 and <500 mg/dL) studies
- In addition to previously reported TG- and non-HDL-C–lowering effects, which were observed without increases in LDL-C,[8,9] icosapent ethyl significantly lowered RLP-C levels in patients from the MARINE and ANCHOR studies compared with placebo
- When patients were stratified by baseline TG levels, reductions in RLP-C with the approved dose of icosapent ethyl 4 g/day compared with placebo were greatest among patients with higher baseline TG levels from both the MARINE and ANCHOR studies
- Compared with placebo, icosapent ethyl 4 g/day reduced RLP-C in statin-treated patients in the MARINE and ANCHOR studies
- Reductions in RLP-C with icosapent ethyl 4 g/day may be greater in patients receiving moderate- to higher-intensity statin regimens as demonstrated in the ANCHOR study, although small sample size may be a limiting factor in the subgroup analyses of patients receiving lower-intensity statin regimens in the ANCHOR study, and of patients receiving statin therapy in the MARINE study
- These analyses extend the findings to date of the potentially beneficial lipid effects of icosapent ethyl in patients with elevated TG levels including effects on top of statin therapy

DEFINITIONS AND ABBREVIATIONS

Lower-intensity statin regimens=simvastatin 5 to 10 mg; Medium-intensity statin regimens=rosuvastatin 5 to 10 mg, atorvastatin 10 to 20 mg, simvastatin 20 to 40 mg, simvastatin 10 to 20 mg plus ezetimibe 5 to 10 mg; Higher-intensity statin regimens=rosuvastatin 20 to 40 mg, atorvastatin 40 to 80 mg, simvastatin 80 mg, simvastatin 40 to 80 mg plus ezetimibe 5 to 10 mg; Apo B=apolipoprotein B; BMI=body mass index; CVD=cardiovascular disease; DHA=docosahexaenoic acid; EPA=eicosapentaenoic acid; IDL=intermediate-density lipoprotein; IQR=interquartile range; ITT=intent to treat; LDL-C=low-density lipoprotein cholesterol; MARINE=**M**ulti-Center, Pl**A**cebo Controlled, **R**andomized, Double-Bl**IN**d, 12-week study with an open-label **E**xtension; NCEP ATP III=National Cholesterol Education Program Adult Treatment Panel III; Non-HDL-C=non-high-density lipoprotein cholesterol; RLP-C=remnant-like particle cholesterol; SD=standard deviation; TG=triglyceride; US FDA=United States Food and Drug Administration; VLDL=very-low-density lipoprotein; VLDL-C=very-low-density lipoprotein cholesterol; VLDL-TG=very-low-density lipoprotein triglycerides

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