

**Efficacy and Safety of Prescription
Omega-3-Acid Esters (P-OM3)
for the Prevention of Symptomatic
Atrial Fibrillation**

PR Kowey, JA Reiffel, KA Ellenbogen, GV Naccarelli,
and CM Pratt for the OM-8 Clinical Trial Investigators

Disclosures

Dr. Kowey and his collaborators have furnished consultation services on an ad hoc basis to several pharmaceutical companies listed in the program book, including Reliant Pharmaceuticals and Glaxo SmithKline. None of the authors received payment for the OM-8 trial data review and analysis, or for preparation of presentations or manuscripts.

Top Ten Enrolling Clinical Sites (>15 patients per site)

CLINICAL LEAD	LOCATION
Robert Benton	Capital Cardiology Associates Troy, NY
Eve Gillespie	Glacier View Cardiology P.C. Kalispell, MT
David Drenning	The Heart Center P.C. Huntsville, AB
Steve Kutz	Cardiology Specialists Ltd. Westerly, RI
Henry Lui	Apex Cardiology Jackson, TN
William Pitt	Southern California Cardiology Medical Group San Diego, CA
Sarah Samaan	Legacy Heart Center Plano, TX
Narendra Singh	Northside Cardiology PC Atlanta, GA
Andrew Waxler	Berks Cardiologists Ltd. Wyomissing, PA
Robert Weiss	Androscoggin Cardiology Associates Auburn, ME

Objectives

- 1) To evaluate the effect of Prescription Omega-3 Fatty Acids (P-OM3) on the time to the first symptomatic recurrence of atrial fibrillation (AF) in participants with recurrent, paroxysmal atrial fibrillation (PAF) who are not receiving anti-arrhythmic therapy (AAD)
- 2) To explore the efficacy and safety of P-OM3 ([Lovaza[®]] *GlaxoSmithKline, Research Triangle Park, NC) in a small population of participants with persistent AF

*GlaxoSmithKline has US marketing rights to LOVAZA[®] prescription omega-3-acid ethyl esters, indicated as an adjunct to diet to reduce TG levels in adults with severe HTG (≥ 500 mg/dL) at 4 g/day.

Methods

- Prospective, randomized, double-blind study using time to first symptomatic AF recurrence
- 663 patients with paroxysmal (542) or persistent (121) AF assigned to P-OM3 4 g/day or placebo and treated for 24 weeks
- Standard safety assessment

Enrollment Summary

- Study dates*:
 - First date any participant took study medication: 20-Dec-2006
 - Last date any participant took study medication: 20-Jan-2010
- Participating regions: USA
- # of Sites:
 - 145 sites initiated
 - 96 sites enrolled participants

Endpoints

- **Primary**
 - Time to first recurrence of symptomatic AF (including flutter) in subjects with PAF
- **Secondary** (by strata and combined)
 - Time to first onset of symptomatic AF (excluding flutter)
 - Time to any onset of (symptomatic or asymptomatic) AF/flutter
 - Time to first occurrence of AF/flutter after Day 7 completion
 - Time to first occurrence of AF after Day 7 completion
 - Annualized number of rescue episodes
 - Annualized cumulative frequency of symptomatic AF/flutter
 - Annualized cumulative frequency of symptomatic AF
- **Tertiary** (combined)
 - Average heart rate during first recurrence of symptomatic AF/flutter
 - % CFB (change from baseline) in n-3 fatty acids at week 4 and week 24

Study Disposition



Participant Disposition

	Paroxysmal		Persistent	
	Placebo (N = 276)	P-OM3 (N = 266)	Placebo (N = 55)	P-OM3 (N = 66)
Prematurely withdrawn	30 (11%)	33 (12%)	10 (18%)	6 (9%)
Reason for withdrawal				
Adverse event/SAE	14 (5%)	9 (3%)	2 (4%)	2 (3%)
Non-compliance with protocol	5 (2%)	3 (1%)	3 (5%)	0
Withdrew consent	5 (2%)	10 (4%)	1 (2%)	2 (3%)
Lost to follow-up	4 (1%)	5 (2%)	2 (4%)	0
Other	2 (<1%)	6 (2%)	2 (4%)	2 (3%)

Demography

	Paroxysmal		Persistent	
	Placebo (N = 276)	P-OM3 (N = 266)	Placebo (N = 55)	P-OM3 (N = 66)
Age, mean (SD), Years range	61.9 (11.57) 32-88	60.0 (13.56) 18-88	57.6 (14.85) 21-87	58.7 (12.65) 19-83
Female, n (%)	138 (50%)	119 (45%)	19 (35%)	14 (21%)
Race, n (%)				
African American	10 (4%)	10 (4%)	6 (11%)	2 (3%)
White	253 (92%)	246 (92%)	45 (82%)	63 (95%)
Other	13 (5%)	10 (4%)	4 (7%)	1 (2%)
BMI, mean (SD) (kg/m ²)	30.4 (7.02)	30.3 (7.31)	32.2 (8.53)	31.6 (7.06)
Tobacco consumption, n (%)				
Non-smoker	143 (52%)	150 (56%)	27 (49%)	31 (47%)
Ex-smoker	107 (39%)	90 (34%)	20 (36%)	29 (44%)
Smoker	26 (9%)	26 (10%)	8 (15%)	6 (9%)
Alcohol consumption, n (%)	122 (44%)	135 (51%)	23 (42%)	37 (56%)

Concomitant Medications of Special Interest

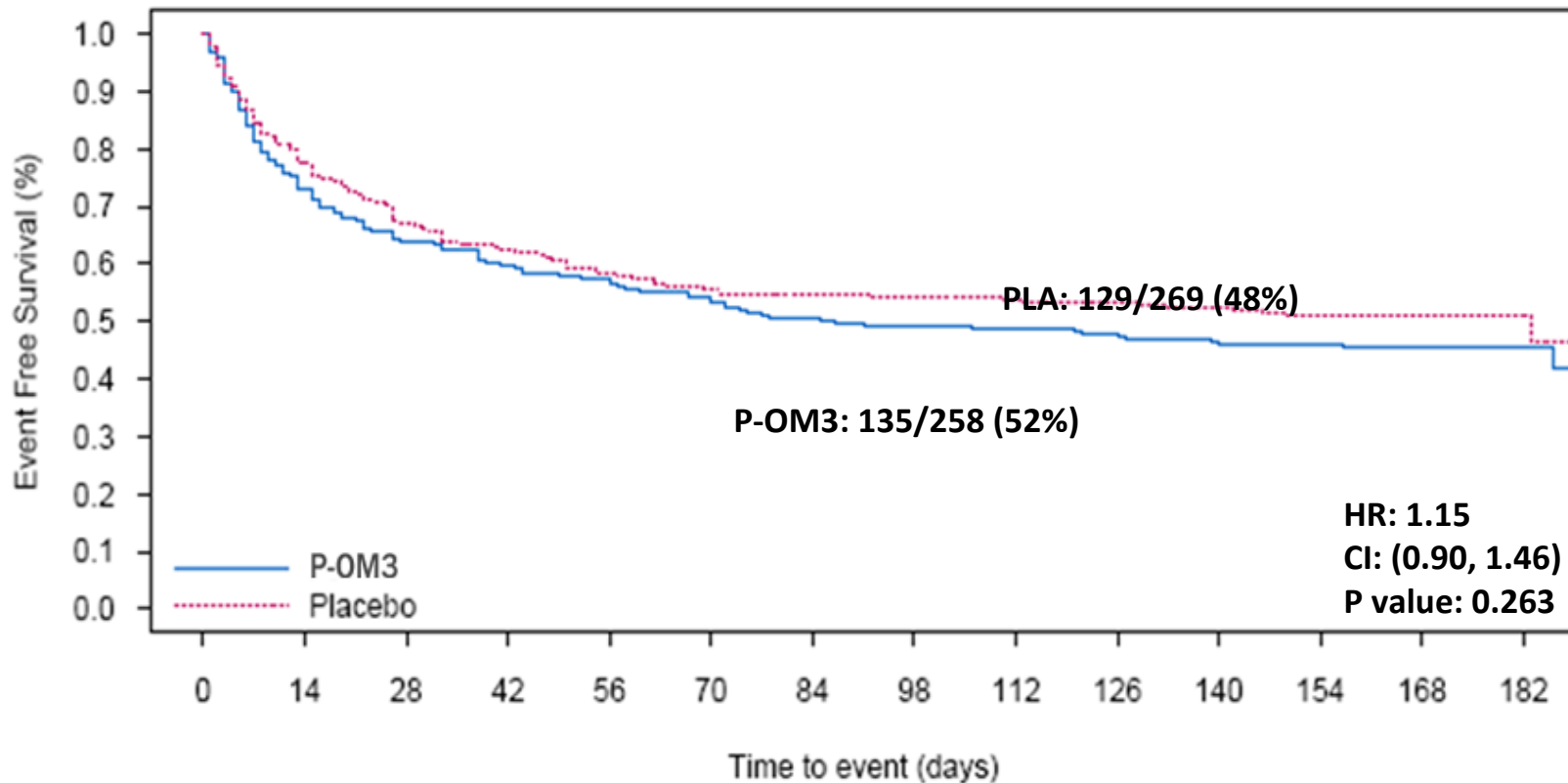
Medication, n (%)	Paroxysmal		Persistent	
	Placebo (N = 276)	P-OM3 (N = 266)	Placebo (N = 55)	P-OM3 (N = 66)
Any medication	252 (91)	242 (91)	50 (91)	61 (92)
Beta-blocker	185 (67)	176 (66)	33 (60)	47 (71)
Statin	127 (46)	117 (44)	21 (38)	33 (50)
ACEi/ARB	103 (37)	106 (40)	21 (38)	29 (44)
CCB	99 (36)	104 (39)	20 (36)	23 (35)
AAD*	28 (10)	35 (13)	6 (11)	14 (21)
Thyroid hormones	34 (12)	25 (9)	6 (11)	9 (14)
Omega-3 FA	4 (1)	0	1 (2)	2 (3)
Aspirin	178 (64)	173 (65)	24 (44)	41 (62)

*refers to at least 14 days of continuous AAD use

Statistical Methods

- Time to event parameters were analyzed using Cox proportional hazard (PH) models and Kaplan-Meier (K-M) plots
- Between treatment group differences for continuous parameters (secondary, tertiary efficacy endpoints and lab and vital signs safety endpoints) were analyzed via ANCOVA or non-parametric ANCOVA using rank transformed data
- Tests of significance were performed at a two-sided 5% significance level (interaction tests at 10% significance level)

Primary Endpoint: Time to First Recurrence of Symptomatic AF/Flutter (PAF)

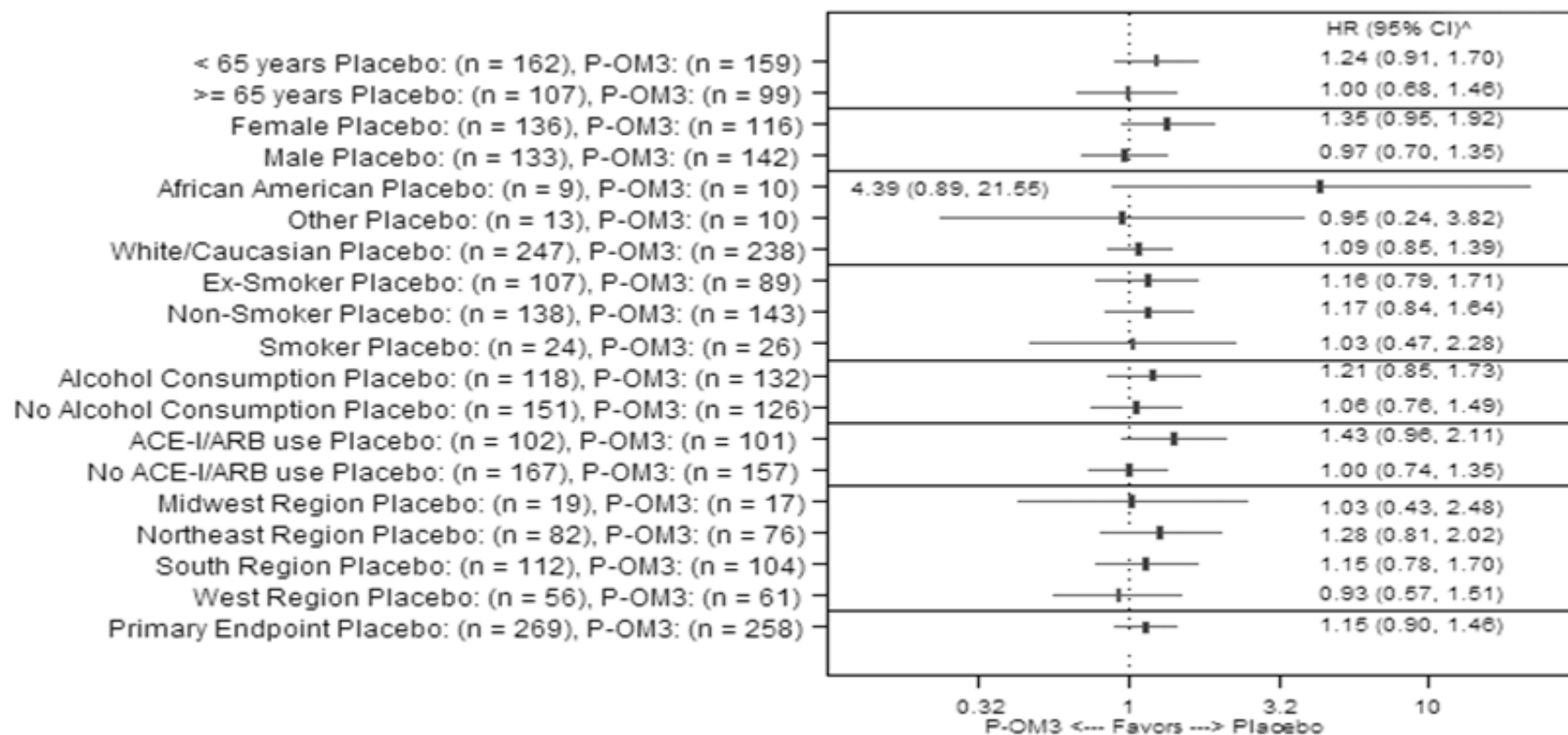


Subjects At Risk

P-OM3	258	184	158	144	137	128	119	114	113	109	104	102	81	13
Placebo	269	205	175	159	148	141	136	133	131	130	128	124	97	15

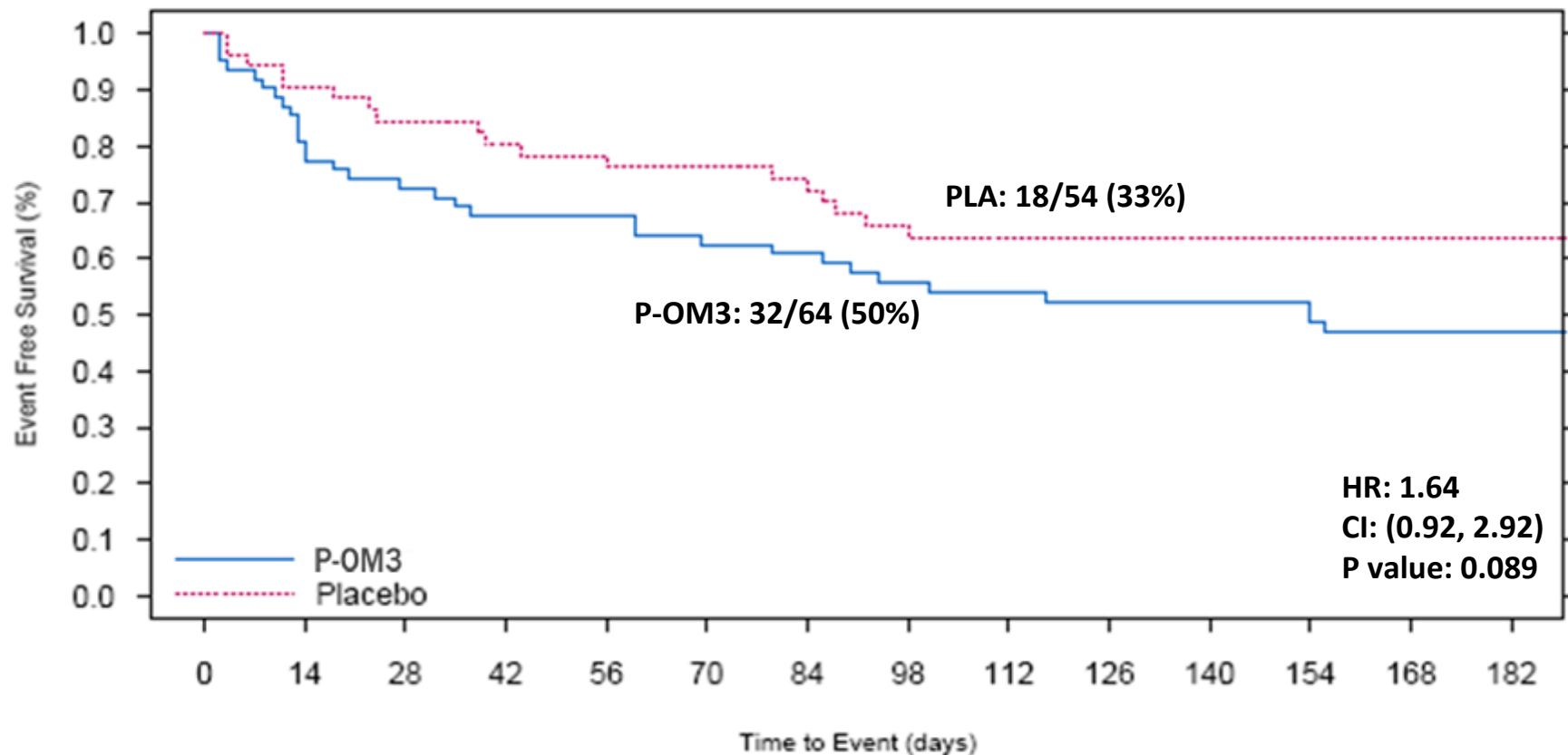
Analysis based on Cox model: $\log(\text{HR}) = \text{treatment} + \text{region} + \text{ACE/ARB} + \text{Statin}$

Primary Endpoint: Subgroup Analyses (PAF)



Hazard Ratio (HR) and 95% Confidence Intervals from the Cox PH Model

Time to First Recurrence of Symptomatic AF/Flutter (Persistent)

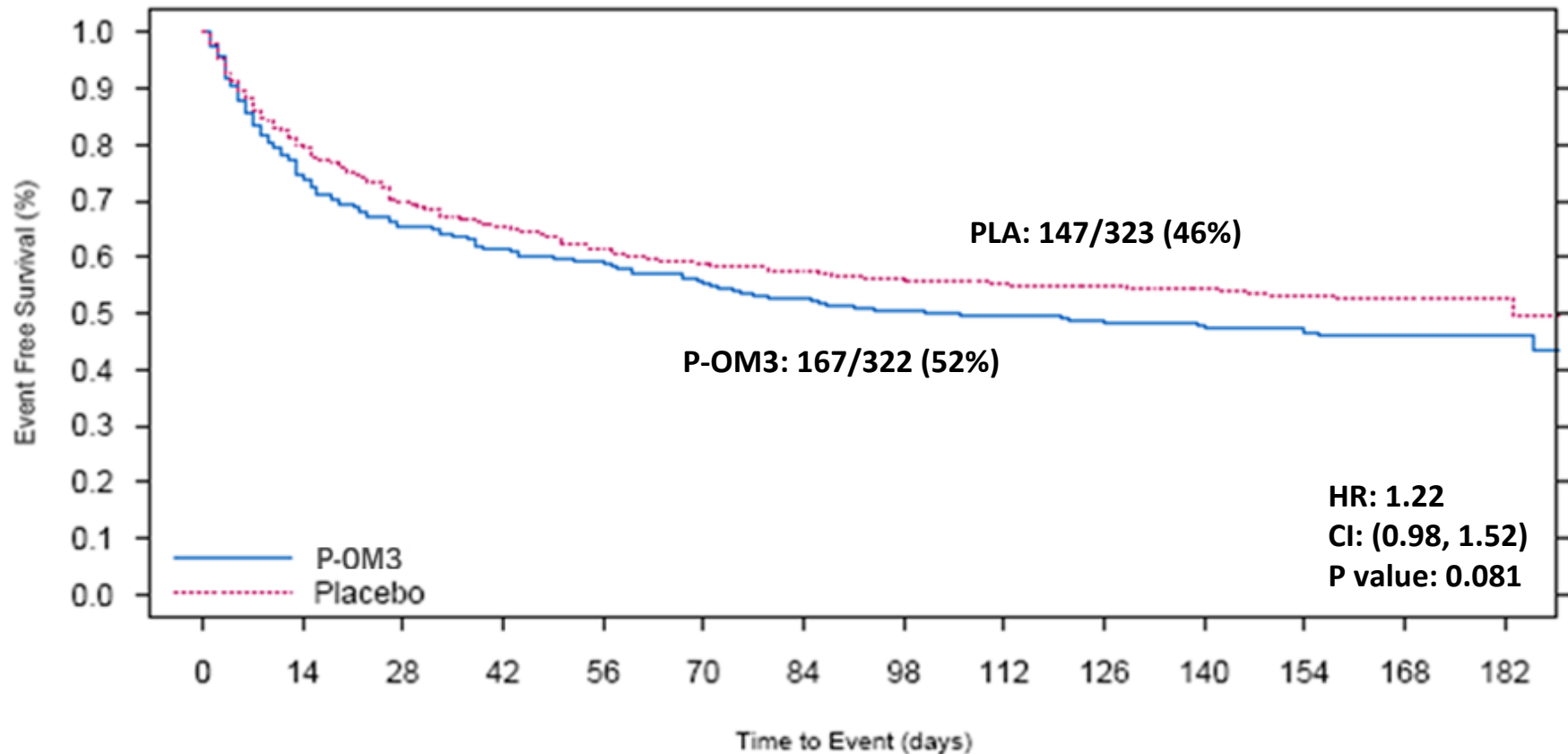


Subjects At Risk

P-OM3	64	50	44	41	41	37	35	32	31	30	30	30	24	6
Placebo	54	46	41	39	38	37	36	30	28	27	26	26	20	6

P-value based on log rank test. HR from Cox model: log (HR) = treatment

Time to First Recurrence of Symptomatic AF/Flutter (Combined)



Subjects At Risk

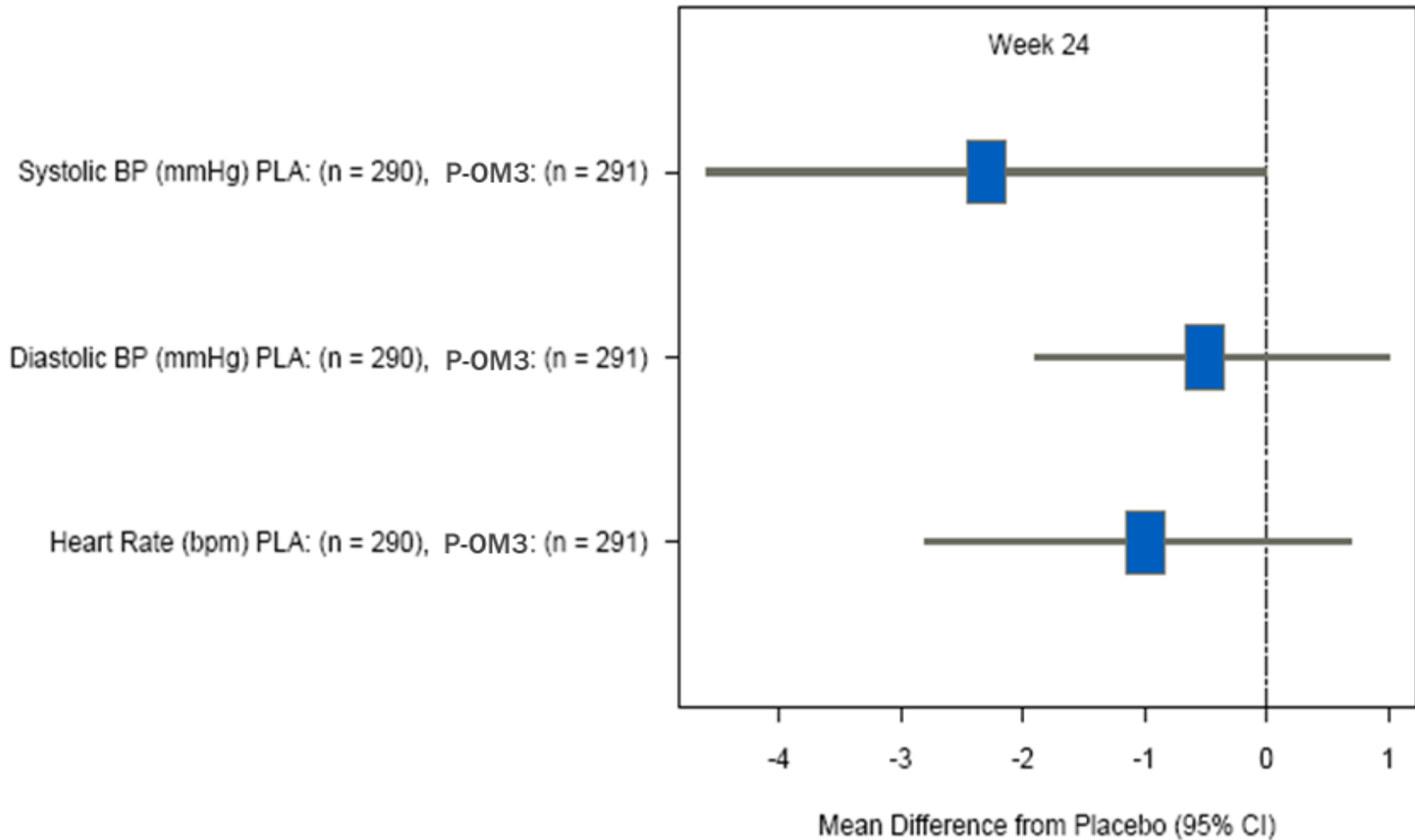
P-OM3	322	234	202	185	178	165	154	146	144	139	134	132	105	19
Placebo	323	251	216	198	186	178	172	163	159	157	154	150	117	21

Analysis based on Cox model: $\log(HR) = \text{treatment} + \text{region} + \text{ACE/ARB} + \text{Statin} + \text{Strata}$

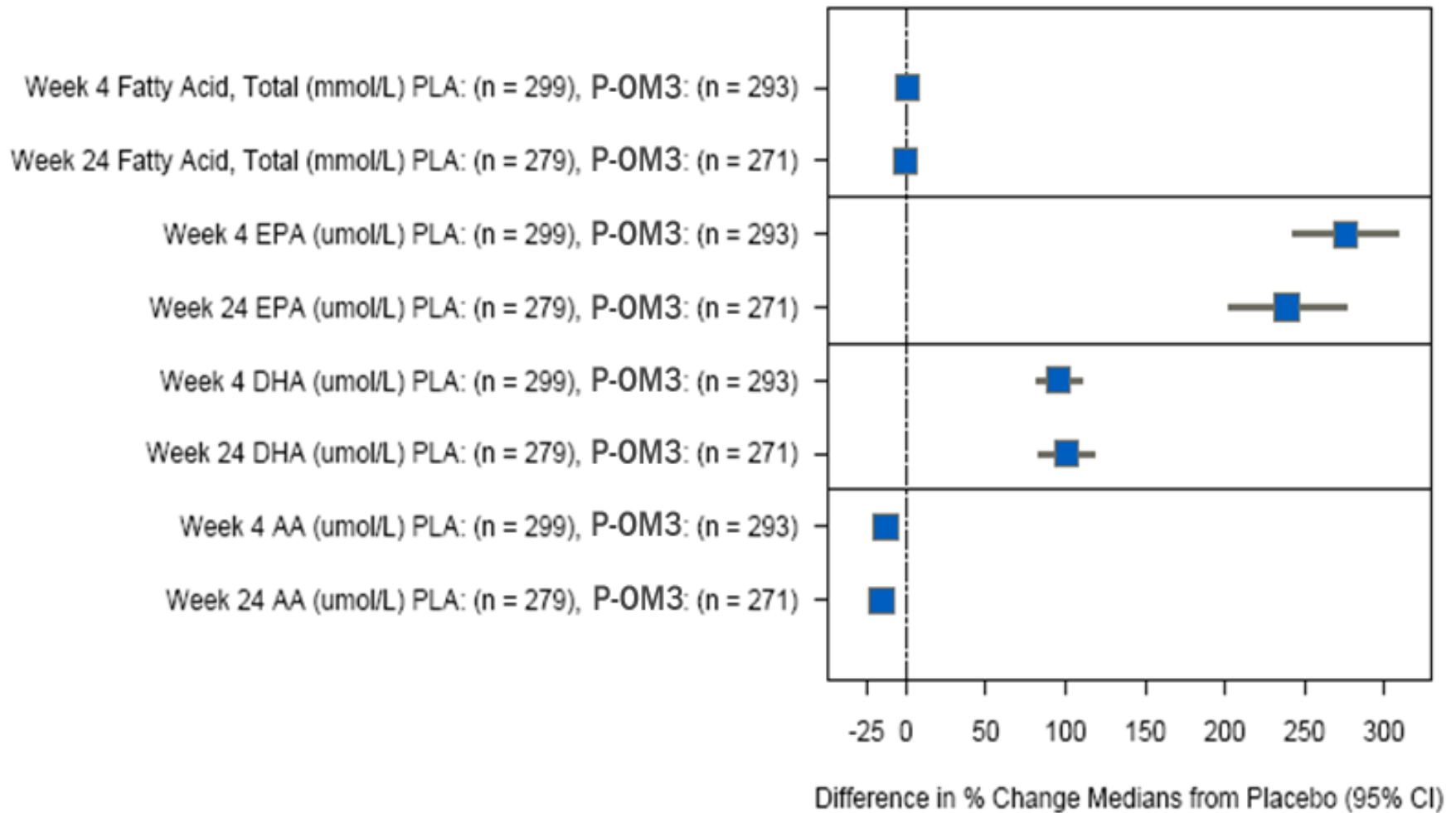
Secondary Endpoint: Continuous Variables (PAF)

	Placebo	P-OM3	Diff. in medians 95% CI <i>P</i> value
Annualized number of “rescue” episodes, median	N = 34 2.4	N = 37 4.2	0.07 (-0.09, 2.08) 0.290
Annualized cumulative frequency of symptomatic AF/flutter recurrences, median	N = 129 6.8	N = 140 8.3	0.32 (-0.18, 2.21) 0.218
Annualized cumulative frequency of symptomatic AF recurrences, median	N = 126 6.9	N = 139 8.3	0.24 (-0.19, 2.17) 0.239

Vital Signs at Week 24 (Combined)



Tertiary Endpoint: Percent Change in n-3 Fatty Acids (Combined)



Note: EPA= Eicosapentaenoic Acid, DHA= Docosahexaenoic Acid, AA= Arachidonic Acid.

Most Common Adverse Events (≥4% in either treatment group)

Event	Placebo (N = 331)	P-OM3 (N = 332)	Total (N = 663)
Any event	199 (60%)	203 (61%)	402 (61%)
Nausea	13 (4%)	16 (5%)	29 (4%)
Dizziness	11 (3%)	13 (4%)	24 (4%)
Urinary tract infection	12 (4%)	12 (4%)	24 (4%)
Sinusitis	12 (4%)	10 (3%)	22 (3%)
Edema peripheral	5 (2)	14 (4)	19 (3)

Serious Fatal Adverse Events

Preferred term	Placebo (N = 331)	P-OM3 (N = 332)
Any event	1 (<1%)	1 (<1%)
Cardiac failure congestive	1 (<1%)	0
Arteriosclerosis	0	1 (<1%)

Summary

- Baseline characteristics
 - Demographic and baseline characteristics were generally comparable between treatment groups and across strata
- Primary and secondary endpoints
 - Primary efficacy endpoint did not achieve statistical significance
 - Primary efficacy results were consistent for all sensitivity and subgroup analyses
 - Consistent efficacy results were observed across strata
 - Secondary efficacy endpoints did not achieve statistical significance

Summary

- Tertiary endpoints

- Average HR at time of first recurrence: mean reductions in P-OM3 compared to placebo
- EPA and DHA: increased in P-OM3 compared to placebo for week 4 and week 24; arachidonic acid: median decreased in P-OM3 compared to placebo for week 4 and 24

Safety

- TG and VLDL: decreased in P-OM3 compared to placebo at week 24
- SBP: mean CFB decreased in P-OM3 compared to placebo at week 24
- Two deaths occurred during the study, one in each treatment group

CONCLUSION

Among patients with no substantial structural heart disease and confirmed, symptomatic AF, P-OM3 compared with placebo did not reduce recurrent AF over 6 months of study.

Efficacy and Safety of Prescription Omega-3 Fatty Acids for the Prevention of Recurrent Symptomatic Atrial Fibrillation

A Randomized Controlled Trial

Peter R. Kowey, MD
James A. Reiffel, MD
Kenneth A. Ellenbogen, MD
Gerald V. Naccarelli, MD
Craig M. Pratt, MD

ATRIAL FIBRILLATION (AF) IS A highly prevalent disease that is responsible for reduced quality of life, costly hospitalizations, heart failure, stroke, and death.^{1,2} No current therapy, drug, device, or ablation is uniformly effective, and several available therapies have the potential to cause harm.^{3,5} Consequently, useful alternatives are being sought.

Fish oils have demonstrable potent electrophysiological, autonomic-modulating, and anti-inflammatory effects in atrial and ventricular tissue and, most importantly, appear to be well tolerated.^{6,7} Thus, these products have been studied in clinical trials involving treatment of AF in a wide range of patients and clinical scenarios, using various doses, and in diverse designs. However, the results of these trials have been mixed,⁸⁻¹³ resulting in confusion among physicians and patients. Many patients use omega-3 polyunsaturated fatty acid supplements or have enhanced their diets heavily with fish products, without a clear idea of why or what they might expect with regard to arrhythmia suppression or safety. Because many omega-3 fatty acid preparations are marketed as food sub-

Context Atrial fibrillation (AF) is common, yet there remains an unmet medical need for additional treatment options. Current pharmacological treatments have limited efficacy and significant adverse events. Limited data from small trials suggest omega-3 polyunsaturated fatty acids may provide a safe, effective treatment option for AF patients.

Objective To evaluate the safety and efficacy of prescription omega-3 fatty acids (prescription omega-3) for the prevention of recurrent symptomatic AF.

Design, Setting, and Participants Prospective, randomized, double-blind, placebo-controlled, parallel-group multicenter trial involving 663 US outpatient participants with confirmed symptomatic paroxysmal (n=542) or persistent (n=121) AF, with no substantial structural heart disease, and in normal sinus rhythm at baseline were recruited from November 2006 to July 2009 (final follow-up was January 2010).

Interventions Prescription omega-3 (8 g/d) or placebo for the first 7 days; prescription omega-3 (4 g/d) or placebo thereafter through week 24.

Main Outcome Measures The primary end point was symptomatic recurrence of AF (first recurrence) in participants with paroxysmal AF. Secondary analyses included first recurrence in the persistent stratum and both strata combined. Participants were followed up for 6 months.

Results At 24 weeks, in the paroxysmal AF stratum, 129 of 269 participants (48%) in the placebo group and 135 of 258 participants (52%) in the prescription group had a recurrent symptomatic AF or flutter event. In the persistent AF stratum, 18 participants (33%) in the placebo group and 32 (50%) in the prescription group had documented symptomatic AF or flutter events. There was no difference between treatment groups for recurrence of symptomatic AF in the paroxysmal stratum (hazard ratio [HR], 1.15; 95% confidence interval [CI], 0.90-1.46; *P* = .26), in the persistent stratum (HR, 1.64; 95% CI, 0.92-2.92; *P* = .09), and both strata combined (HR, 1.22; 95% CI, 0.98-1.52; *P* = .08). Other, secondary end points were supportive of the primary result. A total of 5% of those receiving placebo and 4% of those receiving prescription omega-3 discontinued due to adverse events. Eicosapentaenoic and docosahexaenoic acid blood levels were significantly higher in the prescription group than in the placebo group at weeks 4 and 24.

Conclusion Among participants with paroxysmal AF, 24-week treatment with prescription omega-3 compared with placebo did not reduce recurrent AF over 6 months.

Trial Registration clinicaltrials.gov Identifier: NCT00402363

JAMA. 2010;304(21):doi:10.1001/jama.2010.1735

www.jama.com

Author Affiliations: Division of Cardiovascular Diseases, Lankenau Institute for Medical Research, Wynnewood, and Jefferson Medical College, Philadelphia, Pennsylvania (Dr Kowey); Division of Cardiology, Columbia University Medical Center, New York, New York (Dr Reiffel); Clinical Cardiac Electrophysiology and Pacing, Virginia Commonwealth University Medical Center, Richmond (Dr Ellenbogen);

Division of Cardiology, Penn State University College of Medicine, Hershey, Pennsylvania (Dr Naccarelli); Methodist DeBakey Heart and Vascular Center, Houston, Texas; and Department of Medicine, Weill Cornell Medical College, New York, New York (Dr Pratt).
Corresponding Author: Peter R. Kowey, MD, 558 Lankenau Medical Office Bldg East, 100 Lancaster Ave, Wynnewood, PA 19096 (KoweyP@lms.org).

JAMA. Published online November 15, 2010 E1

JAMA[®]

The Journal of the American Medical Association

Published Online First
[November, 2010]

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Back-up slides

Baseline Characteristics

	Paroxysmal		Persistent	
	Placebo (N = 276)	P-OM3 (N = 266)	Placebo (N = 55)	P-OM3 (N = 66)
Heart rate, mean (SD), bpm range	62.8 (9.41) 43-100	62.5 (9.61) 42-91	65.0 (11.54) 48-95	61.4 (9.69) 45-86
Diastolic BP, mean (SD), mmHg	74.7 (9.26)	74.6 (9.53)	76.2 (11.03)	76.3 (8.58)
Systolic BP, mean (SD), mmHg	126.1 (14.69)	125.8 (15.66)	127.9 (16.86)	126.5 (15.74)
Avg TTM HR, mean (SD), bpm	63.5 (10.50)	63.7 (10.46)	67.9 (12.47)	61.6 (11.08)
12-lead ECG HR, mean (SD), bpm	60.9 (10.09)	60.9 (10.48)	63.9 (11.57)	59.8 (10.14)
12-lead ECG Interpretation, n (%)				
Normal	138 (50%)	144 (54%)	29 (53%)	33 (50%)
Abnormal—not clin. sign.	134 (49%)	117 (44%)	25 (45%)	32 (48%)
Abnormal—clin. sign.	1 (<1%)	5 (2%)	1 (2%)	0
2D Echocardiogram, n (%)				
Normal	113 (41%)	109 (41%)	17 (31%)	23 (35%)
Abnormal—not clin. sign.	152 (55%)	146 (55%)	33 (60%)	38 (58%)
Abnormal—clin. sign.	8 (3%)	7 (3%)	4 (7%)	4 (6%)
AF Hx within 3 months, n (%)	267 (97%)	258 (97%)	53 (96%)	63 (95%)

Current Medical History

Condition, n (%)	Paroxysmal		Persistent	
	Placebo (N = 276)	P-OM3 (N = 266)	Placebo (N = 55)	P-OM3 (N = 66)
Any condition	273 (99)	255 (96)	55 (100)	63 (95)
Cardiovascular	227 (82)	211 (79)	71 (75)	58 (88)
Hypertension	172 (62)	161 (60)	30 (55)	42 (64)
Musculoskeletal	151 (55)	136 (51)	25 (45)	31 (47)
Arthritis	63 (23)	66 (25)	16 (29)	13 (20)
Allergies/Drug sensitivities	126 (46)	122 (46)	18 (33)	23 (35)
Seasonal allergies	28 (10)	37 (14)	5 (1)	10 (15)
Gastrointestinal	116 (42)	113 (42)	20 (36)	23 (35)
GERD	86 (31)	74 (28)	16 (29)	9 (16)
Neurological/Psychiatric	105 (38)	98 (37)	21 (38)	18 (27)
Depression	33 (12)	35 (13)	8 (15)	6 (9)
Endocrine	104 (38)	80 (30)	25 (45)	28 (42)
Diabetes mellitus	42 (15)	33 (12)	9 (16)	11 (17)
Genitourinary	85 (31)	67 (25)	14 (25)	13 (20)
BPH	21 (8)	16 (6)	3 (5)	2 (3)
Respiratory	73 (26)	72 (27)	9 (16)	13 (20)
Sleep apnea	26 (9)	24 (9)	3 (5)	6 (9)

Study Medication Compliance (Combined)

	Placebo (N = 331)	P-OM3 (N = 332)
Compliance, n (%)		
<75%	34 (10%)	35 (11%)
75% -120%	291 (88%)	287 (86%)
>120%	1 (<1%)	4 (1%)
Missing	5 (2%)	6 (2%)

Sample Size Assumptions

Primary Endpoint	Time to first symptomatic recurrence of AF (including flutter) in subjects with PAF
Hazard ratio*	0.682
Placebo event rate*	64.4%
Power	90%
Significance level	5% (two-sided)
Total # PAF events needed	295
Planned PAF participants	550
PAF: persistent stratification ratio (# participants)	5:1 (550:110)

Sample Size Assumptions

Primary Endpoint	Time to first symptomatic recurrence of AF (including flutter) in patients with PAF
Hazard Ratio*	0.682
Placebo event rate*	64.4%
Power	90%
Significance level	5% (two-sided)
# PAF events needed	295
Planned # PAF patients	550
PAF:Persistent stratification ratio (# patients)	5:1 (550:110)

*Assumptions were based on results from the lowest dose of Rythmol SR in the RAFT (Rythmol AF Trial) study and event rate in the placebo arm of RAFT

Statistical Methods

- Time to event parameters were analyzed using Cox proportional hazard (PH) models and Kaplan-Meier (K-M) plots
 - Due to the small number of participants in the persistent AF stratum, time to event parameters were explored via log rank tests and K-M plots
 - Because ACE-I or ARB use has the potential to influence the incidence of AF/flutter events, in each model, unless otherwise specified, ACE-I/ARB use was included as a time-dependent covariate for the primary endpoint and as a binary (yes/no) covariate (fixed effect) for the secondary and tertiary endpoints

Statistical Methods

- Between treatment group differences for continuous parameters:
 - Secondary and tertiary efficacy endpoints, and lab and vital signs safety endpoints were analyzed via analysis of covariance (ANCOVA) or non-parametric ANCOVA using rank transformed data
- Tests of significance were performed at a two-sided 5% significance level (interaction tests at 10% significance level)

Independent Statistical Analysis

- In the protocol pre-specified analyses, patients were censored after initiation of AAD therapy. A pre-specified sensitivity analysis was performed for the persistent stratum in which these patients were not censored. In analyses conducted by an independent statistician, these analysis in which patients were not censored was considered to be primary.
- Results of the independent statistical analyses were consistent with overall findings. For the combined strata group, one secondary endpoint (symptomatic recurrence of AF/flutter) was shown to be statistically significant ($p=0.047$) in favor of placebo.

Decision Tree for Analyses by Strata

Paroxysmal AF

- Time to first recurrence of symptomatic AF/flutter (primary endpoint) analyzed
- All secondary endpoints analyzed

Persistent AF (Primary)

- Time to first recurrence of symptomatic AF/flutter explored (via K-M plots and log-rank test)

Persistent AF (Secondaries)

- If the primary endpoint has a similar pattern of response as the PAF stratum, remaining secondary endpoints analyzed

Combined (All endpoints)

- Primary and secondary endpoints analyzed if the persistent AF and PAF stratum primary endpoint results are consistent
- Tertiary endpoints analyzed regardless of primary and secondary results

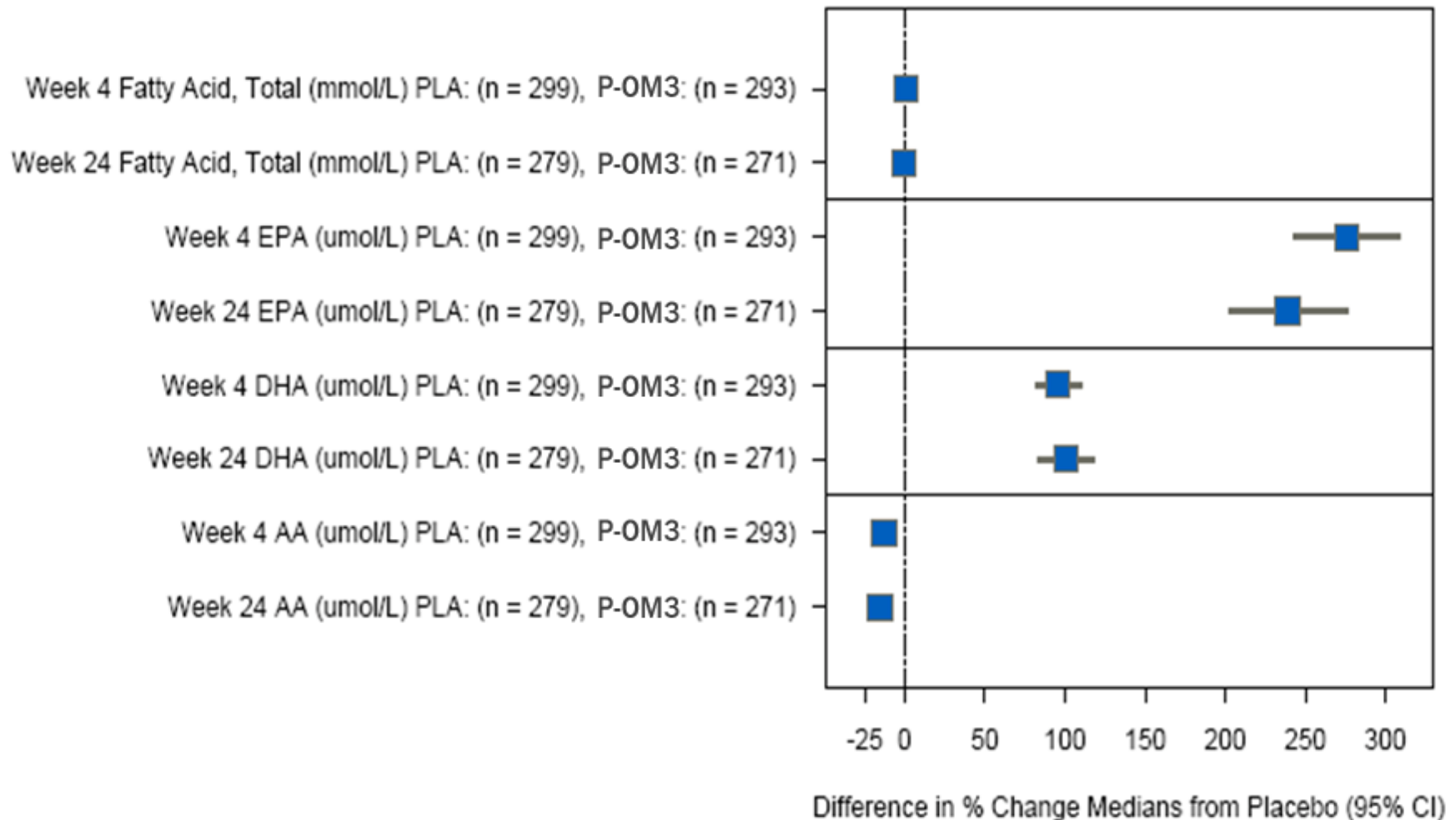
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- Results of the independent statistical analyses were consistent with overall findings. For the combined strata group, one secondary endpoint (symptomatic recurrence of AF/flutter) was shown to be statistically significant ($p=0.047$) in favor of placebo.

Number of Rescue Episodes

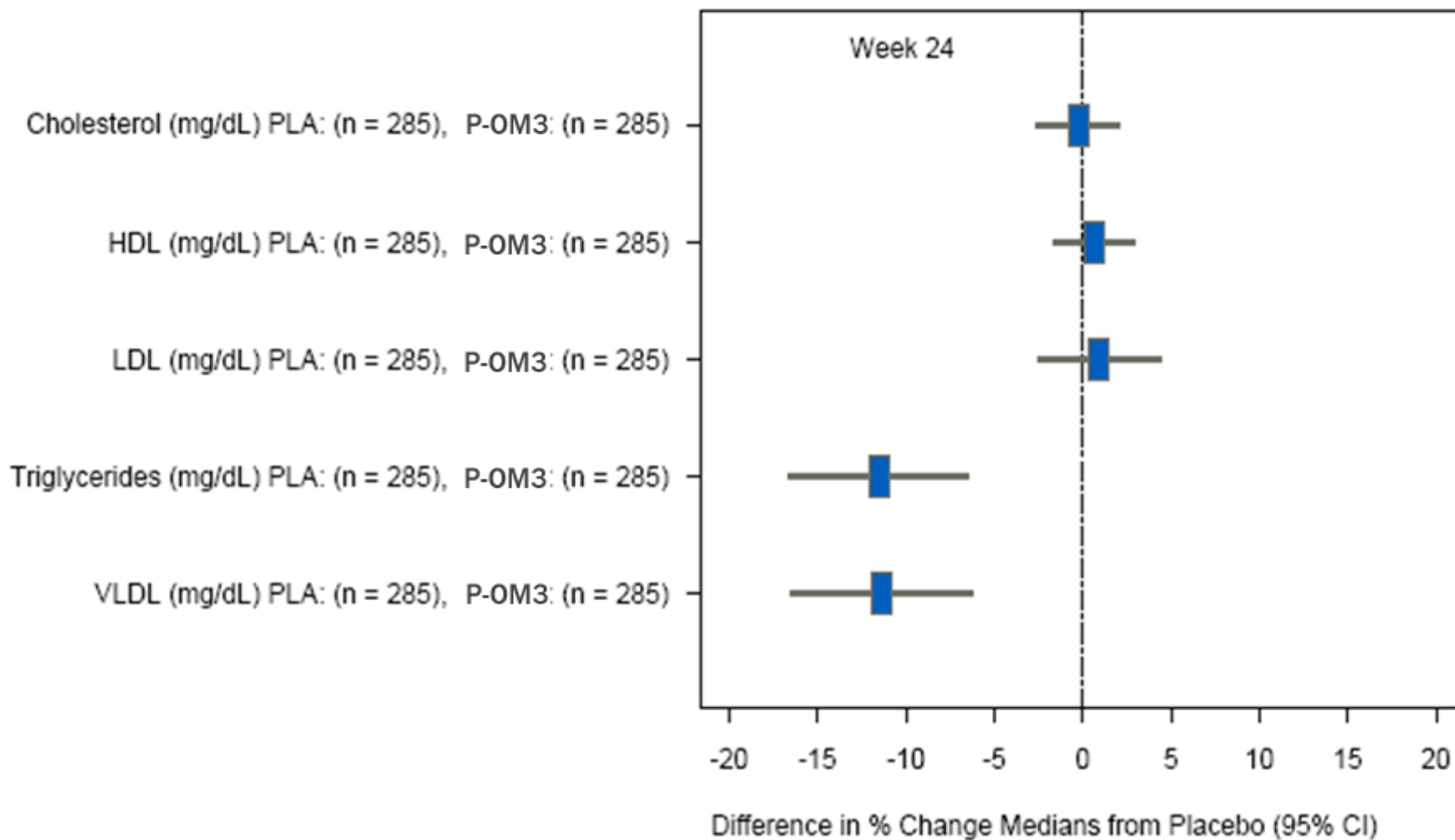
	Paroxysmal		Persistent	
	Placebo (N = 276)	P-OM3 (N = 266)	Placebo (N = 55)	P-OM3 (N = 66)
Any event, n (%) Mean (SD)	34 (12%) 2.1 (1.97)	38 (14%) 2.7 (2.60)	8 (15%) 1.4 (0.52)	21 (32%) 2.0 (1.86)
Pharmacological, n (%) Mean (SD)	34 (12%) 1.8 (1.82)	37 (14%) 2.5 (2.61)	6 (11%) 1.3 (0.52)	14 (21%) 2.0 (2.29)
Electrical, n (%) Mean (SD)	3 (1%) 1.7 (1.15)	7 (3%) 1.4 (0.79)	3 (5%) 1.0 (0.00)	13 (20%) 1.2 (0.38)
Surgical, n (%) Mean (SD)	3 (1%) 1 (0)	2 (<1%) 1 (0)	0	0

n-3 Fatty Acids (Combined)



Note: EPA= Eicosapentaenoic Acid, DHA= Docosahexaenoic Acid, AA= Arachidonic Acid.

Fasting Lipid Parameters at Week 24 (Combined)



Independent Statistical Analysis

- In the protocol pre-specified analyses, patients were censored after initiation of AAD therapy. A pre-specified sensitivity analysis was performed for the persistent stratum in which these patients were not censored. In analyses conducted by an independent statistician, these analysis in which patients were not censored was considered to be primary.
- Results of the independent statistical analyses were consistent with overall findings. For the combined strata group, one secondary endpoint (symptomatic recurrence of AF/flutter) was shown to be statistically significant ($p=0.047$) in favor of placebo.

Tertiary Endpoint: Average Heart Rate (bpm) During the First Recurrence of Symptomatic AF/Flutter (Combined)

	Placebo	P-OM3	Mean diff. from placebo (95% CI); <i>P</i> value
Number of participants	149	177	
Unadjusted means (SD)	127.9 (28.90)	120.8 (27.59)	
*Model adjusted means (SE)	128.6 (3.05)	121.7 (2.73)	-6.88 (-13.12,-0.64); 0.031

Common Non-Serious Treatment-Emergent Adverse Events Occurring in >5% of Subjects in Any Treatment During the On-Therapy Phase

Preferred term	Placebo (N = 331)	P-OM3 (N = 332)
Any event	195 (59%)	201 (61%)

There were no non-serious treatment emergent AEs with frequency of >5%

Bleeding Events

Event	Placebo (N = 331)	P-OM3 (N = 332)	Total (N = 663)
Rectal hemorrhage	2 (<1%)	0	2 (<1%)
Gastrointestinal hemorrhage	0	1 (<1%)	1 (<1%)
Hemorrhoid hemorrhage	0	1 (<1%)	1 (<1%)
Vaginal hemorrhage	0	1 (<1%)	1 (<1%)
Retroperitoneal hematoma	0	1 (<1%)	1 (<1%)
Subcutaneous hematoma	0	1 (<1%)	1 (<1%)
Hematoma	1 (<1%)	0	1 (<1%)

Serious Non-Fatal Related Treatment-Emergent Adverse Events

Preferred term	Placebo (N = 331)	P-OM3 (N = 332)
Any event	2 (<1%)	0
Syncope	1 (<1%)	0
Vasculitis	1 (<1%)	0