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

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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

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

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

Randomized		663		
Randomized by strata		Paroxysmal 542		Persistent 121
Randomized by treatment	Placebo 276	P-OM3 266	Placebo 55	P-OM3 66
Safety	276 (100%)	266 (100%)	55 (100%)	66 (100%)
Modified intent-to treat	269 (97%)	258 (97%)	54 (98%)	64 (97%)
Per protocol	236 (86%)	222 (83%)	41 (75%)	56 (85%)
Completed	246 (89%)	233 (88%)	45 (82%)	60 (91%)

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)

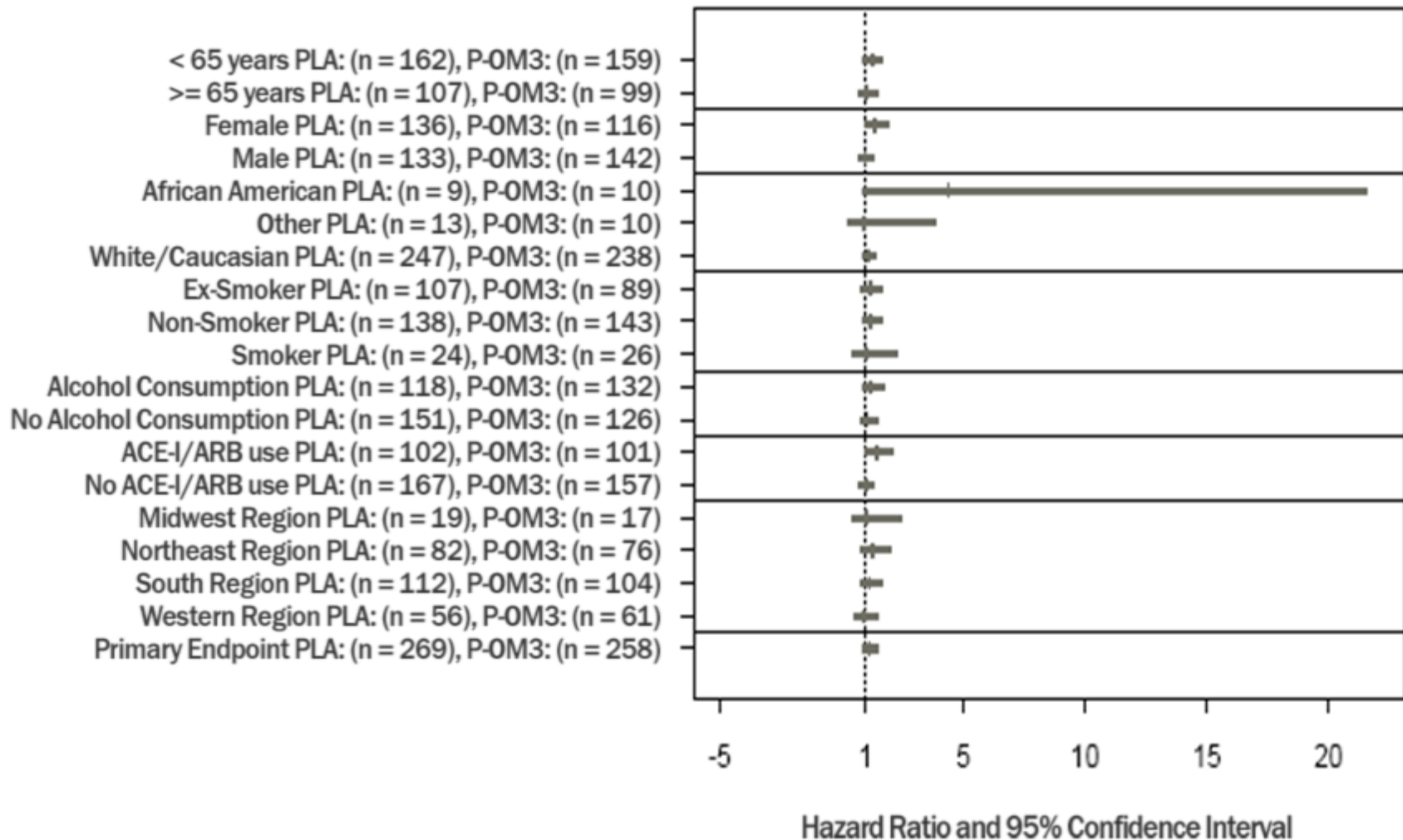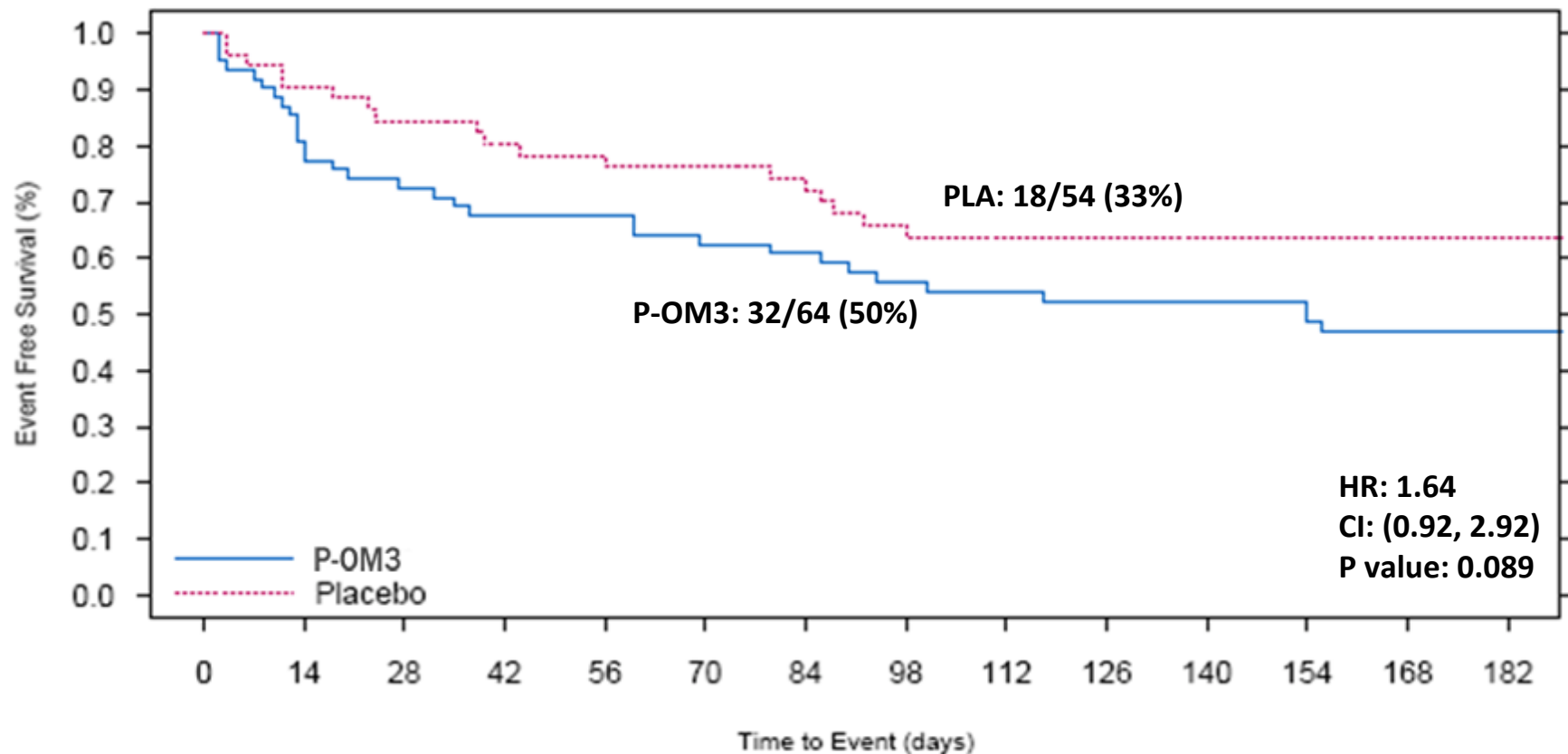# Primary Endpoint: Time to First Recurrence of Symptomatic AF/Flutter (PAF)
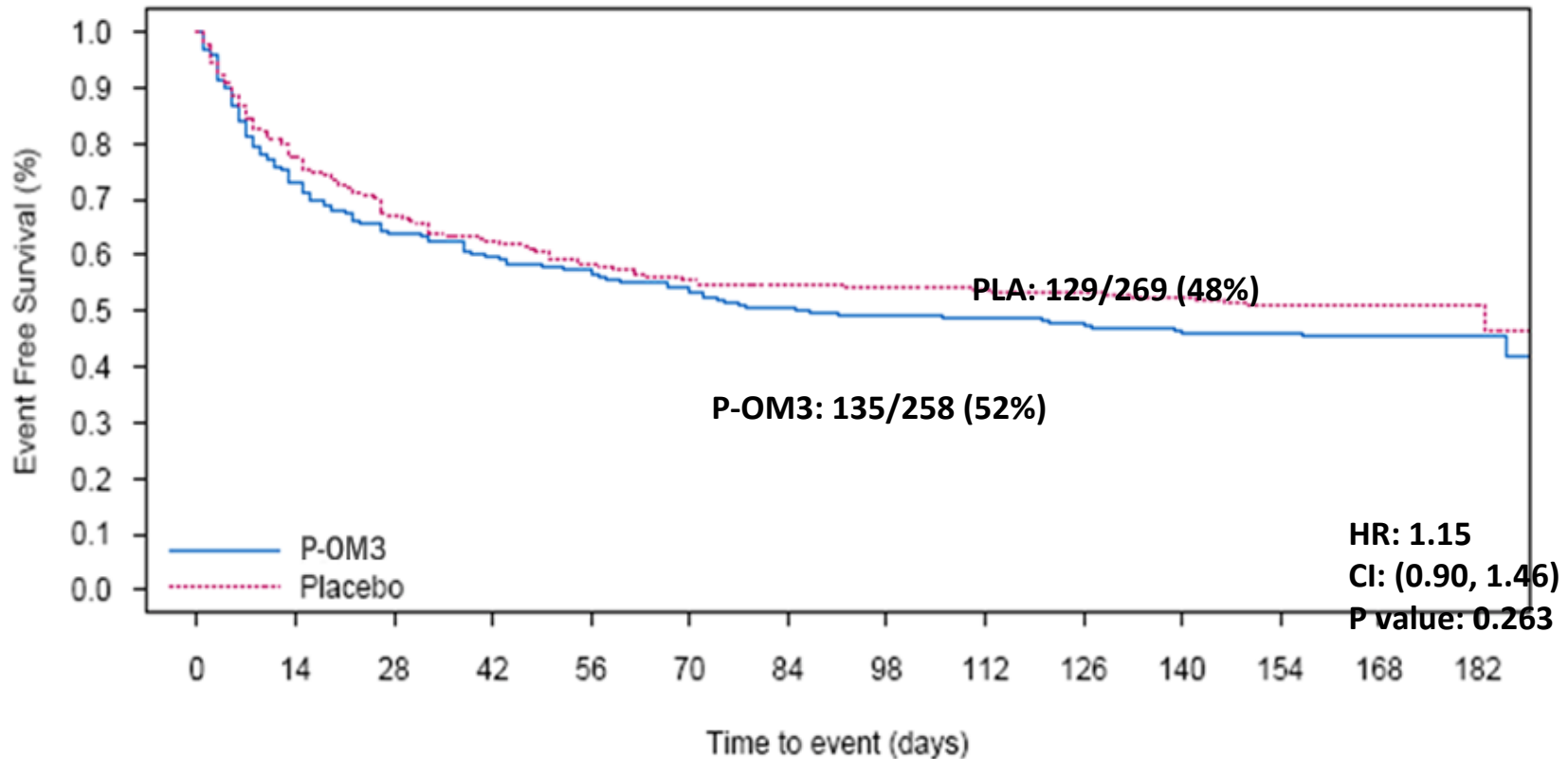
Analysis based on Cox model: log (HR)=treatment+region+ACE/ARB+Statin

Primary Endpoint: Subgroup Analyses (PAF)

Hazard Ratio and 95% Confidence Interval

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

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

Time to First Recurrence of Symptomatic AF/Flutter (Combined)
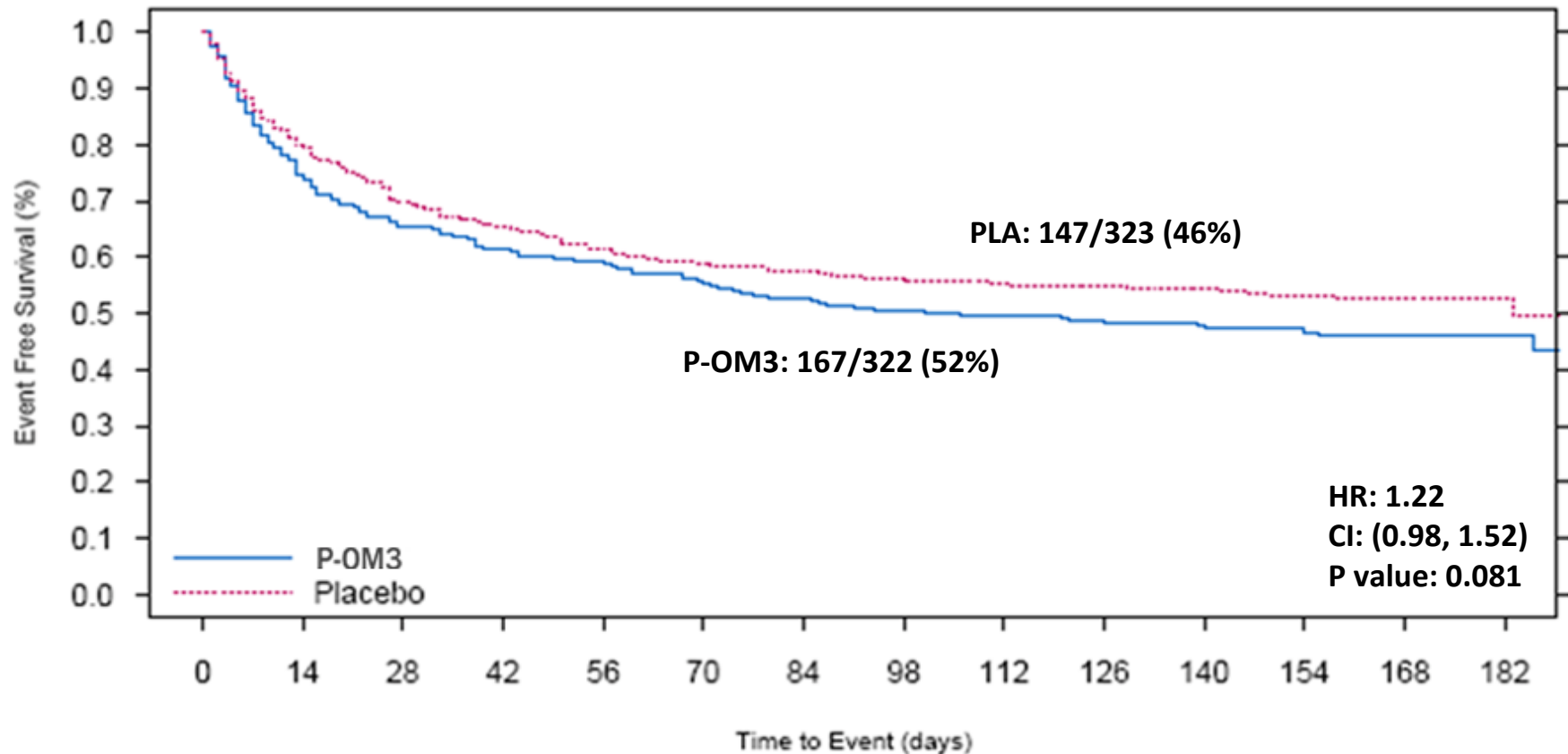
PLA: 147/323 (46%)
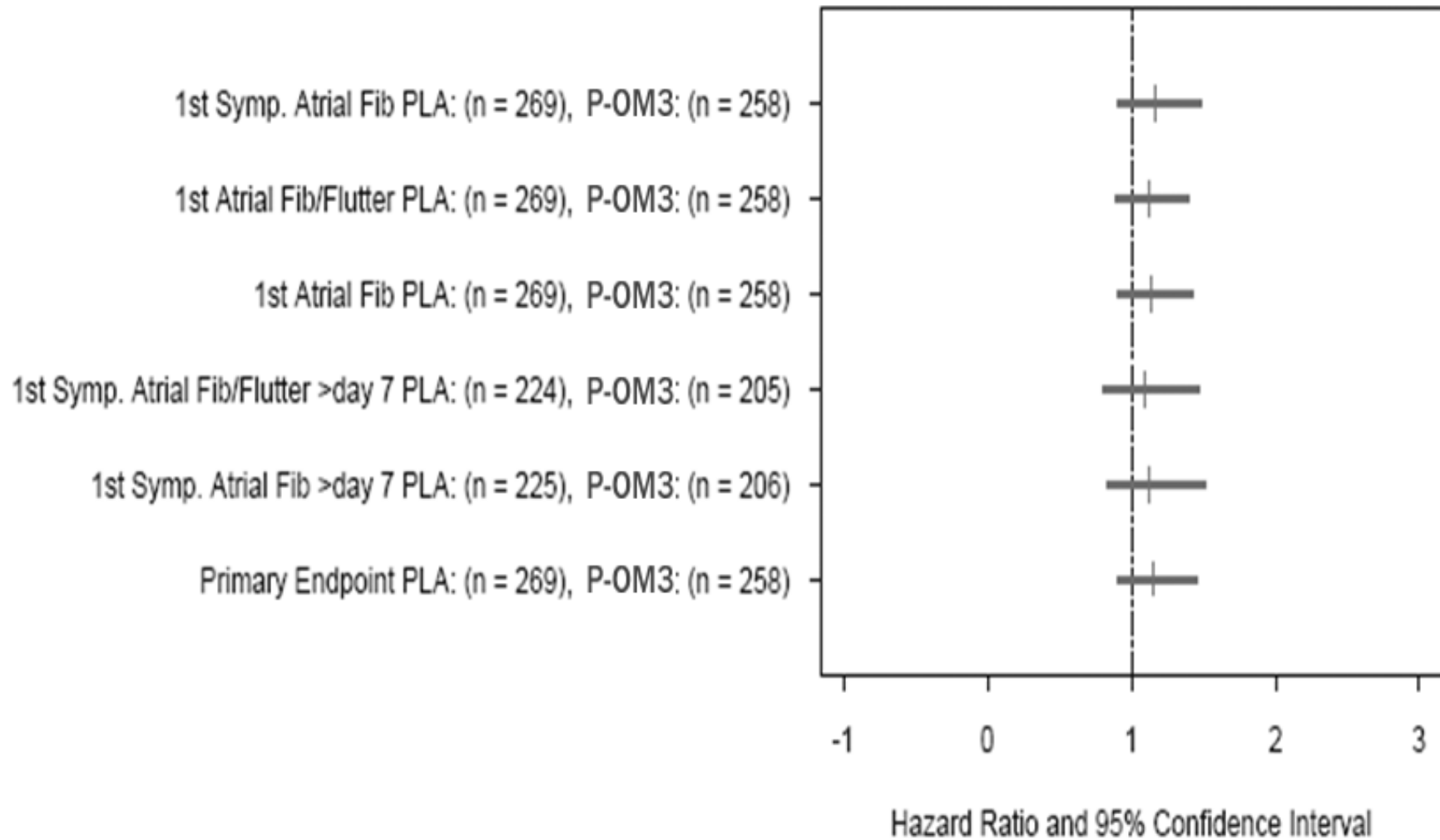
P-OM3: 167/322 (52%)

HR: 1.22
CI: (0.98, 1.52)
P value: 0.081

Analysis based on Cox model: log (HR) = treatment+region+ACE/ARB+Statin+Strata

Secondary Endpoint: Time to Event (PAF)

1st Symp. Atrial Fib PLA: (n = 269), P-OM3: (n = 258)

1st Atrial Fib/Flutter PLA: (n = 269), P-OM3: (n = 258)

1st Atrial Fib PLA: (n = 269), P-OM3: (n = 258)

1st Symp. Atrial Fib/Flutter >day 7 PLA: (n = 224), P-OM3: (n = 205)

1st Symp. Atrial Fib >day 7 PLA: (n = 225), P-OM3: (n = 206)

Primary Endpoint PLA: (n = 269), P-OM3: (n = 258)

-1   0   1   2   3

Hazard Ratio and 95% Confidence Interval

Secondary Endpoint: Continuous Variables (PAF)

	Placebo	P-OM3	Diff. in medians 95% CI *P* 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

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

	Placebo	P-OM3	Mean difference from Placebo 95% CI P-value
Number of patients	149	177	
Unadjusted Means (SD)	127.9 (28.90)	120.8 (27.59)	
*Model Adjusted Means	128.6 (3.05)	121.7 (2.73)	-6.88 (-13.12, -0.64) 0.031

*Estimates based on ANCOVA model: Average HR=treatment + region + strata + ACE/ARB use

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

Difference in % Change Medians from Placebo (95% CI)
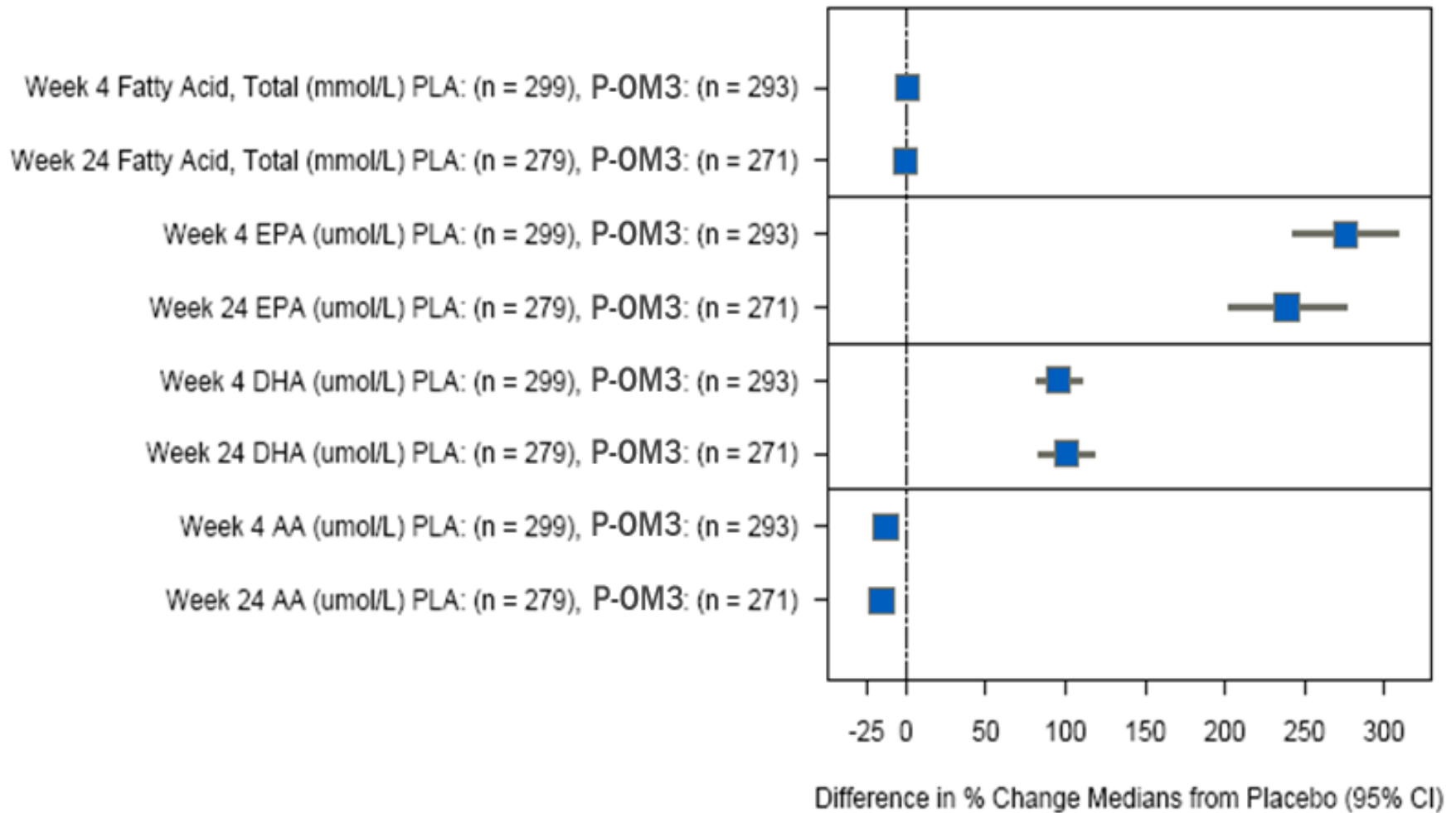
Note: EPA= Eicosapentaenoic Acid, DHA= Docosahexaenoic Acid, AA= Arachidonic Acid.

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.

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%)

Vital Signs at Week 24 (Combined)
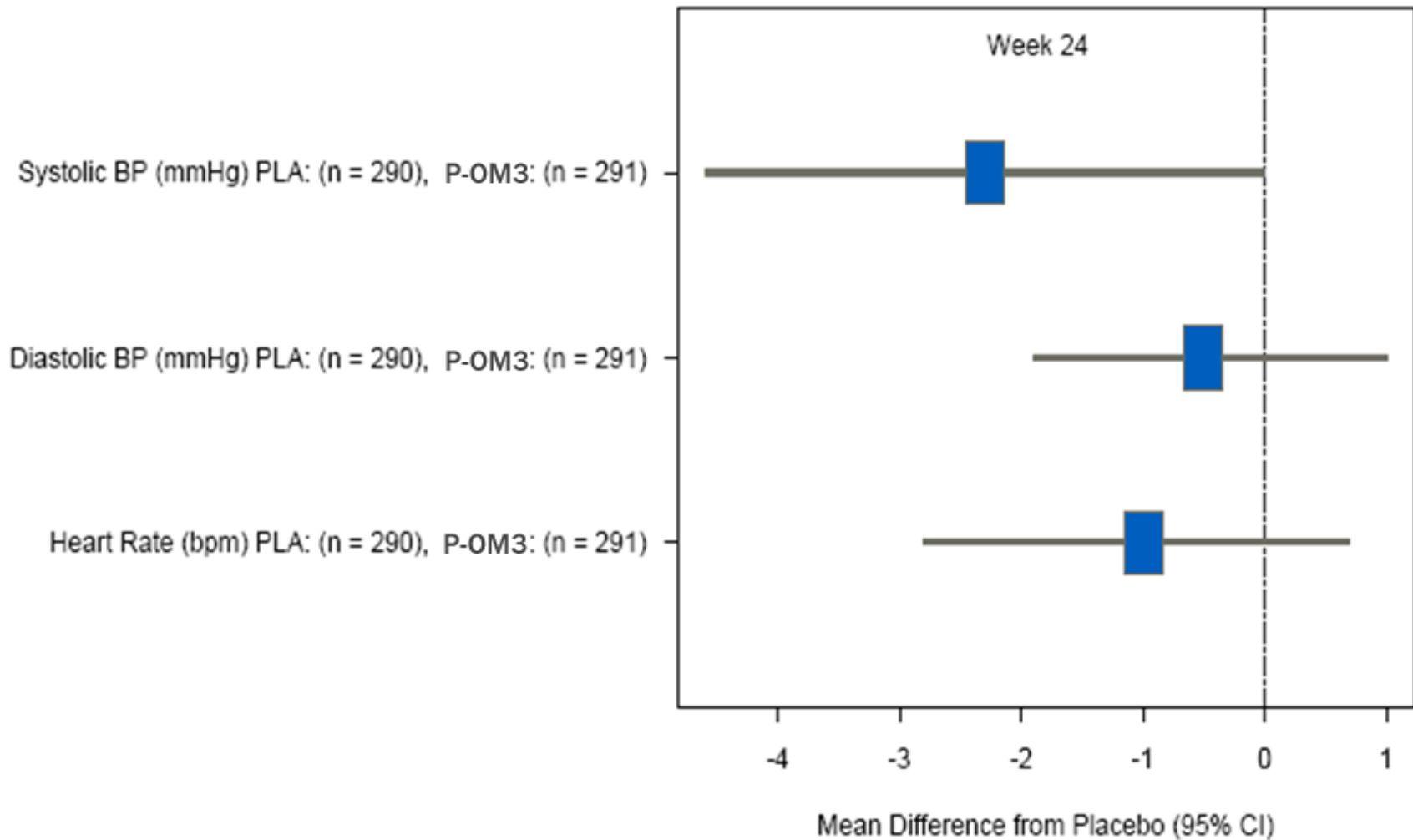
Summary

- 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 for any strata

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

gap3   don't forget the one other event (suicide) which occurred 100+ days after completion of the study
gap12991, 10/26/2010

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 Abnormal—not clin. sign. Abnormal—clin. sign.	138 (50%) 134 (49%) 1 (<1%)	144 (54%) 117 (44%) 5 (2%)	29 (53%) 25 (45%) 1 (2%)	33 (50%) 32 (48%) 0
2D Echocardiogram, n (%) Normal Abnormal—not clin. sign. Abnormal—clin. sign.	113 (41%) 152 (55%) 8 (3%)	109 (41%) 146 (55%) 7 (3%)	17 (31%) 33 (60%) 4 (7%)	23 (35%) 38 (58%) 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)

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)

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
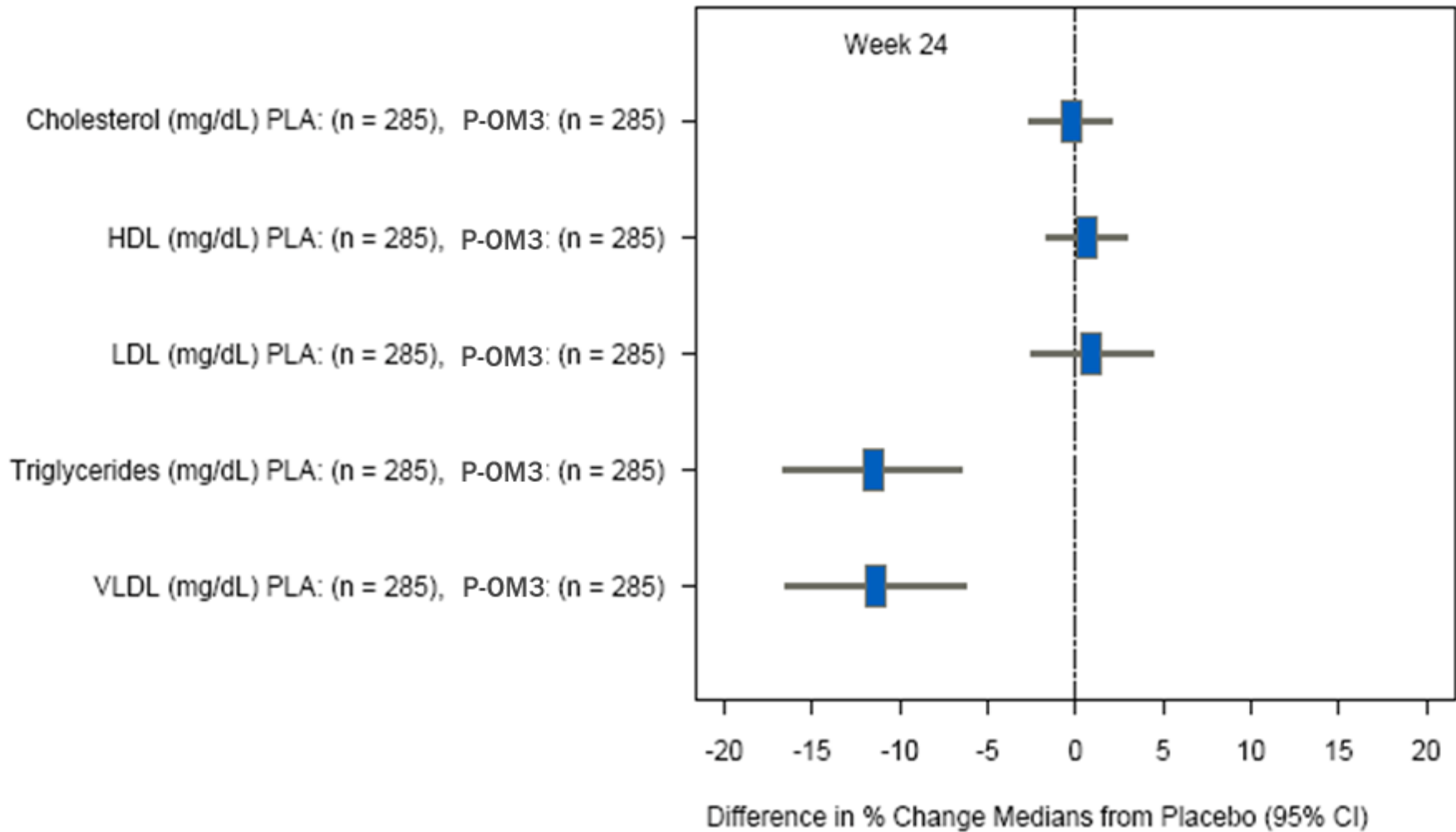
Number of Rescue Episodes

	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)

Difference in % Change Medians from Placebo (95% CI)
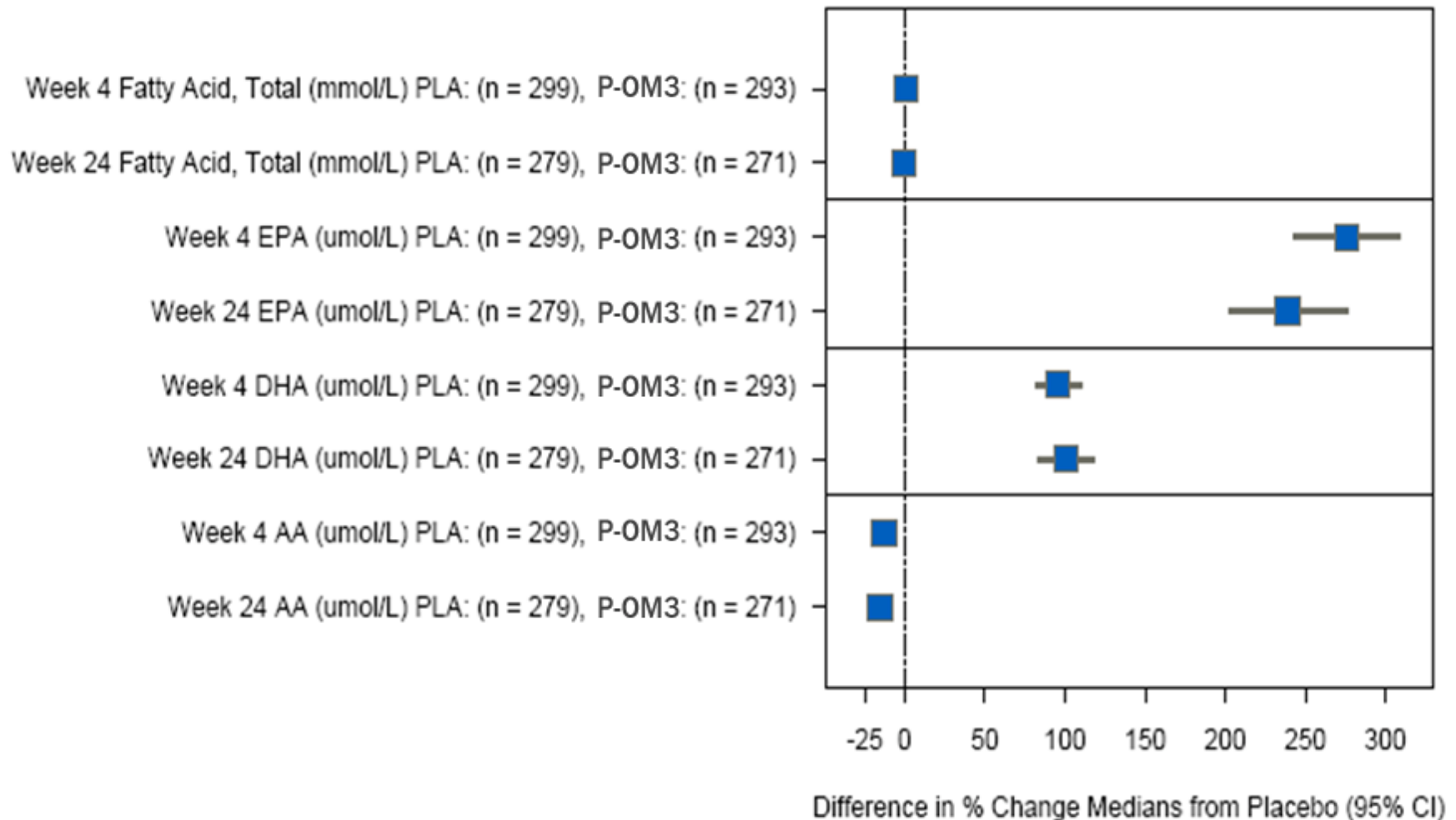
Note: EPA= Eicosapentaenoic Acid, DHA= Docosahexaenoic Acid, AA= Arachidonic Acid.

Fasting Lipid Parameters at Week 24 (Combined)

Week 24

Cholesterol (mg/dL) PLA: (n = 285), P-OM3: (n = 285)

HDL (mg/dL) PLA: (n = 285), P-OM3: (n = 285)

LDL (mg/dL) PLA: (n = 285), P-OM3: (n = 285)

Triglycerides (mg/dL) PLA: (n = 285), P-OM3: (n = 285)

VLDL (mg/dL) PLA: (n = 285), P-OM3: (n = 285)

-20 -15 -10 -5 0 5 10 15 20

Difference in % Change Medians from Placebo (95% CI)

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

	Placebo	P-OM3	Mean diff. from placebo (95% CI); *P* 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