

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE BRIEFING DOCUMENT

Vascepa[®] (icosapent ethyl; AMR101)
REDUCE-IT[®] (Reduction of Cardiovascular Events with EPA – Intervention Trial)
NDA Number: 202057

Applicant:
Amarin Pharmaceuticals Ireland Limited

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ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

1 EXECUTIVE SUMMARY

1.1 Introduction

Amarin Pharmaceuticals Ireland Limited (hereafter referred to as Amarin or the Sponsor) submitted a supplemental New Drug Application (sNDA) on 28 March 2019, providing results from the Reduction of Cardiovascular Events with EPA – Intervention Trial (REDUCE-IT) to extend the indicated use of Vascepa® (icosapent ethyl) to include the prevention of cardiovascular (CV) events in statin-treated patients with controlled (≤ 100 mg/dL) low-density lipoprotein cholesterol (LDL-C), but elevated (≥ 135 mg/dL) triglyceride (TG) levels and other cardiovascular disease (CVD) risk factors.

REDUCE-IT was conducted under a United States (US) Food and Drug Administration (FDA) Special Protocol Assessment (SPA) agreement. Development, finalization and amendment of this SPA agreement included FDA input and agreement on critical study design features; regulatory scientific dialogue with FDA included such topics as prespecified endpoints, the statistical testing hierarchy as captured in the protocol and statistical analysis plan (SAP), and the selection of placebo.

This briefing document outlines the key results from REDUCE-IT and provides background information for discussion of the trial results at the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) meeting scheduled for 14 November 2019. This briefing document was prepared by Amarin prior to release of the FDA briefing book or the question(s) within. Accordingly, this briefing book also presents anticipated topics of interest for deeper review and discussion, including efficacy findings in the secondary prevention and high-risk primary prevention cohorts, safety findings for bleeding and atrial fibrillation/flutter, the lack of impact on study conclusions with the use of light liquid paraffin (mineral oil) as the placebo, and mechanisms of action for eicosapentaenoic acid (EPA; the active metabolite of icosapent ethyl) that likely contribute to the observed CV risk reduction.

1.2 Long-Standing Unmet Medical Need and Public Health Burden

CVD remains the most common cause of morbidity and mortality in the US and globally, accounting for an estimated 31.5% (17 million) of all global deaths in 2013 (Roth 2017), despite increased use of statins and other therapies that target reduction of LDL-C. Public health and healthcare costs are burdened by the clinical need for treatments that effectively lower CV risk including in statin-treated patients well managed for other modifiable risk factors such as hypertension and hemoglobin A1c (HbA1c) who still remain at high risk for CVD events, and yet investment in the multi-year, multi-hundred million dollar outcomes trials that are required to demonstrate CV risk reduction have been rare. Failures outnumber successes while significant residual CV risk persists. Reducing CV events in at-risk patients beyond available therapies is a public health priority that likely contributed toward the current application being designated for priority review by the FDA.

We must endeavor toward further reducing the impact of CV disease beyond the benefits observed with statin therapy. New hypotheses and strategies must be encouraged, and one such strategy is to identify markers of CV risk that persist in statin-treated patients, and to develop clinically meaningful adjunct therapies for these patients. As discussed below, epidemiologic, clinical, and

genetic studies support elevated TG levels despite controlled LDL-C on statin therapy as one such marker of risk, while TG as a modifiable risk factor has yet to be established.

1.3 Icosapent Ethyl Distinct Mechanisms of Action

REDUCE-IT was designed to assess the clinical efficacy and safety of icosapent ethyl in statin-treated patients with elevated TG levels. REDUCE-IT was not designed to explore the mechanisms of action of Vascepa. Determination of the mechanisms of action for a given therapy is not required for regulatory approval of a drug indication. Nonetheless, a broad array of scientific literature has explored the mechanisms of action of EPA, and many of these mechanisms differ from other therapies, including individual or mixed omega-3 fatty acid products. The active ingredient of Vascepa, icosapent ethyl, was granted new chemical entity (NCE) status by FDA, with its single active molecule considered by the agency to be a different active ingredient than the previously approved, multiple-constituent, primarily omega-3, fatty acid product Lovaza® (omega-3 ethyl esters). Omega-3 fatty acids are prone to oxidation and can be readily damaged, therefore delivery in a stable and protected form such as icosapent ethyl is critical. The totality of evidence suggests that EPA may impact multiple stages along atherosclerotic processes, resulting in reduced development, slowed progression, and increased stabilization of atherosclerotic plaque. Importantly, while based on hypothesis-generating and/or *post hoc* analyses, achieving substantially increased blood EPA concentrations appears necessary for an observed CV benefit in statin-treated patients as observed in REDUCE-IT and other studies.

1.4 REDUCE-IT

Trial Design and Population

REDUCE-IT was a multi-national, prospective, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the effect of 4 g/day icosapent ethyl (2 g twice daily [BID]) for preventing CV events in statin-treated patients with controlled LDL-C (≤ 100 mg/dL), moderately elevated TG levels (≥ 135 mg/dL), and other CVD risk factors. Patients remained on statin therapy and were treated based on the standard of care by their individual clinicians regarding cholesterol, diabetes, blood pressure and other therapies. A REDUCE-IT protocol amendment was implemented midway through patient enrollment that raised the lower TG inclusion criterion limit for the remaining patient enrollment from 135 to 200 mg/dL to ensure substantial enrollment of patients with TG > 200 mg/dL and the ability to explore efficacy in a range of elevated TG levels; all enrolled patients were followed for the duration of the study. All patients enrolled before and after the protocol amendment were maintained and followed per protocol. Complete inclusion criteria can be found in [Appendix A](#).

REDUCE-IT was designed as an event-driven study. Approximately 7990 patients were to be randomized in a 1:1 fashion to icosapent ethyl or placebo and followed until approximately 1612 first occurrences of primary endpoint events. Enrollment targeted a blend of 70% secondary prevention patients with established CVD (per protocol “CV Risk Category 1”) and 30% of primary prevention patients at high-risk for developing CVD (diabetes requiring medication and additional risk factor(s), per protocol “CV Risk Category 2”). Primary endpoint attainment in this mixed patient population was agreed with FDA to support the broad assessment of the utility of icosapent ethyl in at-risk patients within one composite primary endpoint. Randomization was stratified by CV risk category, use of ezetimibe (yes/no), and geographical region (Westernized, Eastern European, and Asia Pacific). The prespecified primary, secondary, tertiary, and

exploratory endpoints were adjudicated by an independent blinded Clinical Endpoint Committee (CEC); see [Appendix B](#) for further details of the endpoint adjudication process. A total of 8179 patients were randomized (4089 to icosapent ethyl; 4090 to placebo) and followed for a median of 4.9 years. Consistent with the design of the study, 70.7% were enrolled in the secondary prevention cohort, and 29.3% in the high-risk primary prevention cohort. Actual versus potential total follow-up time was 93.6% in the icosapent ethyl group and 92.9% in the placebo group. A total of 89.4% (7314/8179) of patients completed the final study visit or were reported as having a fatal event; 90.1% (3684/4089) in the icosapent ethyl group and 88.8% (3630/4090) in the placebo group. Vital status was known for 99.8% (8160/8179) of patients; 99.9% (4083/4089) and 99.7% (4077/4090) in the icosapent ethyl and placebo groups, respectively. Over 35,000 patient years of data was captured.

Efficacy Results

The primary endpoint was the time from randomization to the first occurrence of the composite of CV death, nonfatal myocardial infarction (MI), nonfatal stroke, coronary revascularization, or unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization. A primary endpoint event occurred in 17.2% (705/4089) of patients in the icosapent ethyl group as compared to 22.0% (901/4090) of patients in the placebo group (hazard ratio [HR] of 0.752 [95% confidence interval (CI): 0.682 to 0.830; $p=0.00000001$]; relative risk reduction [RRR] of 24.8%).

The key secondary endpoint was the time from randomization to the first occurrence of the composite of CV death, nonfatal MI, or nonfatal stroke. A key secondary endpoint event occurred in 11.2% (459/4089) of the icosapent ethyl group as compared to 14.8% (606/4090) of the placebo group (HR of 0.735 [95% CI: 0.651 to 0.830; $p=0.00000006$]; RRR of 26.5%).

Consistent with analyses of the primary and key secondary endpoints, significant differences between icosapent ethyl and placebo were observed for each of the individual components of the primary and key secondary endpoints (each analyzed as independent endpoints), including CV death (HR of 0.803 [95% CI: 0.657 to 0.981; $p=0.0315$]), nonfatal MI (HR of 0.697 [95% CI: 0.590 to 0.823; $p<0.0001$]), nonfatal stroke (HR of 0.708 [95% CI: 0.536 to 0.936; $p=0.0149$]), coronary revascularization (HR of 0.664 [95% CI: 0.583 to 0.758; $p<0.0001$]), and unstable angina requiring hospitalization (HR of 0.679 [95% CI: 0.531 to 0.868; $p=0.0018$]).

The effects of icosapent ethyl versus placebo were highly consistent, achieving statistically significant and clinically meaningful reductions in the primary and all secondary endpoints following the prespecified hierarchical testing order, except the final prespecified secondary endpoint of total mortality. Some of these hierarchically tested secondary endpoints included components of the primary or key secondary composite endpoints, such as CV death, fatal or nonfatal MI, fatal or nonfatal stroke, emergent or urgent revascularizations, and unstable angina requiring hospitalization. Clinically meaningful reductions were also observed in CV-related tertiary and exploratory endpoints. The primary and key secondary endpoint findings were generally consistent across subgroups, and primary and key secondary endpoint total event analyses suggest persistent and substantial risk reduction with icosapent ethyl.

TG as a Marker of Risk; Lack of Substantial Evidence to Validate TG-lowering as a Surrogate for CV Risk Reduction in Patients with Elevated TG levels Despite Statin Therapy

Epidemiological, clinical, and genetic studies support a causal link between increased TG levels and increased CV risk, with such CV risk beginning to rise even with TG levels below 100 mg/dL. However, establishment of TG as a modifiable risk factor has not been demonstrated. REDUCE-IT was not designed to validate changes in biomarkers as surrogates for CV risk reduction. Exploration of TG changes within REDUCE-IT suggest baseline TG levels above or below 150 mg/dL or 200 mg/dL do not impact the relative CV risk reduction with icosapent ethyl. Achieved on-treatment TG levels above or below 150 mg/dL at one year also did not alter the CV benefit of icosapent ethyl over placebo. Finally, analyses considering on-study TG levels suggest the observed reduction of TG with icosapent ethyl in REDUCE-IT had limited contribution to the 25% relative risk reduction observed in REDUCE-IT. Therefore, while TG-lowering likely contributed to the observed CV risk reduction with icosapent ethyl in REDUCE-IT, as expected and consistent with the multifactorial effects of EPA, reduction of TG does not appear to be the sole underlying mechanism of the observed 25% relative risk reduction.

Control Group Response Analyses

REDUCE-IT is the third Phase 3 study of icosapent ethyl within a development program commenced over a decade ago, with each study conducted under an SPA agreement. The Phase 3, Multi-Center, Placebo-Controlled, Randomized, Double-Blind, 12-Week Study With an Open-Label Extension to Evaluate the Efficacy and Safety of AMR101 in Patients With Fasting Triglyceride Levels ≥ 500 mg/dL and ≤ 2000 mg/dL (MARINE) study evaluated the effect of icosapent ethyl on biomarkers in patients with very high TG levels (>500 mg/dL). The Phase 3, Multi-Center, Placebo-Controlled, Randomized, Double-Blind, 12-Week Study to Evaluate the Effect of Two Doses of AMR101 on Fasting Serum Triglyceride Levels in Patients With Persistent High Triglyceride Levels (≥ 200 mg/dL and <500 mg/dL) Despite Statin Therapy (ANCHOR) study evaluated the effect of icosapent ethyl on biomarkers in patients with mixed dyslipidemia and high TG levels (200 to 499 mg/dL) despite statin therapy. All three Phase 3 studies achieved their respective primary endpoints.

The selection of an appropriate placebo for use in the study of icosapent ethyl was examined before and after each Phase 3 icosapent ethyl clinical trial ([Appendix C](#)). Mineral oil has been used as a laxative at high doses (typically 15–30 g/day) for over 100 years, including extensive use in pediatric populations. The safety of mineral oil is generally inferred from a long history of use with limited adverse effects and from use as placebo in other clinical studies. Some parties have raised questions regarding the relatively small biomarker changes in the placebo group of REDUCE-IT and speculated if light mineral oil may have influenced these changes, and thus may have overestimated the treatment effect of icosapent ethyl in REDUCE-IT.

Per design as a CV outcomes study, REDUCE-IT hierarchical primary and secondary endpoint analyses focused on CV events. Biomarkers were collected as single measures with large spans of time between measurements to support tertiary, exploratory, and *post hoc* analyses. The design of REDUCE-IT recognized from the start that changes in such biomarkers should not be relied upon as primary or secondary endpoints within this outcomes study. Nonetheless, to address the speculation raised, we performed extensive literature searches regarding mineral oil and regarding biomarker changes observed in statin-treated patients, and we conducted a series of *post hoc*

analyses to explore whether or not mineral oil effect may have overestimated REDUCE-IT study results ([Appendix D](#)). The supposition that the light mineral oil used in REDUCE-IT does not exert clinically meaningful effects on medication (including statin) efficacy or absorption, biomarkers, outcomes, or safety, agrees with conclusions from prior FDA reviews, and is supported by multiple lines of evidence. While there is no evidence to support a hypothetical impact of placebo on CVD risk, there is an extensive body of clinical and preclinical studies supporting cardioprotective effects of EPA ([Appendix E](#)). While based on these various sources of evidence we do not agree that placebo caused an overestimation of the REDUCE-IT results, even if we are wrong, such potential influence cannot reasonably be estimated to account for a substantial portion of overall robust and consistent REDUCE-IT findings, including a 25% RRR in the primary endpoint that is consistent with the observed risk reduction in the the Japan EPA Lipid Intervention Study (JELIS) study, which did not administer a mineral oil placebo. Taken together, these various analyses and comparisons are inconsistent with a placebo-mediated effect significantly overestimating the REDUCE-IT results, but rather support a conclusion that icosapent ethyl provided substantial and consistent risk reduction in statin-treated patients.

General Safety

Icosapent ethyl 4 g/day was generally well tolerated over the 4.9-year median follow-up. The relatively long duration of patient follow-up and the high-risk characteristics of the patients enrolled in the study, along with the multiple concomitant therapies, contributed to the majority of patients having some form of adverse event (AE). The proportions of patients with AEs were similar between the icosapent ethyl and placebo groups, respectively, including treatment-emergent AEs (TEAEs; 81.8% versus 81.3%), severe TEAEs (19.7% versus 20.0%), study drug-related TEAEs (12.6% versus 12.2%), serious AEs (SAEs; 30.6% versus 30.7%), study drug-related SAEs (0.2% versus 0.1%), TEAEs leading to study drug withdrawal (7.9% versus 8.2%), SAEs leading to study drug withdrawal (2.2% versus 2.2%), and SAEs leading to death (2.3% versus 2.5%). Baseline medications reflected the CV risk of enrolled patients, including antithrombotic use in 85.5% of the ITT population, and the percentages of patients taking different medications were similar between treatment groups ([Table 4](#) and [Table 40](#)).

A statistically significant higher incidence of total adverse bleeding events was observed with icosapent ethyl compared to placebo (11.8% versus 9.9%, respectively; $p=0.0055$), while serious bleeding events were low and trended toward statistical significance in the icosapent ethyl versus the placebo group (2.7% [111/4089] versus 2.1% [85/4090], respectively; $p=0.0605$). The rates of adjudicated hemorrhagic stroke, and the incidences of serious gastrointestinal (GI) bleeding, serious central nervous system (CNS) bleeding, and serious anemia, were low overall and similar between treatment groups. Bleeding rates observed with icosapent ethyl are generally lower than what has been observed in studies involving low dose aspirin use in higher CV risk patients (ASCEND Study Collaborative Group 2018), although no head-to-head studies have been conducted.

A statistically significant higher incidence of atrial fibrillation/flutter TEAEs was observed with icosapent ethyl (5.8% versus 4.5%, respectively; $p=0.0079$), while the incidence of atrial fibrillation/flutter SAEs were similar between treatment groups (0.5% versus 0.5%, respectively; $p=0.7602$). Atrial fibrillation/flutter requiring hospitalization ≥ 24 hours was an adjudicated endpoint that occurred at a higher incidence with icosapent ethyl than placebo (3.1% versus 2.1%; $p=0.0037$). The observed increase in atrial fibrillation/flutter in REDUCE-IT is consistent with

trends observed for other omega-3 fatty acids (Kowey 2010, Lovaza Prescribing Information). In clinical practice, atrial arrhythmias can contribute to congestive heart failure (CHF), but in REDUCE-IT there were no changes in newly emergent CHF. In addition, stroke, MI, cardiac arrest, and sudden cardiac death are potential clinical outcomes related to atrial fibrillation and/or flutter; yet a substantially lower risk of these events was observed with icosapent ethyl group than placebo. Inclusion of positively adjudicated atrial fibrillation or atrial flutter and serious bleeding events with the composites of the primary and key secondary endpoints in *post hoc* analyses did not alter the overall study benefit/risk conclusions.

Benefit-Risk Considerations

REDUCE-IT provides robust and consistent evidence for CV risk reduction with icosapent ethyl in statin-treated patients with well-controlled LDL-C, as demonstrated by statistically significant reductions in the primary and key secondary composite endpoints, in each individual component of these endpoints, in the prespecified testing hierarchy, and in tertiary, exploratory, and *post hoc* CV endpoints, with findings generally consistent across subgroups.

Icosapent ethyl 4 g/day was generally well tolerated, with few observed safety imbalances between the treatment groups. Events such as serious bleeding and serious or adjudicated cases of atrial fibrillation/flutter occurred at relatively low rates; in context of observed benefits, these imbalances can be effectively communicated to clinicians and patients.

1.5 External Review of the REDUCE-IT Results

REDUCE-IT results have been published in *The New England Journal of Medicine* (NEJM; Bhatt 2019(a); Bhatt 2019(b); [Appendix F]) and the *Journal of the American College of Cardiology* (Bhatt 2019(c), Bhatt 2019(d)), and presented as late-breaking clinical trial presentations at the American Heart Association (AHA) in 2018 and the American College of Cardiology (ACC) in 2019. REDUCE-IT has been extensively evaluated in editorials and other forums, and it was designated as the *NEJM Journal Watch Cardiology 2018* number one cardiology story, one of the *AHA Top 10 Most Important Studies for 2018*, and among the *ACC 2018 Top Clinical Trials*.

Clinical treatment guidelines and position statements were updated based on REDUCE-IT results. Common to each of these updates was that icosapent ethyl should be used in high-risk statin-treated patients with TG levels ≥ 135 mg/dL.

- In March 2019 the American Diabetes Association updated its guidelines with a Level A recommendation – their highest level – in both secondary prevention patients and primary prevention patients with elevated TG levels (American Diabetes Association 2019).
- In August 2019 AHA recognized the results of REDUCE-IT and recommended directing medical care away from unproven fish oil dietary supplements and to prescription drug therapy in patients with elevated TG levels (AHA 2019).
- In September 2019 the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) also updated their guidelines in 2019 with a Level B (Class IIa) recommendation to administer icosapent ethyl therapy in high risk primary and secondary prevention patients with elevated TG despite statin therapy (ESC/EAS 2019).
- In September 2019 the National Lipid Association (NLA) issued a position statement recommending icosapent ethyl (Vascepa) for atherosclerotic cardiovascular disease

(ASCVD) risk reduction in the population studied in REDUCE-IT. The NLA recommendation was issued as a Class I, Level B-R (STRONG) recommendation, its highest designation, for icosapent ethyl (NLA 2019).

Also, in September 2019 the independent drug watchdog group, Institute for Clinical and Economic Review (ICER), presented its analysis, which found icosapent ethyl to be cost effective compared to optimal medical management alone. For these and other reasons, multiple patient advocacy groups and individuals are urging that icosapent ethyl be promptly approved for CV risk reduction to help address the large unmet medical need.

1.6 Conclusion

The Sponsor looks forward to presenting the REDUCE-IT study results to the committee. As the voting question(s) were not available upon submission of this briefing document, we intend to discuss the efficacy and safety data for icosapent ethyl in light of the significant clinical need and societal cost of CVD risk beyond statin therapy. We assume the committee will be asked if a new indication for use of Vascepa should be approved per language similar to that reflected below, or as modified through the standard label discussions among the FDA and the Sponsor.

To reduce the risk of cardiovascular death, myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization as an adjunct to statin therapy in adult patients with elevated triglyceride levels (TG $\geq$ 135 mg/dL) and other risk factors for cardiovascular disease.

Key efficacy and safety results from REDUCE-IT are presented within the main body of this briefing document. Appendices are included to provide additional information that we believe may be of interest to specific reviewers who may wish to learn more about certain topics, but that may not be of deep interest to all reviewers.

REDUCE-IT provides robust and consistent evidence that icosapent ethyl 4 g/day resulted in significant reduction of major adverse CV events, including CV death and a range of prespecified CV endpoints, in statin-treated patients with controlled LDL-C ($\leq$ 100 mg/dL), but elevated TG levels ($\geq$ 135 mg/dL) and established CVD or diabetes and other CV risk factors. Icosapent ethyl 4 g/day was generally well tolerated, with the nature and type of AE findings that provide a favorable benefit/risk profile.

The benefit-risk profile demonstrated in REDUCE-IT supports icosapent ethyl 4 g/day as a beneficial treatment beyond statin therapy to reduce CV events in patients with controlled LDL-C, elevated TG levels, and other CV risk factors, and supports the proposed label expansion.

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2.4 List of Abbreviations and Definition of Terms

Abbreviation	Definition
AA	Arachidonic acid
ACC	American College of Cardiology
ACCELERATE	Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition With Evacetrapib in Patients at a High Risk for Vascular Outcomes
ACCORD-Lipid	Action to Control Cardiovascular Risk in Diabetes-Lipid
ACM	All cause mortality
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
AE	Adverse event
AFCAPS/TexCAPS	Air Force/Texas Coronary Atherosclerosis Prevention Study
AHA	American Heart Association
AIM-HIGH	Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes
ALLIANCE	Aggressive Lipid-Lowering Initiation Abates New Cardiac Events
Alpha-Omega	Omega-3 Fatty Acids on Kidney Function after Myocardial Infarction
AMR101	Development code name for Vascepa (icosapent ethyl)
ANCHOR	Multi-Center, Placebo-Controlled, Randomized, Double-Blind, 12-Week Study to Evaluate the Effect of Two Doses of AMR101 on Fasting Serum Triglyceride Levels in Patients With Persistent High Triglyceride Levels (≥ 200 mg/dL and < 500 mg/dL) Despite Statin Therapy:
ARR	Absolute risk reduction
ASAP	ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology
ASCEND	A Study of Cardiovascular Events in Diabetes
ASCVD	Atherosclerotic cardiovascular disease
AURORA	A study to evaluate the Use of Rosuvastatin in subjects On Regular haemodialysis: an Assessment of survival and cardiovascular events
BID	Twice daily
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CANTOS	Canakinumab Antiinflammatory Thrombosis Outcome Study
CDER	Center for Drug Evaluation and Research
CEC	Clinical Endpoint Committee
cGMP	Current Good Manufacturing Practice
CHARISMA	Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance
CHD	Coronary heart disease

CHERRY	Combination Therapy of Eicosapentaenoic Acid and Pitavastatin for Coronary Plaque Regression Evaluated by Integrated Backscatter Intravascular Ultrasonography
CI	Confidence interval
CIRT	Cardiovascular Inflammation Reduction Trial
CNS	Central nervous system
CRP	C-reactive protein
CV	Cardiovascular
CVA	Cerebrovascular accident
CVD	Cardiovascular disease
dal-OUTCOMES	A phase III, double-blind, randomized placebo-controlled study, to evaluate the effects of dalcetrapib on cardiovascular (CV) risk in stable CHD patients, with a documented recent Acute Coronary Syndrome (ACS)
DGAT	Diacylglycerol transferase
DHA	Docosahexaenoic acid
DM	Diabetes mellitus
DMC	Data Monitoring Committee
DMEP	Division of Metabolism and Endocrinology Products
EAS	European Atherosclerosis Society
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
ELIXA	Evaluation of LIXisenatide in Acute coronary syndrome
EMDAC	Endocrinologic and Metabolic Drugs Advisory Committee
EPA	Eicosapentaenoic acid
ERFC	Emerging Risk Factor Collaboration
ESC	European Society of Cardiology
EVAPORATE	Effect of Vascepa on Improving Coronary Atherosclerosis in People With High Triglycerides Taking Statin Therapy
FDA	Food and Drug Administration
FOURIER	Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk
GI	Gastrointestinal
GISSI-HF	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto-Heart Failure
GISSI-P	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto-Prevenzione
GRAS	Generally Recognized as Safe
HbA1c	Hemoglobin A1c
HDL-C	High-density lipoprotein-cholesterol
HOPE-3	Heart Outcomes Prevention Evaluation-3

HPS2-THRIVE	Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events
HR	Hazard ratio
hsCRP	High-sensitivity C-reactive protein
HTG	Hypertriglyceridemia
HO-1	Heme oxygenase-1
IB-IVUS	Integrated backscatter intravascular ultrasound
ICAM	Intercellular adhesion molecule
ICER	Institute for Clinical and Economic Review
IDEAL	Incremental Decrease in End Points Through Aggressive Lipid Lowering
IL-10	Interleukin-10
IMPROVE-IT	IMProved Reduction of Outcomes: Vytorin Efficacy International Trial
IND	Investigational New Drug
ITT	Intent-to-Treat or Intention-to-Treat
IWRS	Interactive Web Response System
JAS	Japanese Atherosclerosis Society
J-STARS	The Japan Statin Treatment Against Recurrent Stroke
JUPITER	Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin
JELIS	Japan EPA Lipid Intervention Study
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LIPID	Long-Term Intervention with Pravastatin in Ischemic Disease
LPL	Lipoprotein lipase
Lp-PLA2	Lipoprotein phospholipase A2
LVEF	Left ventricular ejection fraction
LXR	Liver X receptor
LY3015014	A Study of LY3015014 in Participants With High Cholesterol
MACE	Major adverse cardiac event
MARINE	Phase 3, Multi-Center, Placebo-Controlled, Randomized, Double-Blind, 12-Week Study With an Open-Label Extension to Evaluate the Efficacy and Safety of AMR101 in Patients With Fasting Triglyceride Levels ≥ 500 mg/dL and ≤ 2000 mg/dL
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
NCE	New chemical entity
NDA	New Drug Application
NEJM	The New England Journal of Medicine
NIH	National Institute of Health

NLA	National Lipid Association
NNT	Number needed to treat
ODYSSEY COMBO	Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins
ODYSSEY LONGTERM	Long-term Safety and Tolerability of Alirocumab Versus Placebo on Top of Lipid-Modifying Therapy in High Cardiovascular Risk Patients With Hypercholesterolemia
ODIS	Off drug in study
OMEGA	Omega 3-Fatty Acids on the Reduction of Sudden Cardiac Death After Myocardial Infarction
ORIGIN	Outcome Reduction With Initial Glargine Intervention
OSLER	Open Label Study of Long Term Evaluation Against LDL-C Trial
PAD	Peripheral artery disease
PCI	Percutaneous coronary intervention
PDUFA	Prescription Drug User Fee Act
PEACE	Prevention of Events with Angiotensin Converting Enzyme Inhibition
PGI2	Prostaglandin I2
PGI3	Prostaglandin I3
Ph Eur	European Pharmacopeia
PPAR	Peroxisome proliferator-activated receptor
PRINCE	Platelet Reactivity in Acute Stroke or Transient Ischaemic Attack
PROBE	Prospective, randomized, open-label, blinded endpoint evaluation
PROVE IT-TIMI 22	Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22
pVal	P-value
PVD	Peripheral vascular disease
RBC	Red blood cell
REAL-CAD	Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy With Pitavastatin in Coronary Artery Disease
REDUCE-IT	Reduction of Cardiovascular Events with EPA – Intervention Trial
Risk & Prevention	Evaluation of the Efficacy of n-3 PUFA in Subjects at High Cardiovascular Risk
RLP-C	Remnant lipoprotein cholesterol
RRR	Relative risk reduction
RXR	Retinoid X receptor
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Steering Committee
sdLDL	Small dense low density lipoprotein
sNDA	Supplemental New Drug Application
SPA agreement	Special Protocol Assessment agreement

SPIRE	Studies of PCSK9 Inhibition and the Reduction in vascular Events
SREBP	Sterol regulatory element binding protein
STRENGTH	STatin Residual Risk Reduction With EpaNova in HiGh CV Risk PatienTs With Hypertriglyceridemia
SU.FOL.OM3	SUPplemented with natural FOLate, vitamin B6 and B12 and/or OMega-3 fatty acids
T2DM	Type 2 diabetes mellitus
TEAE	Treatment-emergent adverse event
TG	Triglyceride(s)
TIA	Transient ischemic attack
UA	Unstable angina
US	United States
USP	United States Pharmacopeia
VCAM	Vascular cell adhesion molecule
VITAL	VITamin D and OmegA-3 TriaL
VLDL-C	Very low density lipoprotein cholesterol
VLDL-TG	Very low density lipoprotein triglyceride
WOSCOPS	West of Scotland Coronary Prevention Study

Note: SI units not included.

3 INTRODUCTION

3.1 Purpose of the Briefing Document

The Sponsor submitted an sNDA on 28 March 2019, with results from REDUCE-IT as the basis of seeking an expansion of the current TG-focused indication of Vascepa (icosapent ethyl) to include CV risk-reduction in an appropriate statin-treated patient population along the lines of the following:

To reduce the risk of cardiovascular death, myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization as an adjunct to statin therapy in adult patients with elevated triglyceride levels (TG $\geq$ 135 mg/dL) and other risk factors for cardiovascular disease.

This draft indication statement is meant to represent the REDUCE-IT patient population and study results in language that is accessible to patients and their treating clinicians. We understand and expect further discussion with the FDA regarding the proposed label language following the EMDAC meeting.

Icosapent ethyl (Vascepa) is a stable ethyl ester of EPA that, since initial US regulatory approval in 2012, has been indicated as an adjunct to diet to reduce TG levels in adult patients with severe hypertriglyceridemia (HTG; $\geq$ 500 mg/dL), where pancreatitis is a principal concern. Vascepa has been prescribed in the US more than five million times since approval.

REDUCE-IT was a multi-national, prospective, randomized, double-blind, placebo-controlled, parallel-group study evaluating the effect of 4 g/day of icosapent ethyl (2 g BID) for preventing CV events in statin-treated patients with controlled LDL-C ($\leq$ 100 mg/dL), but moderately elevated TG levels ($\geq$ 135 mg/dL) and other CVD risk factors.

REDUCE-IT was the third Phase 3 clinical trial of icosapent ethyl, each successfully conducted under a US FDA SPA agreement, including advance agreement regarding design features, selection of placebo, prespecified endpoints and testing hierarchy as reflected in the protocol and the SAP. An SPA agreement indicates concurrence by FDA with the adequacy and acceptability of specific critical elements of overall protocol design for a study intended to support a future marketing application (see FDA, Guidance for Industry: Special Protocol Assessment 1 (April 2018); see also [Appendix C](#) for further details regarding the regulatory history of icosapent ethyl). The first two clinical trials of icosapent ethyl were the MARINE and ANCHOR trials ([Table 1](#)). During the Advisory Committee meeting reviewing the results of ANCHOR, the committee was asked to consider if they believed the observed TG reductions observed in the 12-week ANCHOR study would result in CV risk reduction; the committee recommended to defer conclusions until the completion of REDUCE-IT.

Table 1. Icosapent Ethyl Lipid and Cardiovascular Studies

	MARINE (N=229) NCT01047683	ANCHOR (N=702) NCT01047501	REDUCE-IT (N=8179) NCT01492361
Key Inclusion	Severe HTG	Statin controlled LDL-C with elevated TG	Statin controlled LDL-C with elevated TG
CV Risk	--	High risk for CVD	High risk for CVD
TG Level	≥500 to ≤2000 mg/dL	≥200 to <500 mg/dL	≥135 to <500 mg/dL
Primary Endpoint	TG reduction	TG reduction	CV events
Timing (years)	2009 – 2011	2009 – 2011	2011 – 2018

Abbreviations: CV = cardiovascular; CVD = cardiovascular disease; HTG = hypertriglyceridemia; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides

This briefing document, including its appendices, outlines the design and key results of the REDUCE-IT study, and provides background information for discussion of the trial results at the EMDAC meeting scheduled for 14 November 2019. In addition to the key results, covered in added detail are anticipated topics of potential interest for deeper review and discussion, including efficacy findings in the secondary prevention and high-risk primary prevention cohorts, safety findings for bleeding and atrial fibrillation/flutter, and the lack of impact on efficacy conclusions from the use of FDA-agreed light liquid paraffin (mineral oil) as the placebo.

3.2 Cardiovascular Disease and Unmet Need

CVD remains the most common cause of morbidity and mortality in the US and globally, accounting for an estimated 31.5% (17 million) of all global deaths in 2013 (Roth 2017). The most recent AHA and National Institute of Health (NIH) analyses place CVD as the leading global cause of death, expected to account for greater than 23 million deaths by 2030 (Benjamin 2019). An estimated 92.1 million American adults (more than one in three) has at least one manifestation of CVD, and US mortality data show that CVD is the underlying cause of death, accounting for 28% of all deaths in 2016 (about 740,083 of all 2.6 million deaths) (Xu 2016). In addition to death, CVD also causes many serious nonfatal events and is a major cause of disability (Benjamin 2019).

Despite the use of statin (and other LDL-C-lowering) therapies that generally lower CV risk by approximately 25% to 35%, substantial residual risk remains, which has significant personal and societal impact (Ganda 2018). This residual risk is effectively greater in patients with diabetes, as these patients have a two out of three chance of developing CVD during their lifetime (Fox 2008), which is between 1.5 and 2 times the risk for developing CVD in the general population (Rana 2016). Atherosclerotic CVD (ASCVD), one of the most common manifestations of CVD in patients with diabetes, is one of the greatest causes of morbidity and mortality for these patients (Benjamin 2019).

3.3 TG as a Marker of Risk; Lack of Substantial Evidence to Validate TG-Lowering as a Surrogate for CV Risk Reduction in Patients with Elevated TGs After Statin Therapy

Elevation in TG is a common lipid abnormality and often occurs in conjunction with obesity, insulin resistance, Type 2 diabetes mellitus, and metabolic syndrome, and can persist despite

optimal statin treatment (Bays 2008, Jacobson 2007). Epidemiological studies have demonstrated an independent correlation of increased TG levels and increased CV events, with increases in risk being observed starting at TG levels less than 100 mg/dL (e.g., Jacobson 2007; Manninen 1992; Navar 2019; Sarwar 2007). More recently, several genetic studies support a causal link between elevated TG levels and increased CV risk (Dewey 2016, Do 2013, Do 2015, Jørgensen 2014, Nordestgaard 2016, Pollin 2008, Schunkert 2011, Stitzel 2016, TG and HDL Working Group 2014, Wittrup 1999). Of note, in many of these studies, similar genetic correlations were observed between LDL-C and CVD, but not between high-density lipoprotein cholesterol (HDL-C) and CVD.

Despite substantial evidence that TGs are in the causal pathway of CVD, there is far less evidence that TG is a modifiable risk factor. CV outcome studies administering therapies that lower TG levels, including niacin and fibrates, have failed to confirm that lowering TG levels in statin-treated patients results in CV risk reduction. The CV outcomes studies ACCORD-Lipid (Ginsberg 2010), AIM-HIGH (Guyton 2013), and HPS2-THRIVE (Landray 2014) administered agents that lower TG levels (i.e., niacin or fibrate) in statin-treated patients and observed no CV benefit in the full cohort of patients studied. These studies did not prospectively enroll statin-treated patients with persistently elevated TG levels, and subgroup analyses of patients with dyslipidemia (defined as elevated TG and low HDL-C) suggest there could be benefit to therapy in these patients (Bhatt 2017). PROVE IT-TIMI 22 subgroup analyses also support the association of TG levels and CV risk, where statin-treated achievement of TG <150 mg/dL was associated with reduced CV risk, regardless of achieved LDL-C levels (Miller 2008). Therefore, while there is supportive evidence that TG-lowering (or achievement of lower TG levels) may result in CV benefit, this has yet to be shown across multiple prospectively designed studies, and there is little understanding of how such benefit may be related specifically to TG-lowering or to other effects of individual therapies. It is worth noting that clinical guidelines have inferred TG levels to denote risk, largely based on the epidemiology of untreated TG levels. Since statins lower TG levels and influence TG-rich lipoproteins, residual TG levels on statin therapy may not be comparable to untreated TG levels in terms of risk. At this time, reference ranges for residual TG levels have not been determined, as they have for untreated TG levels. Therefore, clinical ranges of TG levels may not adequately capture the residual CV risk associated with residual elevated TG levels.

Overall, there is substantial evidence for elevated TG levels as a marker of CV risk, but far less understanding regarding the CV benefit to TG-lowering, particularly as might be achieved by differing agents that lower TG levels. The TG-lowering effects of icosapent ethyl were evaluated in the earlier MARINE and ANCHOR clinical studies, and REDUCE-IT was not designed to validate TG as a modifiable risk factor. REDUCE-IT was designed to assess the multifactorial effects of icosapent ethyl on CV risk reduction in statin treated patients with elevated TG levels and other CV risk factors, with biomarker measurements supporting tertiary, exploratory, and *post hoc* hypothesis-generating analyses.

3.4 Eicosapentaenoic Acid to Reduce the Risk of Cardiovascular Events

Early data suggest that regular intake of omega-3 fatty acids (e.g., EPA and docosahexaenoic acid [DHA]) exerts cardioprotective effects in both primary and secondary CVD prevention (Harris 2008, Lee 2008). Several mechanisms have been proposed to account for these beneficial effects, including the reduction of TG and other lipids and lipoproteins, improved plaque composition and stabilization, anti-inflammatory and antioxidant effects, and anti-platelet and anti-coagulant

effects. Evidence also supports that mechanistic effects of different omega-3 fatty acid molecules (e.g., EPA, DHA) may differ, suggesting that each agent or mixture should be considered individually and subjected to individual rigorous controlled evaluation (see [Section 3.5.2](#)). Importantly, in June 2019 the FDA deemed EPA and DHA omega-3 fatty acids in food or dietary supplements to be generally recognized as safe (GRAS) at dose levels up to 5 g/day in connection with the examination of qualified health claims for the risk of hypertension and coronary heart disease. FDA determined that a daily intake limit of ≤ 5 g/day of EPA and DHA is an amount that is unlikely to cause excessive bleeding (FDA 2019).

[Table 2](#) provides an overview of omega-3 CV outcome trials. Despite CV benefit observed in early outcome studies administering low-dose omega-3 fatty acid mixtures (e.g., GISSI-P [Marchioli 1999], GISSI-HF [Marchioli 2008]) [Table 2](#) more modern CV therapies (e.g., statins) were limited or not administered. CV outcome studies administering more modern background therapies, particularly those with high (or complete) statin use, observed no benefit to low-dose omega-3 fatty acid mixtures, including the very recent VITAL and ASCEND trials (see Manson 2018; Bowman 2018).

A single CV outcome study administered a higher 1.8 g/day dose of an EPA-only therapy in statin-treated patients and observed a CV benefit as compared to the statin-alone group. The Japan EPA Lipid Intervention Study (JELIS) was a prospective, randomized, open-label, blinded endpoint evaluation (PROBE design) study that enrolled 18,645 Japanese patients with statin-naïve hypercholesterolemia. JELIS enrolled 80% primary prevention patients and 69% women. Patients were randomly assigned to receive either 1.8 g/day EPA with statin (EPA group; n=9326) or statin only (controls; n=9319). The primary endpoint was a composite of the first occurrence of any major coronary event, including sudden cardiac death, fatal and non-fatal MI, and other non-fatal events including unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting. After a mean follow-up of 4.6 years, JELIS reported a 19% RRR in major coronary events with EPA therapy versus control (Yokoyama 2007).

JELIS patients had statin-naïve baseline TG levels that were only modestly elevated (approximately 153 mg/dL; 1.7 mmol/L), which were reduced approximately 5% from baseline in the EPA plus statin group as compared to the statin-alone group. In a subgroup analysis of patients with atherogenic dyslipidemia (defined as baseline statin-naïve TG ≥ 150 mg/dL and HDL-C < 40 mg/dL), a more substantial 53% reduction in the primary endpoint was observed (Saito 2008). Similar to the full study cohort, there was only about a 5% differential reduction in TG levels in this subgroup of patients treated with EPA plus statin as compared to the subgroup of patients treated with statin-only therapy. Therefore, while TG-reduction may have contributed to the overall CV benefit observed in JELIS, it is likely this was a relatively small contribution to the reported 19% and 53% RRRs in the full and dyslipidemic cohorts, respectively. Also, the achievement of more substantial risk reduction in the cohort with dyslipidemia agrees with other studies administering therapies that lower TG levels ([Section 3.3](#)), suggesting potential additional benefit to treating these patients. Of distinction, the studies administering therapies that lower TG levels in [Section 3.3](#) did not demonstrated CV benefit to these therapies in patients with essentially normal TG levels, while in contrast, JELIS reported a statistically significant 19% reduction in CV events in the full study cohort. Together, in observing these data it remains possible that treating patients with elevated TG levels may confer additional CV benefit, but the benefits of EPA therapy likely extend beyond TG-lowering, extend to patients with essentially normal TG levels, and TG-lowering *per se* is not likely a central driver of these benefits.

The 1.8 g/day EPA dose administered in JELIS was 2.1- to 4.8-fold higher than the total EPA+DHA doses administered in the omega-3 fatty acid mixture trials noted in [Table 2](#) (i.e., 376-850 mg/day EPA+DHA), with even higher relative delivery of EPA specifically. Also, the average dietary intake of fish in Japan is about five times higher than other countries, likely contributing to the relatively high 2.9 mol% baseline plasma EPA in JELIS, as compared to a US level of approximately 0.3 mol% (Yokoyama 2007). A comparison of EPA blood levels across relevant trials suggests that a 4 g/day dose of EPA results in similar EPA blood levels in Western populations when compared to the 1.8 g/day EPA dose in the Japanese population studied in JELIS. JELIS investigators reported that the mean plasma EPA level in the EPA-treated group increased from 97 µg/mL at baseline to 170 µg/mL on study (Itakura 2011). Similar effects were observed in patients treated with 4 g/day icosapent ethyl in the ANCHOR study (statin-treated patients with TG $\geq$ 200 and $<$ 500 mg/dL), in which mean plasma EPA increased from 28 µg/mL to 183 µg/mL, and the MARINE study (patients with TG $\geq$ 500 mg/dL), in which mean plasma EPA increased from 61 µg/mL to 327 µg/mL (Bays 2016). While based on hypothesis-generating and/or *post hoc* analyses, exploration across Amarin-sponsored studies suggests achieving, effective plasma EPA concentration appears to be an important determinant of the beneficial effects of EPA, which likely include improved plaque composition and stabilization, anti-inflammatory and antioxidant effects, and anti-platelet and anti-coagulant effects (see [Section 3.5.2](#)). In addition, similar to icosapent ethyl used in REDUCE-IT, extensive work was done to ensure that the EPA administered in JELIS was in a stable form to avoid the potential mitigation of effect or increase in risk associated with oxidation of omega-3 fatty acids. Based on the JELIS results, the results of REDUCE-IT, and other analyses, keys to the successful effects of EPA within the products studied include the unique effects of EPA, the high dose of administration, and the stable protected form of EPA administered. These results should not be generalized to other products that contain omega-3 fatty acids.

There were limitations to the JELIS study design, including enrolling exclusively Japanese patients, with low overall event rates (particularly for CV death), having an open-label design without a placebo (although blinded endpoint evaluation), and administering lower dose statin therapy than is currently recommended per modern non-Japanese guidelines (although in agreement with Japanese Atherosclerosis Society [JAS] guidelines at the time of study conduct). Nonetheless, in light of the robust REDUCE-IT trial design and results on top of modern standard of care treatments, JELIS results can be viewed as supportive of the observation that a stable dosage form of a pure, isolated EPA administered at a dose sufficient to achieve high plasma EPA levels has potential benefits in the management of patients with high CV risk despite statin therapy. These benefits are likely at least partially driven by mechanisms beyond plasma lipid or lipoprotein modification, many of which appear to be unique from other omega-3 fatty acids or agents that lower TG levels. These possible mechanisms of EPA, particularly along the continuum of atherosclerotic plaque development, progression, and stabilization, are further discussed in [Section 3.5.2](#).

Table 2. Historical Trials with Omega-3 Fatty Acids and CV Outcomes

Study	Pub Date	Patient Population	Statin Use	Baseline LDL-C, mg/dL ¹	Baseline TG, mg/dL ¹	Interventions	Duration, years	Primary Endpoint	Outcomes, HR or OR (95% CI) or RRR (P-value)
Omega-acid mixture studies									
GISSI-P	1999	N=11,324; recent MI (≤3 mo)	Cholesterol-lowering: BL=5%; EOS=46%	137	162	850-882 mg EPA + DHA vs Vit E vs n-3 + Vit E vs PBO	3.5	Death or nonfatal MI or nonfatal stroke	HR: 0.85 (0.74-0.98), 4-way analysis
GISSI-HF	2008	N=6975; chronic HF (NYHA class II-IV)	22.3%-23.0%	NR; provided; TC=188	126	850-882 mg EPA + DHA vs PBO	3.9	Co-primary of death, and CV death or CV hosp	Death: HR: 0.91 (0.833-0.998); death or CV hosp: HR: 0.92 (0.849-0.999)
OMEGA	2010	N=3851; recent MI (≤2 wk)	94%-95%	NR; EOS=95	NR; EOS=121 - 127	840 mg EPA + DHA vs PBO	1	SCD	OR: 0.95 (0.56-1.60)
Alpha-Omega	2010	N=4837; prior MI	BL lipid-lowering: 85%-87%	99-102	144-150	376 mg EPA + DHA vs PBO and ALA (1.9 g)	3.4	Expanded MACE	HR: 1.01 (0.87-1.17)
SU.FOL. OM3	2010	N=2501; prior CVD event (≤12 mo)	BL lipid-lowering: 83%-87%	101-104	97-115	600 mg EPA + DHA vs PBO and B vit	4.7	MACE	HR: 1.08 (0.79-1.47)
ORIGIN	2012	N=12,536; dysglycemia + prior or high-risk CVD	53%-54%	112	140-142	840 mg EPA + DHA vs PBO	6.2	CV death	HR: 0.98 (0.87-1.10)
Risk & Prevention	2013	N=12,513; high-risk CVD	41%	132	150	850-882 mg EPA + DHA vs PBO	5	CV death or CV hosp	HR: 0.97 (0.88-1.08)
VITAL	2018	N=25,871; Age Men ≥50 Women ≥55	Cholesterol-lowering: 37%-38%	NR	NR	840 mg EPA + DHA +/- Vit D3 vs PBO	5.3	Co-prim. of invas. cancer and MACE	MACE HR: 0.92 (0.80 - 1.06)
ASCEND	2018	N=15,480; Diabetes	75%-76%	NR	NR	840 mg EPA + DHA vs PBO	7.4	Serious vasc. events	RR: 0.97 (0.87 - 1.08)
Pure EPA Study									
JELIS	2007	N=18,645; hypercholesterolemic	100%	181-182	153-154	1800 mg EPA + statin vs statin	4.6	Expanded MACE	HR: 0.81 (0.69-0.95)

Abbreviations: ALA = alpha-linolenic acid; AMD = age-related macular degeneration; ASCVD = atherosclerotic cardiovascular disease; BL = baseline; CI = confidence interval; CV = cardiovascular; CVD = cardiovascular disease; DHA = docosahexaenoic acid; EOS = end of study; EPA = eicosapentaenoic acid; HF = heart failure; HR = hazard ratio; LDL-C = low density lipoprotein cholesterol; LUT = lutein; MACE = major adverse cardiovascular events; MI = myocardial infarction; n-3 = omega 3 fatty acids; non-HDL = non-high density lipoprotein cholesterol; NR = not reported; NYHA = New York Heart Association; OR = odds ratio; PBO = placebo; SCD = sudden cardiac death; TC = total cholesterol; TG = triglycerides; Vit D3 = vitamin D3; Vit E = vitamin E; ZEA = zeaxanthin.

3.5 Icosapent Ethyl Overview

3.5.1 Description

Icosapent ethyl is a highly purified, pharmaceutical grade, stable, ethyl ester of EPA. Icosapent ethyl is $\geq 96\%$ pure as a result of multiple intermediate process steps, including distillation and chromatography. The chemical integrity of omega-3 fatty acids, including EPA, is known to be prone to oxidation and, therefore, nitrogen gas is used during every step of the manufacturing process to minimize the potential for oxidation, which impacts *in vitro* activity and likely also clinical efficacy. Recent research has suggested that the presence of oxidized lipids in common fish oil dietary supplements may mitigate the biological benefits of the omega-3 fatty acids. Elevated levels of oxidized lipids also play a central role in atherogenesis, may contribute to vascular injury, and may pose an increased potential for CV risk in individuals with coronary disease. (Mason 2017). Icosapent ethyl in Vascepa has been appropriately protected to ensure chemical integrity remains unaltered throughout the life of the product, thus ensuring the safety and efficacy of the product.

3.5.2 Mechanism of Action

REDUCE-IT was not designed to explore the mechanisms of action of Vascepa. Determination of the mechanisms of action for a given therapy is not required for regulatory approval of a drug indication. Nonetheless, exploring mechanism of action can provide insight into the possible reasons for observed clinical efficacy and a broad array of scientific literature has explored the mechanisms of action of EPA, and many of these mechanisms differ from other therapies, including individual or mixed omega-3 fatty acid products.

Similar to statins, although with a greater diversity of putative effects, pleiotropic mechanisms of action are hypothesized to contribute to the reduction in CV events observed with EPA. Evidence suggests that EPA may impact a number of atherosclerotic processes, resulting in reduced development, slowed progression, and increased stabilization of atherosclerotic plaque. Lipid and lipoprotein profiles are improved, without raising LDL-C levels, likely through reduced production and faster clearance of TG and decreased production of very low-density lipoprotein (VLDL) particles, as well as increased clearance of low density lipoprotein (LDL) particles. In addition, EPA may exert anti-inflammatory effects through displacement of pro-inflammatory arachidonic acid (AA), directing catabolism away from eicosanoids (2-series prostaglandins and thromboxanes, and 4-series leukotrienes) to non- or anti-inflammatory mediators. EPA may also exert systemic anti-inflammatory and antioxidant effects as reflected by reductions in various biomarkers including C-reactive protein (CRP) and lipoprotein phospholipase A2 (Lp-PLA2), and oxidized LDL compared to placebo. EPA may inhibit platelet activation and aggregation and reduce mean platelet volume and count, thereby exerting both anti-platelet and anti-coagulant effects.

The science related to the various omega-3 fatty acids, and mixtures comprised primarily thereof, is complex. Clinical and pre-clinical studies suggest that EPA has differential effects as compared to other long-chain omega-3 fatty acids. EPA is comprised of 20 carbons and five double bonds, which is different from other omega-3 fatty acid molecules, such as another common long-chain omega-3 fatty acid DHA that consists of 22 carbons and six double bonds; such differences can have substantial impact on biological function. In addition, the complex *in vivo* interactions for the multiple constituents in omega-3 fatty acid mixtures raise significant questions regarding how

the constituents might react and compete *in vivo* to cause a mixture's physiological and pharmacological effects. Consistently, mixtures comprised of different relative compositions of omega-3 fatty acids have been treated by FDA as distinct active ingredients given the inability to determine and explain differing clinical effects. For example, clinical studies such as the Sponsor's MARINE study in patients with very high TG levels (≥ 500 mg/dL) suggest no change in LDL-C levels with icosapent ethyl therapy, while substantial increases in LDL-C have been observed in studies enrolling similar patient populations and administering omega-3 fatty acid mixtures that contain DHA. Other clinical studies have also observed increases in LDL-C with DHA administration, but not with EPA. Further, other distinctions are observed between EPA and DHA in clinical and preclinical studies, such as at the levels of apolipoprotein B (apoB)-containing particle production or uptake, or regulation of transcription or membrane function. There is a general lack of benefit observed in CV outcome studies that administered low-dose (<1 g/day) omega-3 fatty acid mixtures in statin-treated patients, and no outcome studies have been completed that administered higher dose omega-3 fatty acid mixtures or DHA-only. While data may become available in the future regarding possible CV benefit of high-dose omega-3 fatty acid mixtures (e.g., from the ongoing STRENGTH study; NCT02104817), the clinical and preclinical differences between these compounds demonstrate that the relative clinical efficacy and safety of different omega-3 fatty acids cannot be presumed to be equivalent.

JELIS administered 1.8 g/day EPA-only therapy in statin-treated Japanese patients, and achieved high plasma concentrations of EPA and a statistically significant 19% reduction in the primary composite endpoint of coronary events in primary and secondary prevention patients enrolled based on statin-naïve hypercholesterolemia. An even greater 53% reduction in coronary events was observed in patients with dyslipidemia (elevated TG and low levels of HDL-C). Of note, these CV reductions in the full and dyslipidemic cohorts did not appear to correlate with TG reductions, as only minimal TG changes were observed due to EPA therapy.

Overall, preclinical and clinical studies, including outcomes data, support EPA reducing CV events through multiple mechanisms of action, and while reductions of TG and other lipid/lipoprotein levels may contribute to the REDUCE-IT results, they do not appear to substantially drive the observed CV risk reductions. The relative contribution of individual mechanisms to the observed CV benefit of EPA therapy is not fully known, but the totality of evidence suggests that EPA may beneficially impact multiple stages within atherosclerotic processes, and, while based on hypothesis-generating and/or *post hoc* analyses, achieving substantially increased blood concentrations of EPA appears to be necessary for an observed CV benefit in statin-treated patients. While EPA is not predominantly an LDL-C lowering moiety, scientific literature suggests that EPA modestly lowers LDL-C levels likely due, at least in part, to reduced production and increased clearance of apoB particles and improved HDL function.

Clinical and preclinical data strongly support that the relative clinical efficacy and safety of different omega-3 fatty acids cannot be presumed to be equivalent and, therefore, results from mixed omega-3 fatty acid studies will not alter the evidence for EPA-only therapy.

While mechanisms of action are of clinical and scientific interest, they do not need to be fully elucidated for clear demonstration of clinical benefit, such as observed in the REDUCE-IT study.

A more detailed discussion of the multiple mechanisms of action for icosapent ethyl is presented in [Appendix E](#).

3.6 Icosapent Ethyl Profile and Regulatory Status

Vascepa capsules are currently approved and indicated as an adjunct to diet to reduce TG levels in adult patients with severe (≥ 500 mg/dL) HTG. The approved dose of Vascepa is 4 g/day as either four 0.5 g capsules (2 g) taken with food BID or as two 1 g capsules (2g) taken with food BID. Vascepa received initial approval for marketing in the US in 2012 based primarily on the results of the Phase 3 studies, MARINE and ANCHOR.

In MARINE and ANCHOR, the effect of icosapent ethyl on CV mortality and morbidity in patients with elevated TG was not evaluated. Accordingly, REDUCE-IT was conducted to specifically assess the hypothesis that adjunctive therapy comprised of LDL-C control with statin therapy (with or without ezetimibe) and icosapent ethyl 4 g/day would be superior to statin therapy alone when used to reduce long-term CV events in patients with persistent elevated TG (≥ 135 mg/dL) and other CVD risk factors. The trial design allowed for other medical conditions, such as hypertension and diabetes, to be managed based on established standards of care during the randomized, blinded study.

A fuller discussion of the regulatory history of icosapent ethyl can be found in [Appendix C](#).

The Sponsor submitted an sNDA on 28 March 2019, providing results from REDUCE-IT. The FDA granted priority review for this application based on the drug's potential to dramatically alter the course of CVD management, and it is to be discussed at the EMDAC meeting scheduled for 14 November 2019.

Based on the results of REDUCE-IT the Sponsor has proposed the following additional indication for icosapent ethyl:

To reduce the risk of cardiovascular death, myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization as an adjunct to statin therapy in adult patients with elevated triglyceride levels (TG ≥ 135 mg/dL) and other risk factors for cardiovascular disease.

We believe that the proposed indication reflects the design and results of the REDUCE-IT study and that such language, or something similar, will be accessible to clinicians and patients, and that clinicians can assess the appropriate high CV risk patient, which together would support discussions regarding whether or not to prescribe icosapent ethyl to statin-treated patients with significant residual CV risk.

4 REDUCE-IT TRIAL DESIGN AND STATISTICAL CONSIDERATIONS

REDUCE-IT was designed to extend the indication of Vascepa (icosapent ethyl) to include the prevention of CV events in statin-treated patients with controlled (≤ 100 mg/dL) LDL-C, but elevated (≥ 135 mg/dL) residual TG levels and other CV risk factors. REDUCE-IT was conducted under an SPA agreement, which included FDA input and agreement regarding critical study design features such as prespecified endpoints, the statistical testing hierarchy as captured in the protocol and SAP, and the selection of placebo ([Appendix C](#)).

4.1 Trial Governance

The REDUCE-IT study involved several governing committees, including:

- Steering Committee (SC)
- Study Operations Committee
- Clinical Endpoint Committee (CEC)
- Data Monitoring Committee (DMC)

See [Appendix G](#) for further information regarding the responsibilities of these committees and a list of members and affiliations.

4.2 Trial Design

REDUCE-IT was a multi-national, prospective, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the effect of 4 g/day of icosapent ethyl (2 g BID) for preventing CV events. Patients were well-managed on modern statin therapy for at least 4 weeks with a well-controlled LDL-C >40 and ≤ 100 mg/dL, but persistently elevated TG levels ≥ 135 and <500 mg/dL and other CV risk factors.

In brief, secondary prevention patients in the established CVD cohort were defined as men and women ≥ 45 years old with a previous history of CVD (per protocol “CV risk category 1”; having documented coronary artery disease, cerebrovascular, carotid, or peripheral artery disease). The primary prevention cohort was considered a high risk population including men and women ≥ 50 years with diabetes requiring medication and at least one other CV risk factor such as hypertension, low HDL-C, elevated high-sensitivity C-reactive protein (hsCRP), or others (per protocol “CV risk category 2”). Patients with established CVD and diabetes requiring medication were included in the established CVD cohort (CV risk category 1). REDUCE-IT was designed such that the established CVD (secondary prevention) cohort was to contribute approximately 70% of randomized patients, as there was a higher CV event rate expected in this cohort, while the high risk primary prevention cohort was to contribute approximately 30% of patients. This ratio was determined sufficiently robust to support the entire patient population within an indication. The composite primary endpoint analysis was conducted on the Intention-to-Treat (ITT) population, per protocol, SAP, and SPA agreement. Select subgroup analyses were prespecified for tertiary and exploratory analyses, but by design, REDUCE-IT was not powered to support conclusions regarding independent primary endpoint analyses within such subgroups, including the established CVD or high risk cohorts.

All patients remained on statin therapy and other standard-of-care medications, except TG-lowering therapies such as fibrates, niacin, and omega-3 prescription products and dietary

supplements, which were discontinued and washed-out prior to lipid qualification. A protocol amendment was implemented that raised the lower residual TG inclusion criterion limit from 135 to 200 mg/dL; all patients enrolled before and after the protocol amendment were maintained and followed per protocol. Complete inclusion and exclusion criteria, including the residual CV risk threshold and all contributing risk factors, can be found in [Appendix A](#).

REDUCE-IT was designed as an event-driven study. A total of approximately 7990 patients were planned to be enrolled (i.e., randomized) in the study to receive either icosapent ethyl or placebo in a 1:1 ratio (approximately 3995 patients per treatment group) to observe an estimated 1612 primary endpoint events. The initial study design assumed an annualized placebo group primary endpoint event rate of 5.9%, based on published CV outcome studies with high CV risk statin-treated patients and endpoint components similar to those outlined within the REDUCE-IT study design. The planned enrollment population of 7990 patients reflects a more conservative projected annualized placebo event rate of 5.2%, which was decided prior to study initiation and following input from FDA to ensure adequate powering should trial experience differ from projections. A provision within the protocol permitted the enrollment beyond the projected 7990 and ultimately, a total of 8179 patients were enrolled (i.e., randomized) and followed during the study for a median of 4.9 years, resulting in a total of 1606 patients with positively adjudicated primary endpoint events. There were no mandatory stopping rules for efficacy, even in the event that statistical significance was reached prior to reaching the target 1612 primary endpoint events.

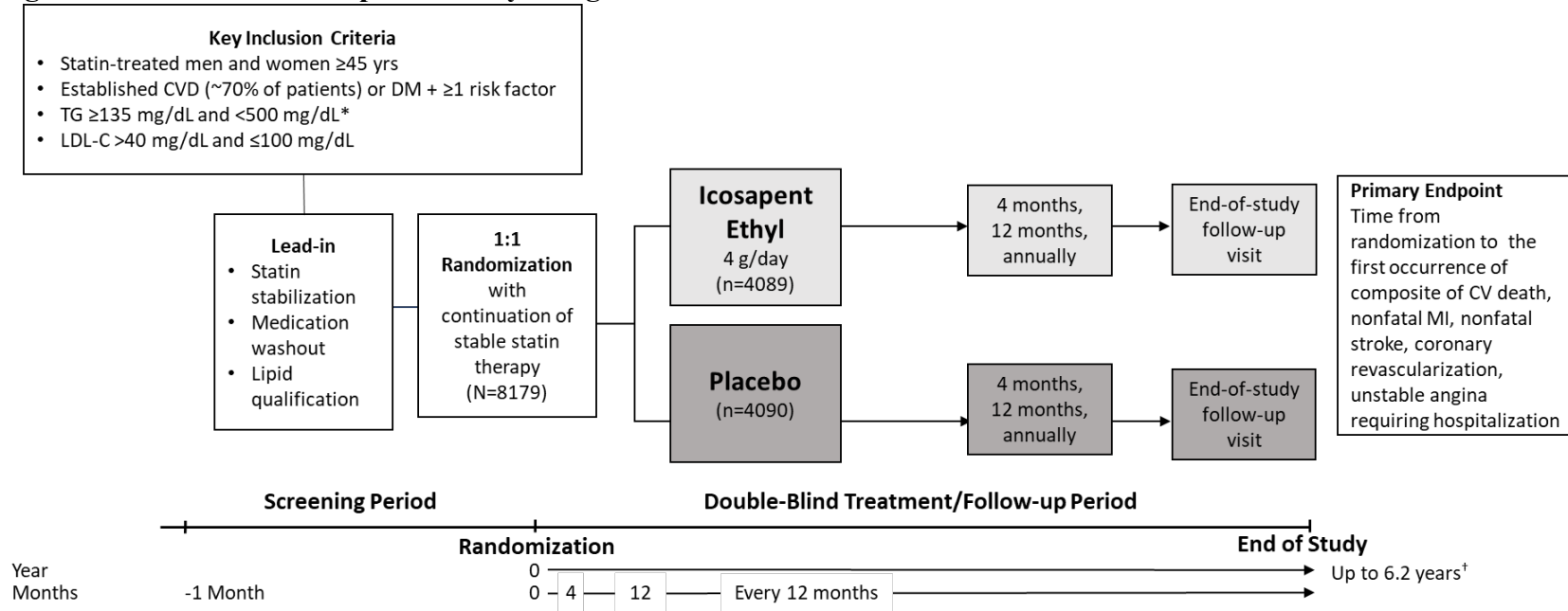
At the Randomization Visit (per protocol “Visit 2”), patients were assigned in a blinded manner according to a computer-generated randomization scheme to one of two treatment groups at a 1:1 ratio via the Interactive Web Response System (IWRS), as follows:

- Group 1: icosapent ethyl 4 g daily (two 1 g capsules BID)
- Group 2: placebo 4 g daily (two 1 g capsules BID)

Study drug dosing of 4 g daily was chosen based on clinical efficacy and safety studies suggesting the need for higher dosing (ANCHOR [Ballantyne 2012], MARINE [Bays 2011], and JELIS [Yokoyama 2007]). Study drug was to be taken with food on a BID regimen.

See [Figure 1](#) for a graphical representation of the REDUCE-IT design.

Figure 1. REDUCE-IT Graphical Study Design



*Due to the variability of triglycerides, a 10% allowance from the lower qualifying target of ≥150 mg/dL existed in the initial protocol, which permitted patients to be enrolled with qualifying triglycerides ≥135 mg/dL. Protocol amendment 1 (May 2013) changed the lower limit of acceptable triglycerides from 135 mg/dL to 200 mg/dL, with no variability allowance.

[†]Median trial follow-up duration was 4.9 years (minimum 0.0, maximum 6.2 years).

Abbreviations: CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; LDL-C = low-density lipoprotein-cholesterol; MI = myocardial infarction; TG = triglycerides.

Randomization was balanced (i.e., stratified) by CV risk category, use of ezetimibe (yes/no), and by geographical region (Eastern European, Asia Pacific, and Westernized). Stratification was accounted for and recorded in the IWRS at the time of enrollment. Approximately 70% of the planned 7990 randomized patients were planned to be in the established CVD cohort, and approximately 30% of randomized patients were planned to be in high risk primary prevention subgroup. This planned allocation between categories is essentially the inverse of the JELIS study, which enrolled approximately 80% primary prevention patients. In REDUCE-IT, if total study enrollment exceeded 7990 patients, enrollment of new patients was to be limited to patients with established CVD.

Individual patient duration of the treatment was dependent on the timing of randomization, as patients were randomized at different times during the enrollment period but completed the study on approximately the same date (study end date). It was planned that all patients randomized would receive study drug and be followed until the study end date and that all patients would remain on therapies as needed to manage other medical conditions, such as hypertension and diabetes, throughout the duration of the study.

AEs were either reported by the patient or observed by the investigating facility. AEs were considered treatment-emergent if they were not pre-existing conditions known at baseline. Signs or symptoms not tied to a specific disease were also recorded. AE severity was graded by the investigator.

Causality was also assessed by the investigator. AEs were categorized as either “Related, probably related, or possibly related to study drug” (causal) or “Unrelated, not related, or no relation to study drug” (not causal). (The definitions are standard; see [Appendix H](#).) Investigators had discretion to evaluate causality.

Finally, investigators evaluated the seriousness of AEs. The definitions for SAEs are standard; see [Appendix H](#).

Two interim analyses were planned when adjudication of approximately 60% and 80% of the total target number of first occurrences of primary endpoint events (1612) were reached. Interim analysis results were reviewed by the DMC, while the Sponsor, SC, and CEC remained blinded. The need for a mature dataset to support efficacy and safety findings was discussed with the DMC prior to interim analyses decisions were made by the DMC regarding continuing the study or stopping early with no mandatory early stopping requirement (see [Appendix C](#)).

4.3 Endpoints and Statistical Methods

4.3.1 Primary Endpoint

The primary endpoint was the time from randomization to the first occurrence of any component of the composite of the following clinical events (5-point major adverse cardiac events [MACE]):

- CV death
- Nonfatal MI
- Nonfatal stroke
- Coronary revascularization

- Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization

The first occurrence of any of these major adverse CV events during the follow-up period of the study was included in the incidence.

4.3.2 Secondary Endpoints

The key secondary endpoint was the time from randomization to the first occurrence of the composite of CV death, nonfatal MI, or nonfatal stroke (3-point MACE).

Other secondary endpoints were the time from randomization to the first occurrence of the individual or composite endpoints as follows (tested in the order listed):

- Composite of CV death or nonfatal MI
- Fatal or nonfatal MI
- Non-elective coronary revascularization represented as the composite of emergent or urgent classifications
- CV death
- Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization
- Fatal or nonfatal stroke
- Composite of total mortality, nonfatal MI, or nonfatal stroke
- Total mortality

For the secondary endpoints that counted a single event, the time from randomization to the first occurrence of this type of event was counted for each patient. For secondary endpoints that were composites of two or more types of events, the time from randomization to the first occurrence of any of the event types included in the composite was counted for each patient.

For the analysis of all secondary endpoints, the Type 1 error was controlled by testing each endpoint sequentially, starting with the key secondary endpoint. If the risk of the primary composite end point was significantly lower with icosapent ethyl than with placebo at a final two-sided alpha level determined with the use of O'Brien–Fleming boundaries generated with the Lan–DeMets alpha-spending function approach after accounting for two prespecified interim efficacy analyses, the key secondary end point and other prespecified secondary end points were to be tested in a hierarchical fashion at the same final alpha level.

4.3.3 Tertiary Endpoints

Time-to-event tertiary endpoints were analyzed by the same methods as described for the primary endpoint and, unless specified otherwise, endpoint analyses were conducted as time from randomization to the first occurrence of the individual or composite endpoints. No multiple testing adjustments were made, and the nominal 2-sided alpha level of 0.05 was applied, as they are supportive and prespecified as exploratory analyses.

4.3.4 Exploratory Subgroup Analyses

Subgroup analyses with the primary and key secondary endpoints were performed to explore the possibility of an interaction between particular subgroups. These analyses were exploratory and not powered to detect statistically significant results within a particular individual subgroup.

4.3.5 Statistical Handling of Time to Event Analyses

The event time was calculated as the (date of first event – date of randomization + 1 day) for patients who experienced one or more of the primary endpoint events. The following provided detailed considerations for determining the date of event/date of censoring:

- Patients who did not experience a primary endpoint event prior to the end of the study or withdrawal from the study early without a preceding primary endpoint event were censored at the date of their last visit/phone contact.
- Patients who died with an adjudicated undetermined cause of death and without a preceding endpoint event were to be included with adjudicated CV deaths, and these were included as events in the primary analysis.
- In view of the 90-day monitoring period for CV events, patients who had a non-CV death within 90 days of last contact without having had an earlier CV event were censored at the time of death. Patients who had a non-CV death more than 90 days after last contact without having had an earlier CV event were censored at the date of their last visit/phone contact.
- The primary analysis of silent MIs assumed that all newly emergent silent MIs occurred on the date of the first post-randomization electrocardiogram (ECG) tracing indicative of a silent MI.

Kaplan-Meier estimates were used to summarize the time to the first event of the primary endpoint. Event probabilities at 6-month intervals and the median time to event (if estimable) were presented. The log-rank test, balanced by variables at randomization (CV risk category [primary prevention cohort and secondary prevention cohort], use of ezetimibe [yes/no], and geographical region [Westernized, Eastern European, and Asia Pacific]) was used to compare the time-to-event between treatment groups. The 2-sided alpha level for the primary analysis was adjusted to 0.0437 from 0.05 to account for the two interim analyses based on a group sequential design with O'Brien-Fleming boundaries generated using the Lan-DeMets alpha-spending function. The HR comparing the two treatment groups along with the 95% confidence interval (CI) were calculated from a balanced Cox proportional hazards model. Stratification variables included CV risk category at baseline, use of ezetimibe at baseline, and geographical region.

4.3.6 Determination of Sample Size

REDUCE-IT was designed to target a median patient follow-up period of between 4 and 5 years. The initial sample size estimation, as presented in the original study protocol (02 August 2011), assumed the primary endpoint would be reduced by approximately 15% with icosapent ethyl from an event rate by 4 years of 23.6% (5.9% per year) in the placebo group (corresponding to an HR of 0.85). The sample size calculation was based on assumptions of constant hazard, asymmetric recruitment rate over time, and without factoring for dropouts. The initially assumed annual placebo group primary endpoint event rate of 5.9% was based on published CV outcome studies with high CV risk statin-treated patients and endpoint components similar to those outlined within the REDUCE-IT study design. The planned enrollment population of 7990 patients reflects a more

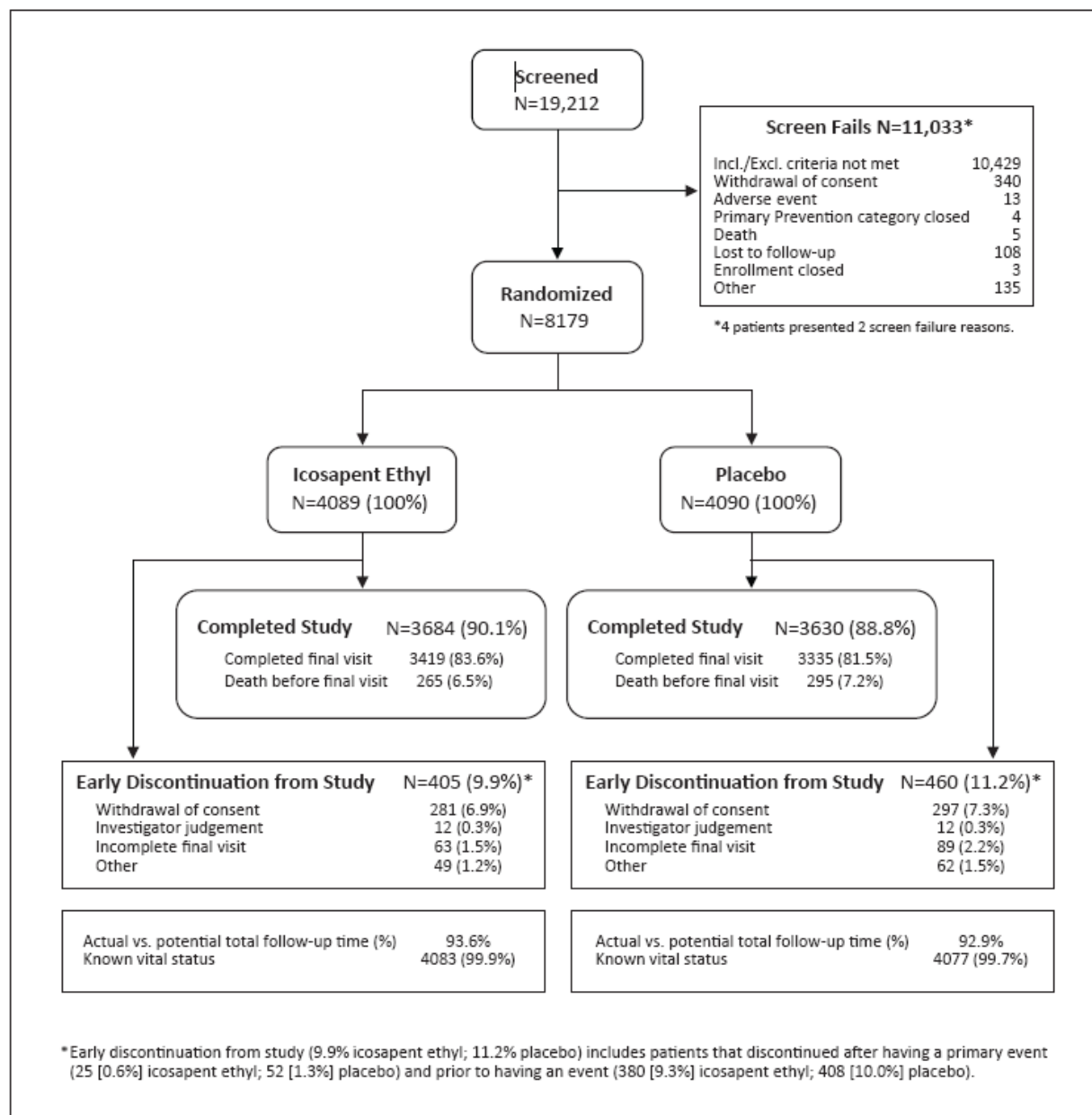
conservative projected annual placebo event rate of 5.2%, which was decided prior to study initiation and following input from the FDA, to ensure adequate powering should the actual placebo event rate be lower than the original estimate of 5.9%. A total of approximately 1612 events were required to detect this HR with approximately 90% power with 2-sided alpha level at 5% and with two interim analyses. See [Appendix I](#) for full details.

5 TRIAL POPULATION CHARACTERISTICS

5.1 Patient Disposition

The patient disposition of REDUCE-IT is displayed in Figure 2.

Figure 2. Patient Disposition



Abbreviations: incl./excl. = inclusion/exclusion; vs. = versus.

Of the 8179 randomized patients, 89.4% (7314/8179) completed the study; 90.1% (3684/4089) and 88.8% (3630/4090) in the icosapent ethyl and placebo groups, respectively. Thus, 10.6% (865/8179) of patients terminated the study early; 9.9% (405/4089) and 11.2% (460/4090) in the icosapent ethyl and placebo groups, respectively. Of patients who terminated the study early, 9.6% (788/8179) terminated prior to having a confirmed primary event; 9.3% (380/4089) and 10.0%

(408/4090) in the icosapent ethyl and placebo groups, respectively. Factoring for time between early discontinuation dates and the study end date, actual versus potential total follow-up time in the study was 93.6% and 92.9% for the icosapent ethyl and placebo groups, respectively.

At the time of database lock, vital status was known for 99.8% (8160/8179) of patients; 99.9% (4083/4089) and 99.7% (4077/4090) in the icosapent ethyl and placebo groups, respectively. Vital status for one additional patient ((b) (6)) was confirmed as alive after database lock.

Median follow-up duration was 4.9 years for both the icosapent ethyl and placebo groups, resulting in 35,014 patient years of follow-up.

5.1.1 Patient Randomization and Stratification

See [Table 31 \(Appendix J\)](#) for stratification factors.

Randomization was balanced based on CV risk category, geographic region, and ezetimibe use, and treatment groups were well balanced across these stratification factors.

Of all randomized patients, 70.7% were enrolled in the established CVD risk category (i.e., the secondary prevention cohort), and 29.3% were enrolled as high risk (i.e., the primary prevention cohort). Of all randomized patients, 10.3% were enrolled with residual TG levels <150 mg/dL and 39.4% of all randomized patients with residual TG levels <200 mg/dL, representing a large representation of patients enrolled prior to implementation of the protocol amendment raising the lower residual TG inclusion criterion from 135 to 200 mg/dL, and providing a sufficient representation of patients above and below 200 mg/dL.

Patients were enrolled from 11 countries in the three geographic regions; the countries contributing the highest proportions of patients overall were the US (38.5% [3146/8179]); the Netherlands (20.5% [1678/8179]); and Ukraine (10.2% [836/8179]). All other participating countries (Australia, Canada, New Zealand, South Africa, Poland, Romania, Russian Federation, and India) each enrolled <10% of the overall patient population.

5.2 Demographic and Baseline Characteristics

Patient demographics and baseline characteristics are summarized in Table 3; treatment groups were well balanced across characteristics. As expected per inclusion/exclusion criteria for REDUCE-IT, there was a high prevalence of diabetes mellitus, metabolic syndrome, overweight/obesity, and hypertension. Compared to many modern CV outcome studies, there was sizable enrollment of women (29%), and the approximately 2:1 enrollment of men compared to women is as expected per the CV inclusion/exclusion criteria of REDUCE-IT and the approximately double prevalence of CV disease in men compared to women based on NHANES and other available data sources around the time of REDUCE-IT initiation (Zhang 2018). The low enrollment of black patients likely also reflects the inclusion/exclusion criteria, particularly in light of the lower prevalence of elevated TG levels in black patients (Sumner 2008).

Table 3. Demographic and Baseline Characteristics (ITT Population)

Parameter Statistic	Icosapent ethyl (N=4089)	Placebo (N=4090)	Overall (N=8179)	P-value ¹
Cardiovascular Risk Stratum				0.9943
Secondary-prevention cohort	2892 (70.7)	2893 (70.7)	5785 (70.7)	
Primary-prevention cohort	1197 (29.3)	1197 (29.3)	2394 (29.3)	
Region				0.9924
Westernized Region ²	2906 (71.1)	2905 (71.0)	5785 (70.7)	
Eastern European Region ³	1053 (25.8)	1053 (25.7)	2106 (25.7)	
Asia Pacific Region ⁴	130 (3.2)	132 (3.2)	262 (3.2)	
Baseline Ezetimibe Use				0.9977
Patients on Ezetimibe	262 (6.4)	262 (6.4)	524 (6.4)	
Patients not on Ezetimibe	3827 (93.6)	3828 (93.6)	7655 (93.6)	
Statin Intensity				0.1551
Low	254 (6.2)	267 (6.5)	521 (6.4)	
Moderate	2533 (61.9)	2575 (63.0)	5108 (62.5)	
High	1290 (31.5)	1226 (30.0)	2516 (30.8)	
Data Missing	12 (0.3)	22 (0.5)	34 (0.4)	
Age (years) at Randomization⁵				0.7524
n	4089	4090	8179	
Mean (SD)	63.4 (8.37)	63.4 (8.43)	63.4 (8.40)	
Median	64.0	64.0	64.0	
Min, Max	45.0, 92.0	44.0, 91.0	44.0, 92.0	
Age Group, n (%)				0.2815
<65 Years	2232 (54.6)	2184 (53.4)	4416 (54.0)	
≥65 Years	1857 (45.4)	1906 (46.6)	3763 (46.0)	
Sex, n (%)				0.4245
Male	2927 (71.6)	2895 (70.8)	5822 (71.2)	
Female	1162 (28.4)	1195 (29.2)	2357 (28.8)	
Race, n (%)				0.3415
White	3691 (90.3)	3688 (90.2)	7379 (90.2)	
Black or African American	69 (1.7)	89 (2.2)	158 (1.9)	
Asian	225 (5.5)	221 (5.4)	446 (5.5)	
American Indian or Alaska Native	18 (0.4)	11 (0.3)	29 (0.4)	
Native Hawaiian or Other Pacific Islander	7 (0.2)	3 (0.1)	10 (0.1)	
Multiple	49 (1.2)	42 (1.0)	91 (1.1)	
Other	30 (0.7)	35 (0.9)	65 (0.8)	
Missing	0 (0.0)	1 (0.0)	1 (0.0)	
Ethnicity, n (%)				0.0877
Hispanic or Latino	188 (4.6)	157 (3.8)	345 (4.2)	
Not Hispanic or Latino	3901 (95.4)	3933 (96.2)	7834 (95.8)	

Parameter Statistic	Icosapent ethyl (N=4089)	Placebo (N=4090)	Overall (N=8179)	P-value ¹
Weight (kg)				0.1347
n	4082	4076	8158	
Mean (SD)	92.7 (18.32)	93.3 (18.46)	93.0 (18.39)	
Median	91.0	91.2	91.1	
Min, Max	46.0, 197.3	40.8, 189.4	40.8, 197.3	
BMI (kg/m²)				0.2803
n	4078	4071	8149	
Mean (SD)	31.5 (5.41)	31.7 (5.47)	31.6 (5.44)	
Median	30.8	30.8	30.8	
Min, Max	18.3, 65.0	16.4, 64.0	16.4, 65.0	
BMI Group, n (%)				0.5287
<25 kg/m ²	320 (7.8)	295 (7.2)	615 (7.5)	
≥25 to <30 kg/m ²	1427 (34.9)	1414 (34.6)	2841 (34.7)	
≥30 kg/m ²	2331 (57.0)	2362 (57.8)	4693 (57.4)	
Missing	11 (0.3)	19 (0.5)	30 (0.4)	
Waist Circumference (cm)				0.4730
n	4025	4031	8056	
Mean (SD)	106.6 (13.39)	106.8 (13.40)	106.7 (13.40)	
Median	105.0	105.5	105.4	
Min, Max	46.5, 182.9	44.0, 170.2	44.0, 182.9	
Hypertension⁶, n (%)				0.9706
Yes	3541 (86.6)	3543 (86.6)	7084 (86.6)	
No	548 (13.4)	547 (13.4)	1095 (13.4)	
Diabetes, n (%)				0.7627
No diabetes at baseline	1695 (41.5)	1694 (41.4)	3389 (41.4)	
Type 1 diabetes	27 (0.7)	30 (0.7)	57 (0.7)	
Type 2 diabetes	2366 (57.9)	2363 (57.8)	4729 (57.8)	
Type 1 or 2 ⁷	2394 (58.5)	2393 (58.5)	4787 (58.5)	0.9622
Both Type 1 and Type 2 diabetes	1 (0.0)	0 (0.0)	1 (0.0)	
Missing	0 (0.0)	3 (0.1)	3 (0.0)	
Impaired Glucose Metabolism⁸, n (%)				0.1570
Yes	1454 (35.6)	1517 (37.1)	2971 (36.3)	
No	2630 (64.3)	2571 (62.9)	5201 (63.6)	
Missing	5 (0.1)	2 (0.0)	7 (0.1)	
Metabolic Syndrome⁹, n (%)				0.0988
Yes	3792 (92.7)	3753 (91.8)	7545 (92.2)	
No	297 (7.3)	337 (8.2)	634 (7.8)	
Renal Impairment¹⁰, n (%)				0.8872
Yes	905 (22.1)	911 (22.3)	1816 (22.2)	
No	3180 (77.8)	3177 (77.7)	6357 (77.7)	
Missing	4 (0.1)	2 (0.0)	6 (0.1)	
Baseline eGFR, n (%)				0.8104
<60 mL/min/1.73m ²	905 (22.1)	911 (22.3)	1816 (22.2)	

Parameter Statistic	Icosapent ethyl (N=4089)	Placebo (N=4090)	Overall (N=8179)	P-value ¹
≥60 and <90 mL/min/1.73m ²	2217 (54.2)	2238 (54.7)	4455 (54.5)	
≥90 mL/min/1.73m ²	963 (23.6)	939 (23.0)	1902 (23.3)	
Missing	4 (0.1)	2 (0.0)	6 (0.1)	

Abbreviations: BMI = body mass index; CRF = case report form; eGFR = estimated glomerular filtration rate; ITT = Intention-to-Treat; Max = maximum; Min = minimum; SD = standard deviation.

Note: Percentages were based on the number of patients randomized to each treatment group in the ITT population (N) except as noted below.

- 1 To assess balance between treatment groups, p-values were reported from a chi-square test for categorical variables and a t-test for continuous variables. Missing categories were excluded from any comparisons.
- 2 Westernized region includes Australia, Canada, the Netherlands, New Zealand, United States, and South Africa.
- 3 Eastern European region includes Poland, Romania, Russian Federation, and Ukraine.
- 4 Asia Pacific region includes India.
- 5 Age (years) was at randomization.
- 6 Hypertension as identified on the CRF "Cardiovascular History."
- 7 Percentages were based on the number of patients with Type 1 or Type 2 diabetes.
- 8 Impaired glucose metabolism was based on Visit 2 fasting blood glucose of 100 to 125 mg/dL.
- 9 Metabolic syndrome as defined by the NCEP ATP III.
- 10 eGFR <60 mL/min/1.73m².

5.2.1 Cardiovascular Disease History

See [Table 32 \(Appendix J\)](#) for reported CV disease history and risk factors based on pre-populated terms on the CV history case report form.

Overall, the most common incidences of reported CV disease history or other prior conditions influencing CV risk were hypertension (86.6% [7084/8179]), Type 2 diabetes (57.8% [4730/8179]), and MI (46.7% [3819/8179]).

The individual incidences of reported CV disease history or other prior conditions influencing CV risk were comparable between the icosapent ethyl and placebo groups.

5.3 Concomitant Medication at Baseline

Additional baseline medication classes of special interest are summarized in [Table 4](#). The proportions of patients taking each type of medication of special interest at baseline were similar between the icosapent ethyl and placebo groups. At baseline, 93.6% of statin-treated patients were receiving moderate or high intensity statins ([Table 3](#)).

The high proportion of patients taking antidiabetic, antihypertensive, and antithrombotic medications is indicative of appropriate treatment of this at-risk patient population.

Table 4. Baseline Medications of Special Interest (ITT Population)

Medication Taken at Baseline, n (%)	Icosapent ethyl (N=4089)	Placebo (N=4090)	Overall (N=8179)
Antihypertensive	3895 (95.3)	3895 (95.2)	7790 (95.2)
Antithrombotic	3505 (85.7)	3489 (85.3)	6994 (85.5)
Antidiabetic	2190 (53.6)	2196 (53.7)	4386 (53.6)
ACE Inhibitors or ARBs	3164 (77.4)	3176 (77.7)	6340 (77.5)
ACE Inhibitors	2112 (51.7)	2131 (52.1)	4243 (51.9)
ARBs	1108 (27.1)	1096 (26.8)	2204 (26.9)
Beta Blockers	2902 (71.0)	2880 (70.4)	5782 (70.7)

Abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blockers; ITT = Intention-to-Treat.

Note: Percentages were based on the number of patients randomized to each treatment group in the ITT population (N).

5.4 Treatment Exposure

The median duration of icosapent ethyl and placebo exposure was 1614 days (4.5 years) and 1512 days (4.2 years), respectively. Overall, 12.3% (1010/8179) of patients received study drug for <1 year (<360 days) and 0.5% (37/8179) of patients received study drug for ≥6 years (≥2160 days).

5.5 Concomitant Medication During the Trial

At each post-randomization time point assessed, over 93% of statin-treated patients were receiving moderate or high intensity statins. The proportions of patients taking each type of medication of special interest throughout the study were similar between the icosapent ethyl and placebo groups.

5.6 Follow-up

A total of 9.9% of subjects in the icosapent ethyl arm and 11.25% of subjects in the placebo arm terminated the study early ($p=0.048$). There was no difference in study termination due to physician decision (0.29% vs. 0.29%, $p>0.99$), subjects choosing to withdraw (6.78% icosapent ethyl vs. 7.26% placebo, $p=0.49$), or other (1.20% icosapent ethyl vs. 1.52% placebo, $p=0.21$).

There were 665/4089 (16.3%) and 790/4090 (19.3%) retrieved dropouts in the icosapent ethyl and the placebo groups, respectively. Among the retrieved dropouts, there was a numerically lower total event count and event rate in the icosapent ethyl group (126/665; 18.9%) for the 5-point MACE endpoint, compared to the placebo group (159/790; 20.1%). Of the total events in retrieved dropouts, approximately 50% occurred in the first year following treatment discontinuation in each group (61/126 [48%] in icosapent ethyl; 92/159 [58%] in placebo), and the observed first year rate was numerically lower in the icosapent ethyl group (61/665; 9.2%) compared to the placebo group (92/790; 11.6%). The event count and rate in the icosapent ethyl group continued to be lower compared to the placebo group in the second year (23/482 [4.8%] versus 31/547 [5.7%], respectively), but this trend is no longer observed in the third year after treatment discontinuation.

6 EFFICACY

6.1 Cardiovascular Outcomes

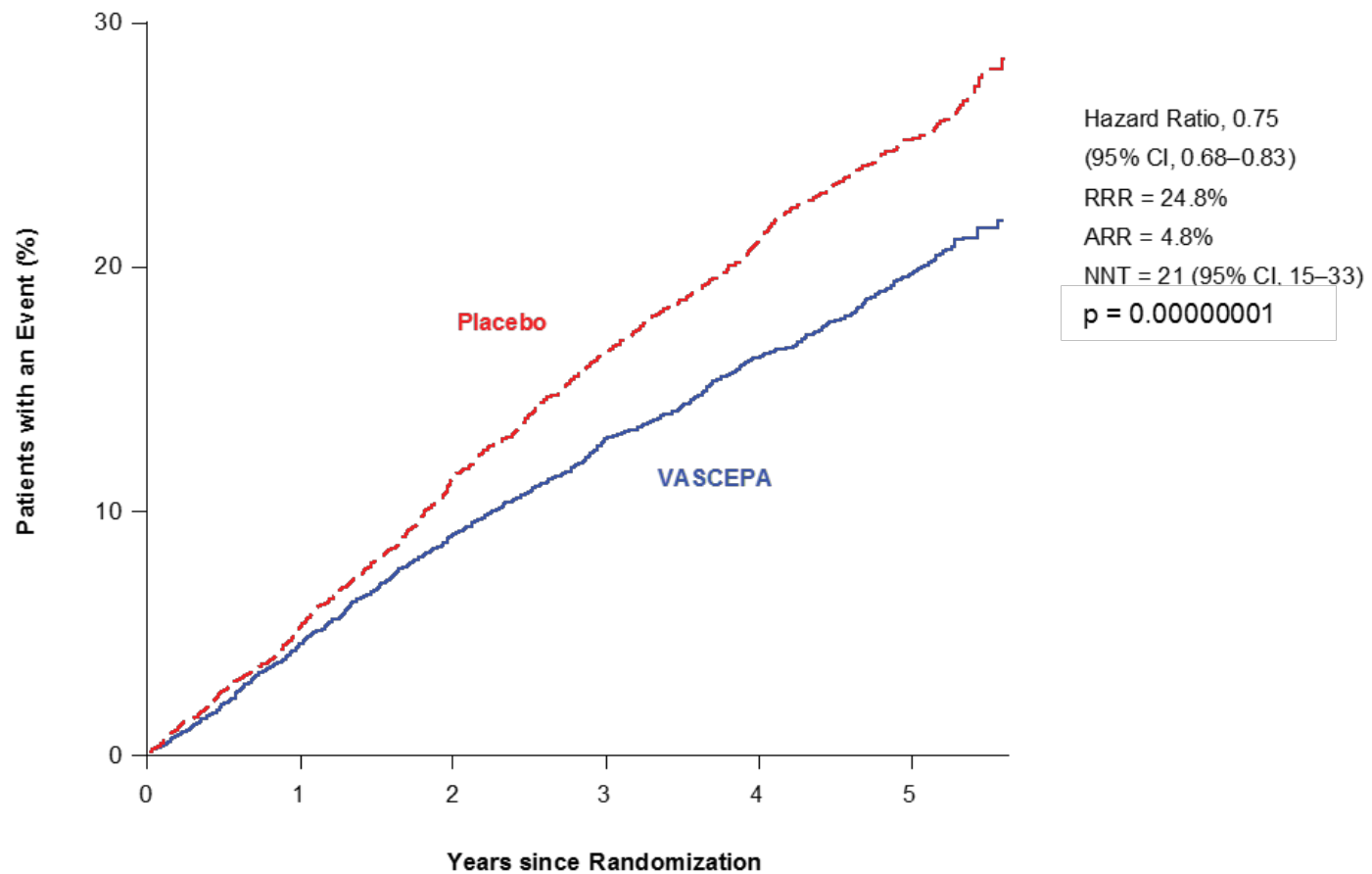
6.1.1 Primary Endpoint

The primary endpoint was the time from randomization to the first occurrence of any component of the composite of the following clinical events: CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization. The duration of follow-up for the primary endpoint encompassed the interval from a patient's randomization to either onset of the primary endpoint (if one occurred) or the patient's last date in the study.

Over a median duration of follow-up for the primary endpoint of 4.7 and 4.5 years, respectively, a primary endpoint event occurred in 17.2% (705/4089) of patients in the icosapent ethyl group, as compared to 22.0% (901/4090) of patients in the placebo group over the median 4.9 year follow-up (HR of 0.752 [95% CI: 0.682 to 0.830; $p=0.00000001$]; RRR of 24.8%; absolute risk reduction [ARR] of 4.8%; and number needed to treat [NNT] of 21). Thus, the primary endpoint was met, demonstrating a substantial and statistically significant lower risk of major adverse CV events with icosapent ethyl than with placebo. The associated Kaplan-Meier curve is displayed in [Figure 3](#); the icosapent ethyl and placebo curves begin to separate at approximately one year after randomization with continued separation thereafter.

Sensitivity analyses were performed that censored patients for death of undetermined cause, study drug discontinuation, study drug discontinuation + 30 days, silent MI at the last normal ECG, and silent MI at mid-point between the date of the last normal ECG and the date of the first indicative ECG. Results were generally consistent with the primary analyses, i.e., there was a substantial and significantly lower risk of major adverse CV events with icosapent ethyl than with placebo (see [Table 33 \[Appendix J\]](#)).

Figure 3. Time to the Primary Endpoint (ITT Population)



No. at Risk

Placebo	4090	3743	3327	2807	2347	1358
VASCEPA	4089	3787	3431	2951	2503	1430

Abbreviations: ARR = absolute risk reduction; CI = confidence interval; ITT = Intention-to-Treat; NNT = number needed to treat; No. = number; p = p-value; RRR = relative risk reduction.

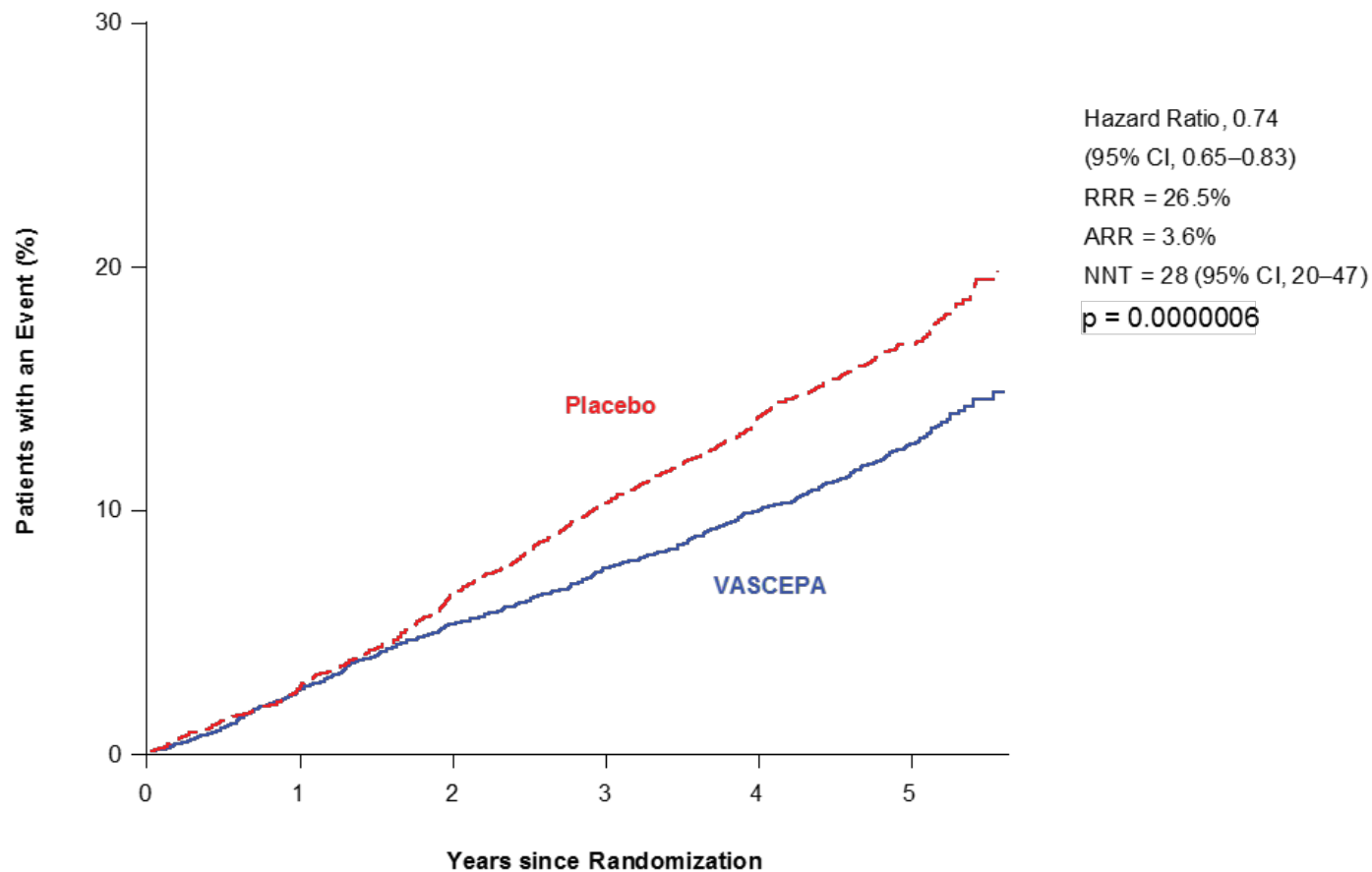
6.1.2 Key Secondary Endpoint

The key secondary endpoint was the time from randomization to the first occurrence of the composite of CV death, nonfatal MI, or nonfatal stroke (hard MACE). The duration of follow-up for the key secondary endpoint encompassed the interval from a patient's randomization to either onset of the key secondary endpoint (if one occurred) or the patient's last date in the study.

Over a median follow-up duration for the key secondary endpoint of 4.8 and 4.7 years for the icosapent ethyl and placebo groups, respectively, a key secondary endpoint event occurred in 11.2% (459/4089) of patients in the icosapent ethyl group, as compared to 14.8% (606/4090) of patients in the placebo group (HR of 0.735 [95% CI: 0.651 to 0.830; $p=0.0000006$]; RRR of 26.5%; ARR of 3.6%; and NNT of 28). Thus, the key secondary endpoint was also met, demonstrating a substantial and statistically significant lower risk of hard MACE with icosapent ethyl than with placebo.

The associated Kaplan-Meier curve is displayed in [Figure 4](#); the icosapent ethyl and placebo curves begin to separate at approximately 1.75 years after randomization with continued separation thereafter.

Figure 4. Time to the Key Secondary Endpoint (ITT Population)



No. at Risk

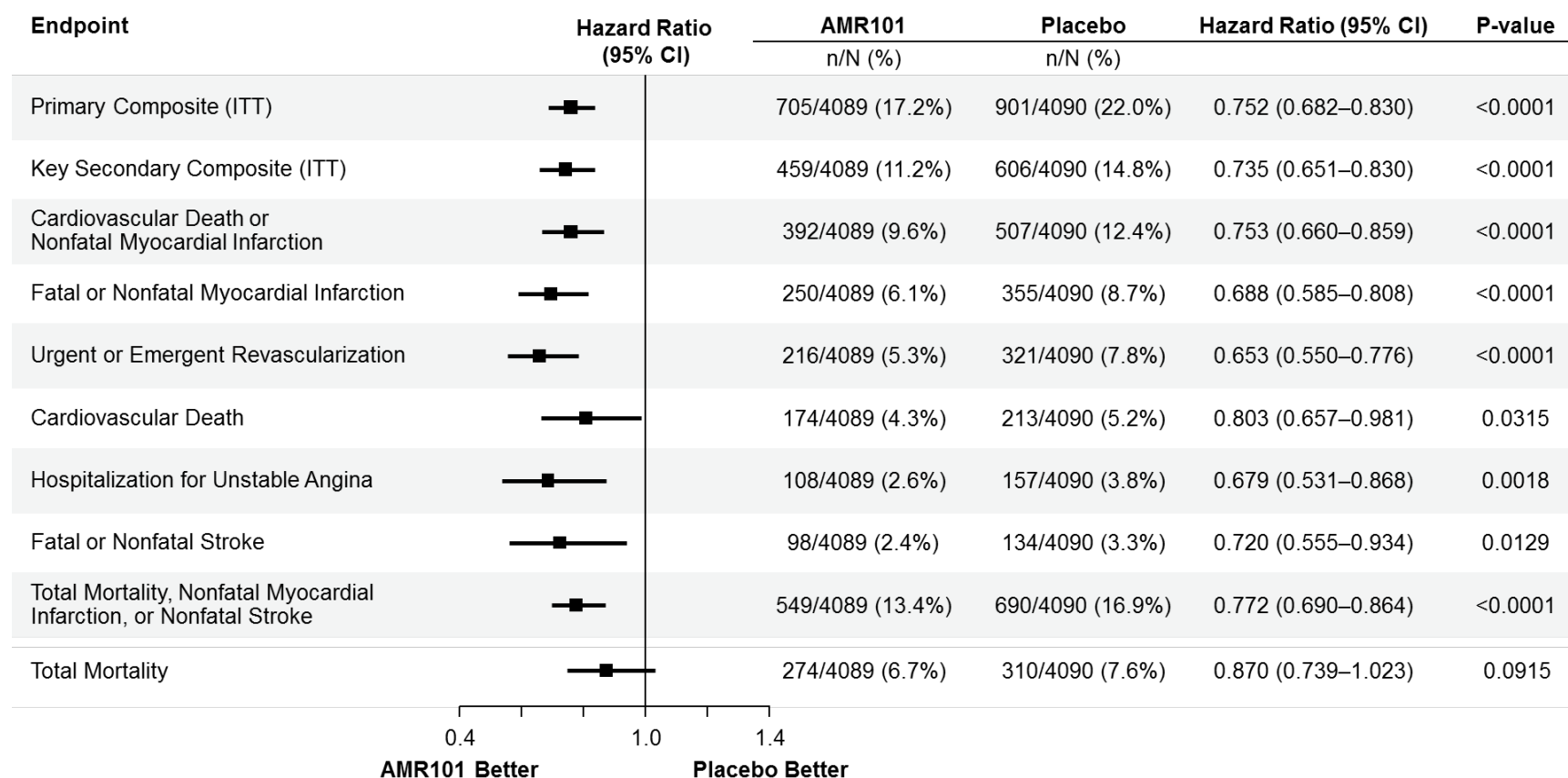
Placebo	4090	3837	3500	3002	2542	1487
VASCEPA	4089	3861	3565	3115	2681	1562

Abbreviations: ARR = absolute risk reduction; CI = confidence interval; ITT = Intention-to-Treat; NNT = number needed to treat; No. = number; p = p-value; RRR = relative risk reduction.

6.1.3 Prespecified Hierarchical Testing Across the Primary and Secondary Endpoints

The effects of icosapent ethyl versus placebo were highly consistent across primary and secondary endpoints. As shown in [Figure 5](#), all secondary endpoints following the prespecified hierarchical testing procedures demonstrated statistically significantly lower incidences of fatal and nonfatal ischemic events in the icosapent ethyl group than in the placebo group, except the final prespecified secondary endpoint of total mortality. Thus, there were significant reductions in the risk of fatal and nonfatal ischemic events with icosapent ethyl compared to placebo, including CV death (HR of 0.803 [95% CI: 0.657 to 0.981; $p=0.0315$]), fatal or nonfatal MI (HR of 0.688 [95% CI: 0.585 to 0.808; $p<0.0001$]), and fatal or nonfatal stroke (HR of 0.720 [95% CI: 0.555 to 0.934.; $p=0.0129$]). There were also significant reductions with icosapent ethyl versus placebo in the risk of hospitalization for unstable angina, and the composite secondary endpoints of CV death or nonfatal MI; urgent or emergent revascularization; and nonfatal MI or nonfatal stroke. Total mortality, the final secondary endpoint in the prespecified hierarchy, as the only secondary endpoint that did not reach statistical significance still trended toward significant reduction (HR of 0.870 [95% CI: 0.739 to 1.023; $p=0.0915$]).

Figure 5. REDUCE-IT Endpoints in Hierarchical Testing Order (ITT Population)



Abbreviations: AMR101 = icosapent ethyl; CI = confidence interval; CV = cardiovascular; ECG = electrocardiogram; ITT = Intention-to-Treat; MI = myocardial infarction.

Note: The number of patients with event (n) is the number of patients with the event in the ITT population within each treatment group (N).

Log-Rank test statistic and p-value are reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

Endpoint events are based on a patient's first post-randomization occurrence of the specified endpoint event.

CV death includes adjudicated CV deaths and deaths of undetermined causality.

Nonfatal MI includes silent MI, which was assumed to occur on the date of the first post-randomization ECG tracing indicative of a silent MI.

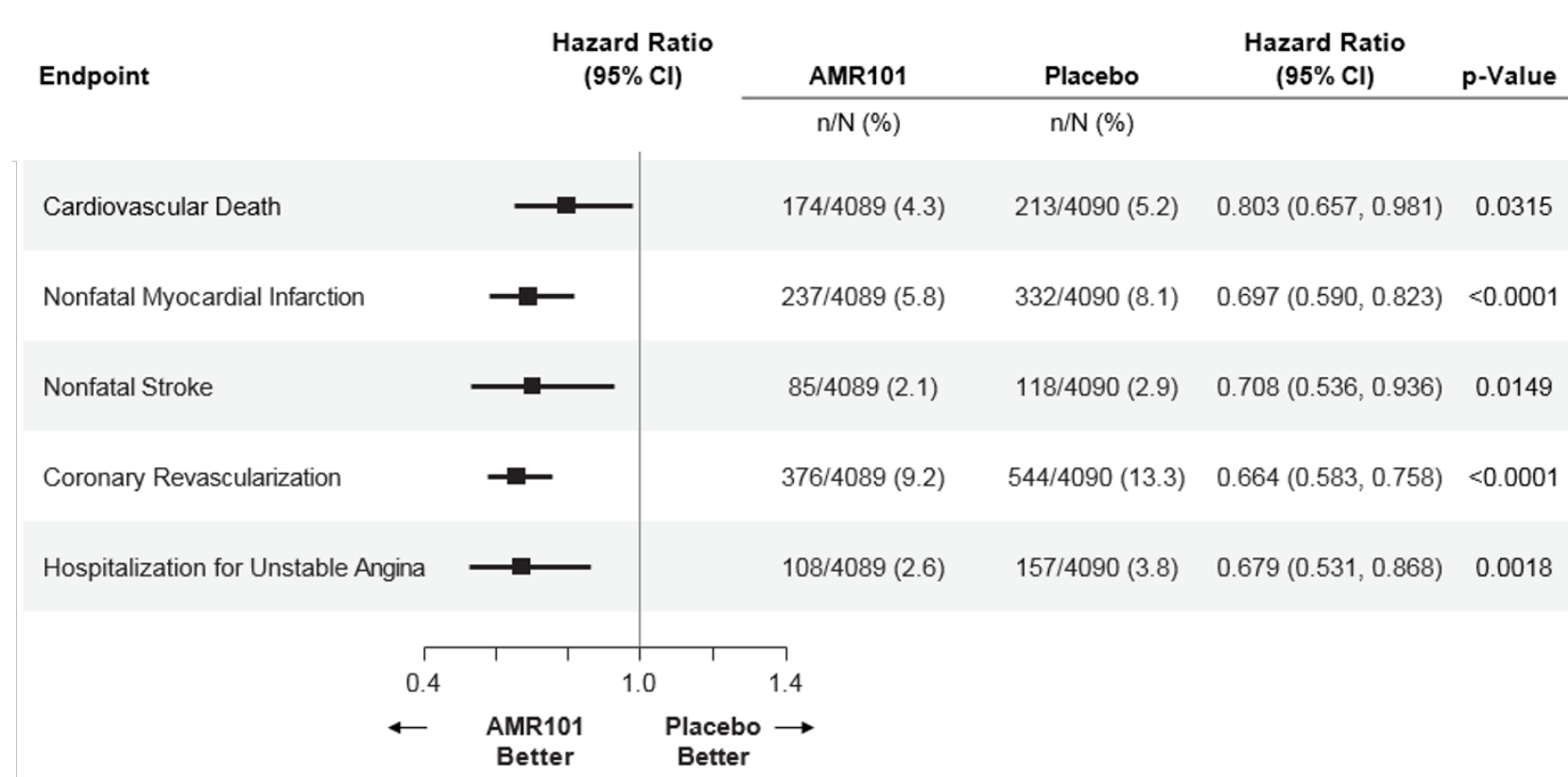
6.1.4 Tertiary and Exploratory Endpoints

The effects of icosapent ethyl versus placebo were also consistent across tertiary and exploratory CV endpoints. Select endpoint results are presented below, with further endpoint results available in [Appendix J](#).

6.1.4.1 Individual Components of the Primary and Key Secondary Endpoints

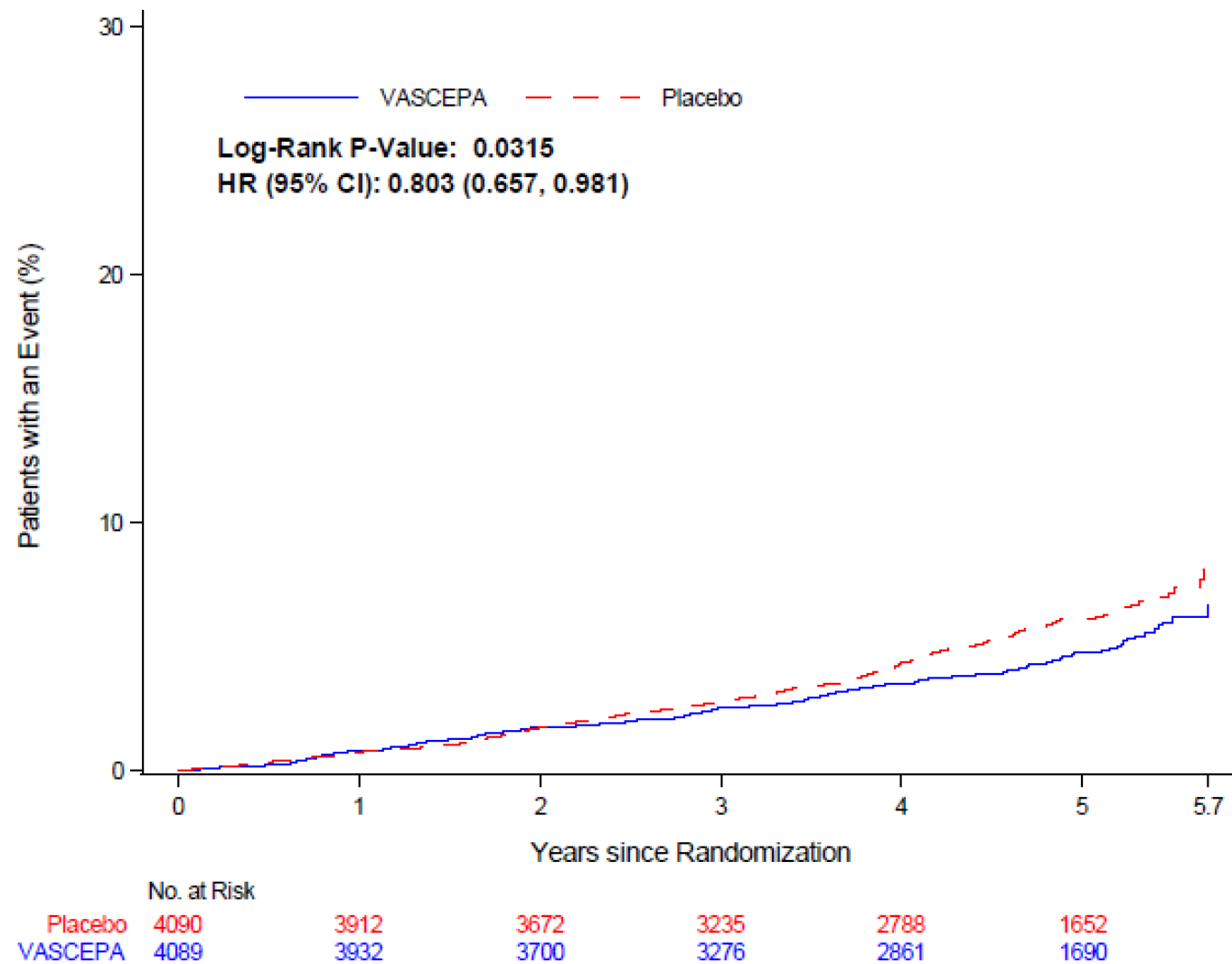
Analyses of the primary and key secondary endpoints along with the five individual components of the primary endpoint, each analyzed as independent endpoints (e.g., time to first occurrence of nonfatal MI, regardless of the time to first occurrence of any other endpoints for the same patient), were prespecified as secondary or tertiary endpoints are presented together in [Figure 6](#). Each individual component of the primary and key secondary endpoints contributed to the overall results, demonstrating statistically significant differences in favor of icosapent ethyl over placebo, including a 20% RRR in CV death (HR of 0.803 [95% CI: 0.657 to 0.981; p=0.0315]). Kaplan-Meier curves for each individual component are provide below, including CV Death ([Figure 7](#)), nonfatal MI ([Figure 8a](#)), nonfatal stroke ([Figure 8b](#)), coronary revascularization ([Figure 8c](#)), and hospitalization for unstable angina ([Figure 8d](#)).

Figure 6. Individual Components of the Primary & Secondary Endpoints (ITT Population)



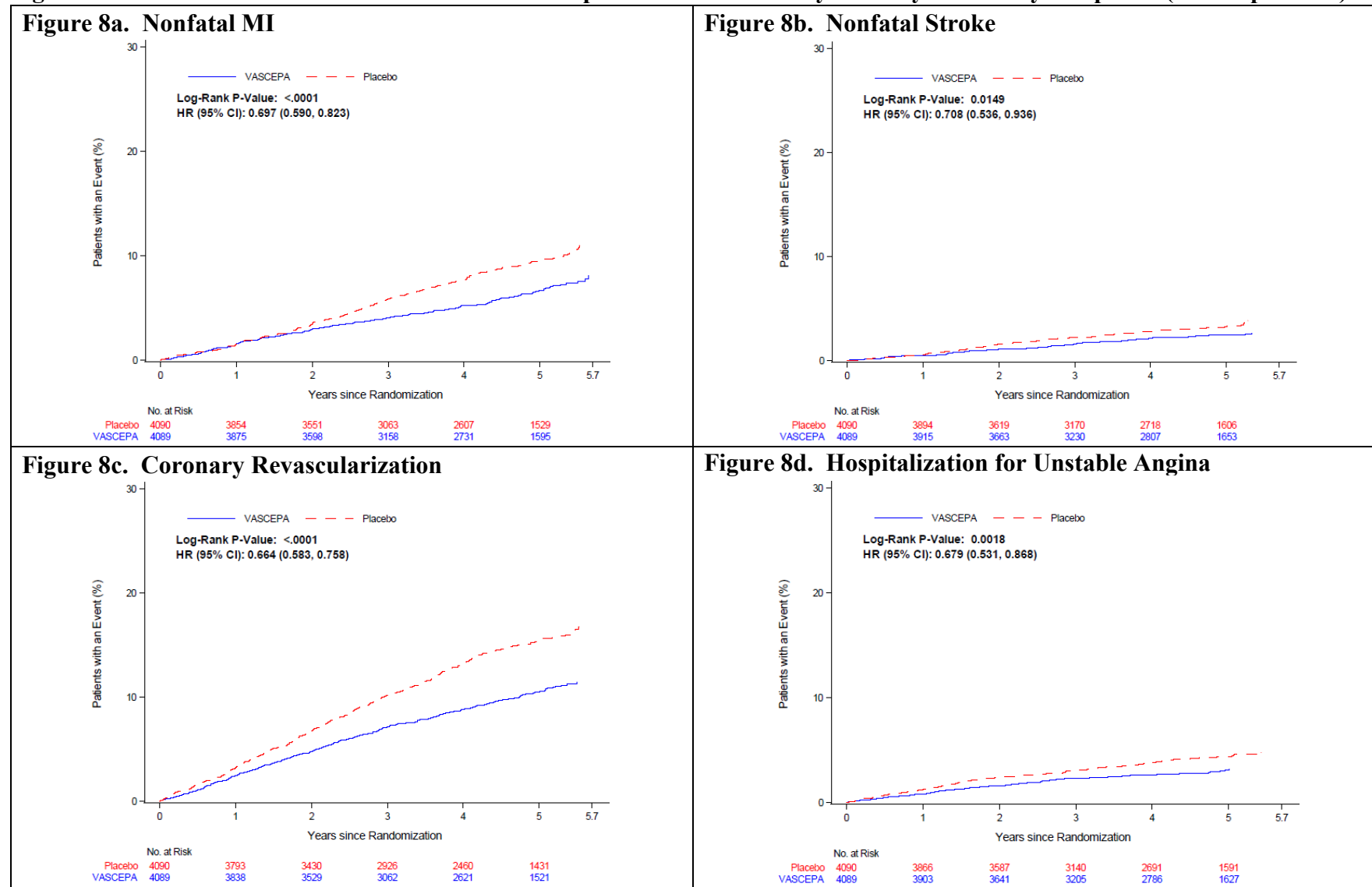
Abbreviations: AMR101 = icosapent ethyl; CI = confidence interval; CV = cardiovascular; MI = myocardial infarction; ITT = Intention-to-Treat.
Note: The key secondary endpoint includes CV death, nonfatal MI (including silent MI), and nonfatal stroke.

Figure 7. Time to the First Occurrence of CV Death (ITT Population)



Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = Intention-to-Treat; p-value.

Figure 8. Time to the First Occurrence of Other Components of the Primary and Key Secondary Endpoints (ITT Population)



Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = Intention-to-Treat

6.1.4.2 Primary and Key Secondary Endpoint Subgroup Analyses

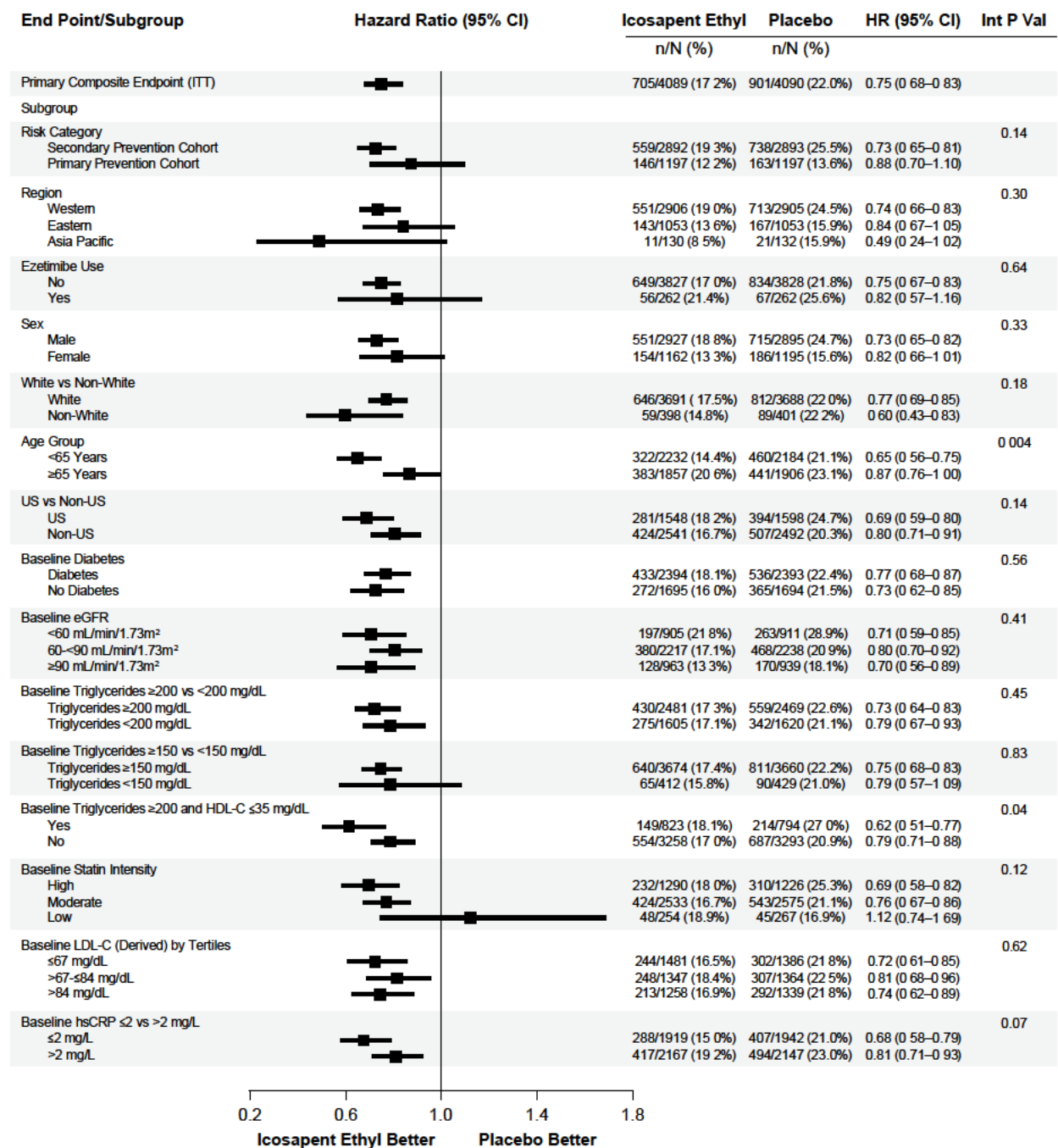
Subgroup analyses of the primary endpoint and the key secondary were prespecified as tertiary and exploratory analyses and are presented in [Figure 9](#) and [Figure 10](#), respectively. Subgroup analyses of the primary endpoint ([Figure 9](#)) and key secondary endpoint ([Figure 10](#)) suggest generally consistent benefit of icosapent ethyl treatment across prespecified subgroups.

Per study design, subgroup analyses were not powered to detect statistically significant results within each individual subgroup, particularly when a subgroup represents a lower proportion of enrolled patients (e.g., less than 50%), and/or when a subgroup has low event rates, which can result in wide 95% CIs and nonsignificant findings for a particular subgroup. For example, analyses of the primary and key secondary endpoints across the high risk primary prevention and established CVD secondary prevention subgroups both demonstrated hazard ratios suggestive of benefit, with an exploratory finding of a possible differential benefit in the primary endpoint (HR[95% CIs] = 0.73 [0.65 to 0.81] for secondary prevention as compared to 0.88 [0.70 to 1.10] for primary prevention; interaction p=0.14; [Figure 9](#)) and no differential benefit observed in the key secondary endpoint (0.72 [0.63 to 0.82] for secondary prevention as compared to 0.81 [0.62 to 1.06] for primary prevention; interaction p = 0.41; [Figure 10](#)). The established CVD secondary prevention cohort represented approximately 71% of enrolled patients with a high observed event rate, which supported these subgroup analyses reaching independent statistical significance for both the primary and key secondary endpoints. In contrast, the high-risk primary prevention cohort represented approximately 29% of enrolled patients with a lower observed event rate, and therefore it is not surprising that these subgroup analyses did not quite achieve statistical significance. Nonetheless, the hazard ratios suggest benefit with icosapent ethyl treatment in both subgroups and the interaction p-values suggest little to no substantial difference in benefit in primary versus secondary prevention patients.

Such exploratory subgroup analyses can be informative for hypothesis-generating efforts, but should not be overly relied upon to substantiate individual subgroup efficacy conclusions.

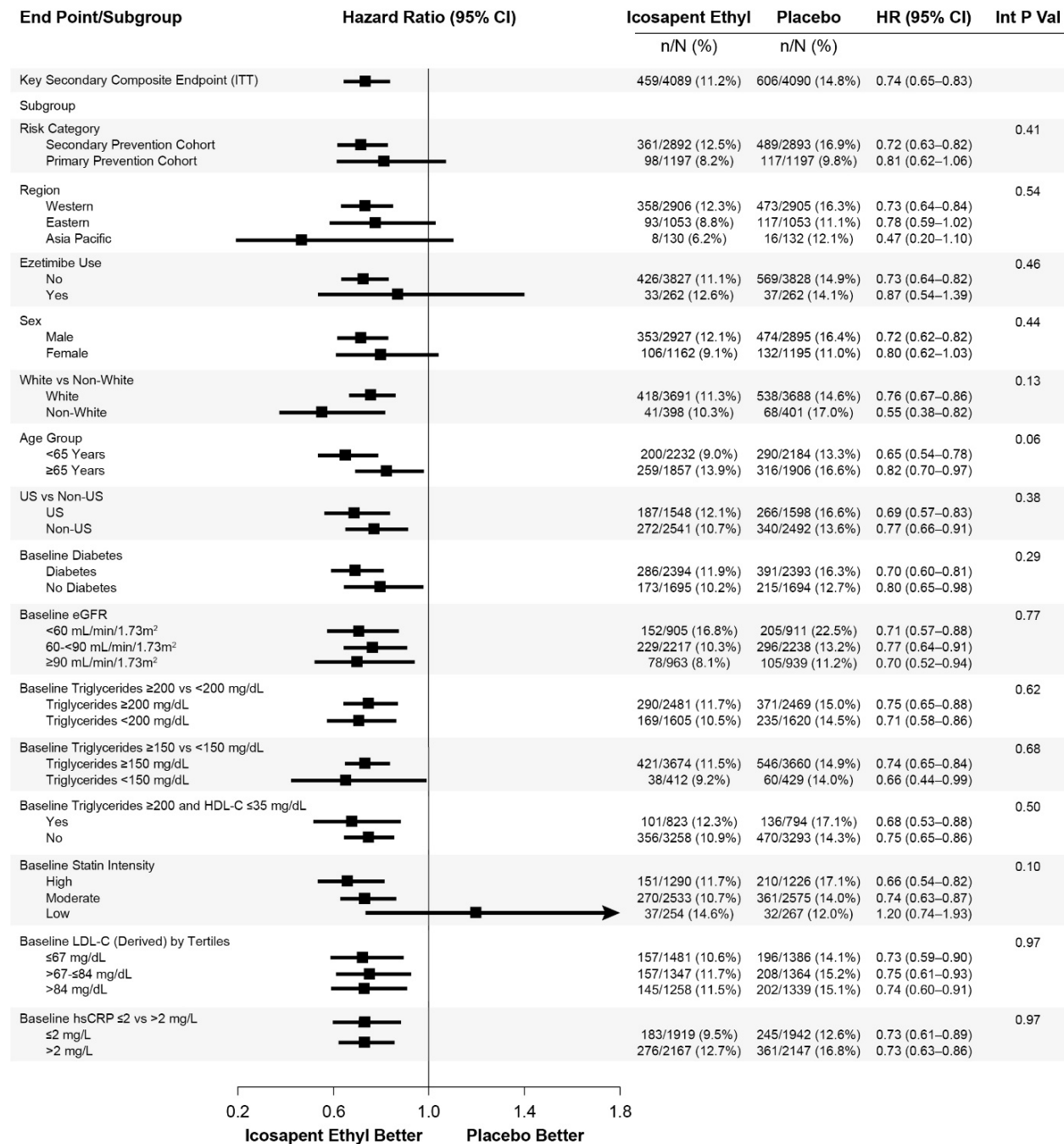
Please see [Appendix K](#) for a further exploration of benefit-risk across the established CVD secondary prevention and high risk primary prevention subgroups.

Figure 9. Forest Plot of the Primary Endpoint in Subgroups (ITT Population)



Abbreviations: CI = confidence interval; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein-cholesterol; HR = hazard ratio; hsCRP = high-sensitivity C-reactive protein; icosapent ethyl = icosapent ethyl/AMR101; Int = interaction; ITT = Intention-to-Treat; LDL-C = low-density lipoprotein-cholesterol; pVal = p-value; US = United States.

Figure 10. Forest Plot of the Key Secondary Endpoint in Subgroups (ITT Population)



Abbreviations: CI = confidence interval; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein-cholesterol; HR = hazard ratio; hsCRP = high-sensitivity C-reactive protein; icosapent ethyl = icosapent ethyl/AMR101; Int = interaction; ITT = Intention-to-Treat; LDL-C = low-density lipoprotein-cholesterol; pVal = p-value; US = United States.

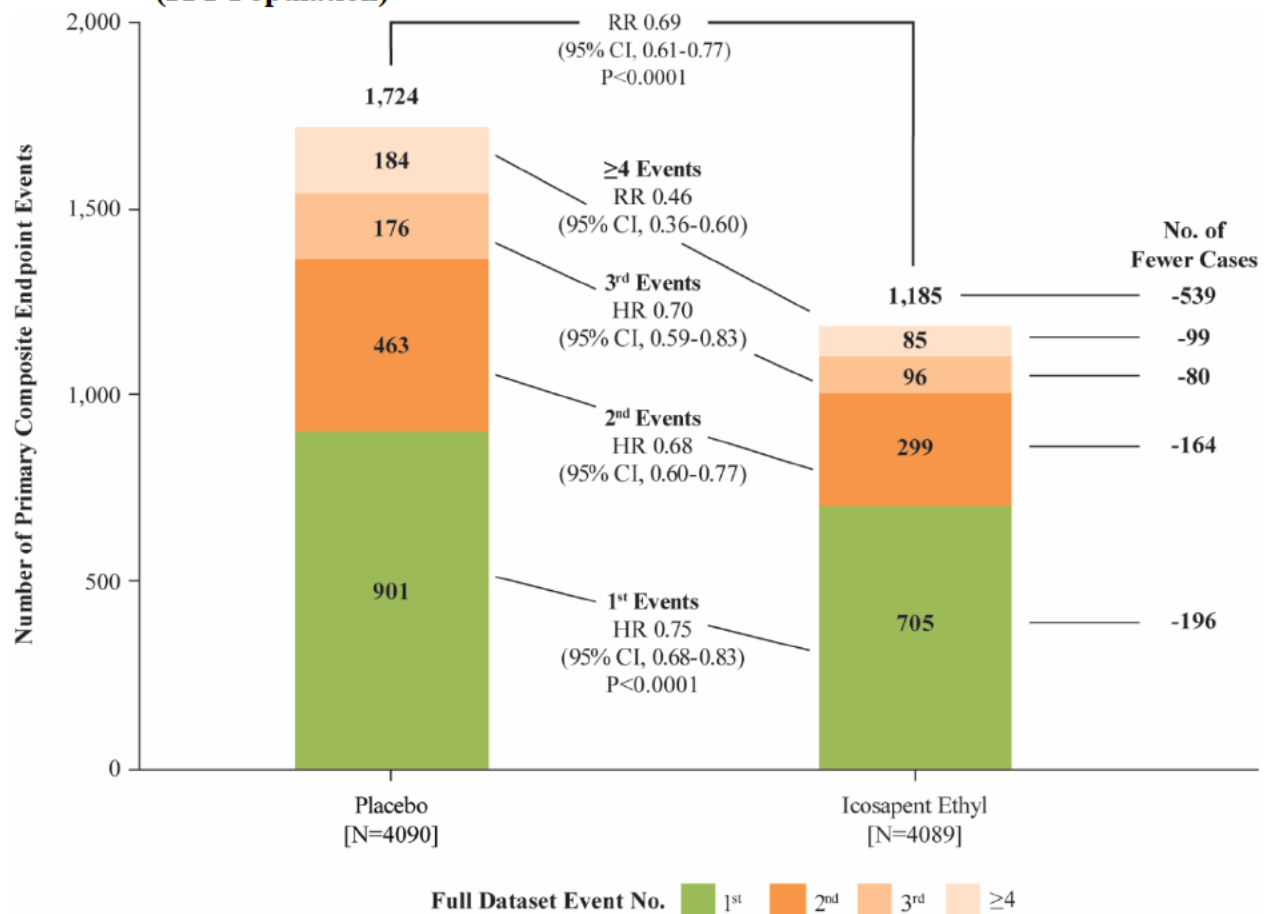
6.1.4.3 Total Cardiovascular Events

Also consistent with the primary and key secondary endpoint findings, clinically meaningful reductions were observed in the tertiary endpoint of total (i.e., all occurrences of) primary endpoint events with icosapent ethyl compared to placebo by multiple prespecified statistical models, including the Andersen-Gill model (HR of 0.68; $p < 0.0001$) and the Negative Binomial model (rate ratio of 0.69; $p < 0.0001$). The prespecified Wei-Lin-Weissfeld (Li and Lagakos modification) demonstrated that reductions in the first and each subsequent occurrence of a primary endpoint event contributed to the observed reduction in total events first occurrence HR of 0.75 [$p < 0.0001$]; second occurrence HR of 0.68 [$p < 0.0001$]; third occurrence HR of 0.70 [$p < 0.0001$].

Similar significant reductions were observed for total occurrences of key secondary endpoint events with icosapent ethyl compared to placebo across models (HR or rate ratio of 0.71; $p < 0.0001$ for both the Andersen-Gill and Negative Binomial models), as well as in first and subsequent occurrences (see Table 34 [Appendix J]).

The distribution of first and subsequent primary endpoint events in the full dataset (ITT population) is presented in Figure 11.

Figure 11. Distribution of First and Subsequent Primary Endpoint Events in the Full Dataset (ITT Population)



Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = Intention-to-Treat; RR = rate ratio.

Hazard ratios and 95% CIs for between treatment group comparisons were generated using Li-Lagakos-modified Wei-Lin-Weissfeld method for the 1st event, 2nd event, and 3rd event categories. Rate ratio and 95% CIs for between group comparisons used a negative binomial model for additional events beyond 1st, 2nd, 3rd occurrences, i.e., 4th event or more and overall treatment comparison. Analyses are based on the total adjudicated event dataset regardless if multiple endpoints occurred in a single calendar day.

6.1.4.4 Additional Tertiary Endpoints

A clinically meaningful lower risk in the icosapent ethyl group versus the placebo group was observed across other tertiary endpoints (see [Table 35 \[Appendix J\]](#)), including four composite endpoints all coronary revascularizations (HR of 0.66 [95% CI: 0.58 to 0.76; $p<0.0001$]) and individually for emergent, urgent, and elective revascularizations; cardiac arrests (HR of 0.52 [95% CI: 0.31 to 0.86; $p=0.0105$]); sudden cardiac deaths (HR of 0.69 [95% CI: 0.50 to 0.96; $p=0.0259$]); and ischemic strokes (HR of 0.64 [95% CI: 0.49 to 0.85; $p=0.0020$]). No difference was observed in the tertiary endpoints of newly emergent congestive heart failure (HR of 0.95 [95% CI: 0.77 to 1.17]; $p=0.6260$), or newly emergent congestive heart failure requiring hospitalization (HR of 0.97 [95% CI: 0.77 to 1.22]; $p=0.7810$).

Across tertiary endpoints, the HRs and 95% CIs are suggestive of a generally lower risk of CV events with icosapent ethyl than with placebo.

6.1.4.5 *Post Hoc* Primary and Key Secondary Endpoint Analyses Based on Events as Reported by Investigators

Analyses of events as reported by investigators (i.e., regardless of CEC adjudication status) generally provide the same overall conclusions for of the primary and key secondary endpoints, and for each contributing component as individual endpoints (see [Table 30](#)).

6.2 Lipids and Other Biomarkers

REDUCE-IT was designed as an outcomes study to evaluate the effects of icosapent ethyl therapy on CV risk. Biomarkers were not considered reliable for the prediction of CV risk reduction and, therefore, biomarkers were agreed during the design of the study to not be included in prespecified primary or secondary endpoints. As support for tertiary, exploratory, and *post hoc* analyses, it was agreed that single biomarker measures at visits separated by large spans of time would be collected. Any results from analyses of these biomarkers would be considered hypothesis-generating, based on these single measures in time, the inherent variability of biomarkers (particularly for patients with elevated residual TG levels), and the inclusion criteria driving LDL-C levels low, which was expected to drive regression to the mean. Biomarker findings include reductions in lipid and inflammatory biomarkers with icosapent ethyl compared to placebo, including TG, LDL-C, and non-HDL-C from baseline to one year, and apoB and hsCRP from baseline to two years ([Table 18](#)). In the icosapent ethyl group, median percent decreases from baseline in residual TG were observed at each time point assessed, with the difference from placebo being significant at each time point; a plot of median TG over time is presented in [Figure 13 \(Appendix J\)](#).

LDL-C was directly measured at randomization and one year by the ultracentrifugation method. LDL-C was approximated from the standard lipid panel for each on-site visit. LDL-C approximation using the methodology published by Johns Hopkins University investigators (Martin 2013) allows for the calculation of LDL-C levels regardless of TG levels, overcoming a constraint of the Friedewald approximation. Median percent decreases from baseline in approximated LDL-C were observed with icosapent ethyl at each time point assessed, with the

difference from placebo being significant at each time point; a plot of median LDL-C (Hopkins approximation) over time is presented in [Figure 14 \(Appendix J\)](#).

Blood levels of EPA (serum) increased substantially in the icosapent ethyl group from 26.1 µg/mL at baseline to 144.0 µg/mL at one year, while little change was observed in the placebo group, resulting in a 386% increase in EPA in the icosapent ethyl over the placebo group. Of note, in *post hoc* analyses, achievement of higher EPA levels correlated with greater CV risk reduction.

For further discussion and analyses regarding biomarkers, please also refer to [Appendix D](#).

6.3 Control Group Response Analyses

The selection of an appropriate placebo for use in the study of icosapent ethyl was thoroughly examined before and after each Phase 3 icosapent ethyl clinical trial, including within the SPA processes for each study and at the FDA advisory committee review of the ANCHOR study results in October 2013 ([Appendix C](#)). The same placebo comprised of light liquid paraffin oil (pharmaceutical grade mineral oil) was selected across studies as the best choice to mimic the color and consistency of icosapent ethyl, and because light mineral oil is not extensively absorbed and not known to interact with the absorption or activity of drugs based on literature review and preclinical and clinical data. Mineral oil has been used as a laxative at high doses (typically 15–30 g/day) for over 100 years, including extensive use in pediatric populations. The safety of mineral oil is generally inferred from a long history of use with limited adverse effects and from other clinical studies in which mineral oil was used as a placebo. Some parties have raised questions regarding the relatively small biomarker changes in the placebo group of REDUCE-IT and speculated if light mineral oil may have influenced these changes, and thus influenced the overall conclusions of REDUCE-IT.

Per design as a CV outcomes study, REDUCE-IT hierarchical primary and secondary analyses focused on CV events, with biomarkers collected as single measures with large spans of time between measurements to support tertiary, exploratory, and *post hoc* analyses. The design of REDUCE-IT recognized that the reported clinical effects of icosapent ethyl extend beyond lipid modification and therefore, were not expected to be defined by changes within specific biomarkers. Nonetheless, we conducted a series of *post hoc* analyses to explore a potential mineral oil effect (or lack thereof) within REDUCE-IT. The supposition that the light mineral oil used in REDUCE-IT does not exert clinically meaningful effects on medication (including statin) efficacy or absorption, biomarkers, outcomes, or safety, agrees with conclusions from prior FDA reviews. It is also supported by multiple lines of evidence, including observed event rate agreement with REDUCE-IT design predictions, extensive literature reviews (EPA mechanisms of action, mineral oil, impact of biomarker changes on CV risk), Amarin nonclinical and clinical studies, independent REDUCE-IT DMC review, and observed event rate and biomarker comparisons with statin-treated patients across other CV outcome studies. This supposition is also supported by *post hoc* REDUCE-IT data analyses (e.g., off drug, statin type, regression to the mean, diarrhea, lack of correlation between placebo biomarker changes and outcomes, and biomarker covariate-adjusted analyses). Contrary to the lack of evidence for a hypothetical placebo impact on CV risk, clinical and preclinical studies provide extensive data supporting cardioprotective effects of EPA ([Appendix E](#)). While based on these various sources of evidence we do not agree that placebo influenced the REDUCE-IT results, even if we are wrong, such potential influence cannot reasonably be estimated to account for a substantial portion of overall robust and consistent

REDUCE-IT findings, including a 25% RRR in the primary endpoint that is consistent with the observed risk reduction in the JELIS study, which did not administer a mineral oil placebo. Taken together, these various analyses and comparisons are inconsistent with a placebo-mediated effect significantly overestimating the REDUCE-IT results, but rather support a conclusion that icosapent ethyl provided substantial and consistent risk reduction in statin-treated patients.

Each of the considerations noted above are discussed in greater detail within [Appendix D](#).

7 SAFETY

Clinical (adverse) events that were positively adjudicated as endpoints were counted only in endpoint analyses; these events were not double counted in the safety analyses. If an AE was not positively adjudicated as an endpoint, this event resided in the safety dataset. Thereby each AE was only counted once across both the efficacy and safety analyses. Seriousness of an AE was assessed by the Investigator.

7.1 Overall Adverse Events

The safety population consists of 8,179 patients with a median follow up of 4.9 years, accounting for 35,014 patient years of experience. An overview of TEAEs is presented in [Table 5](#). TEAEs were similar between the icosapent ethyl and placebo groups. The high overall event rate of 81.5% reflects the at-risk nature of the population studied and the long median follow-up of 4.9 years.

Baseline medication classes of special interest were summarized in [Table 4](#). The proportions of patients taking each type of medication were similar between the icosapent ethyl and placebo groups, and the high proportion of patients taking antihypertensive (95.2%), antithrombotic (85.5%), and antidiabetic (53.6%) medications are indicative of appropriate baseline treatment within this at-risk patient population.

Table 5. Treatment-Emergent Adverse Events (TEAEs) (Safety Population)

	Icosapent ethyl (N=4089) n (%)	Placebo (N=4090) n (%)	Overall (N=8179) n (%)
Patients With at Least 1 TEAE, n (%)	3343 (81.8)	3326 (81.3)	6669 (81.5)
Severe TEAE	805 (19.7)	816 (20.0)	1621 (19.8)
Study Drug-Related TEAE ¹	514 (12.6)	499 (12.2)	1013 (12.4)
Serious TEAE	1252 (30.6)	1254 (30.7)	2506 (30.6)
Study Drug-Related Serious TEAE ¹	8 (0.2)	5 (0.1)	13 (0.2)
TEAE Leading to Withdrawal of Study Drug ²	321 (7.9)	335 (8.2)	656 (8.0)
Study Drug-Related TEAE Leading to Withdrawal of Study Drug ^{1,2}	139 (3.4)	164 (4.0)	303 (3.7)
Serious TEAE Leading to Withdrawal of Study Drug ²	88 (2.2)	88 (2.2)	176 (2.2)
Serious TEAE Leading to Death	94 (2.3)	102 (2.5)	196 (2.4)
Study Drug-Related Serious TEAE Leading to Withdrawal of Study Drug ^{1,2}	2 (0.0)	4 (0.1)	6 (0.1)

Abbreviations: ODIS = off drug in study; TEAE = treatment-emergent adverse event.

Note: A TEAE was defined as an event that first occurred or worsened in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. Percentages were based on the number of patients randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints were not included.

1 Study drug-related TEAEs include those characterized as related, probably related, or possibly related by the Investigator.

2 Withdrawal of study drug excludes patients who were ODIS for 30 days or more and restarted study drug.

7.2 Frequently Reported Treatment-Emergent Adverse Events

The most frequently reported TEAEs, defined as occurring in $\geq 5\%$ of patients in either treatment group and statistically different across treatment groups, are presented in [Table 6](#). Peripheral edema is the only TEAE that occurred in $\geq 5\%$ of patients and at greater frequency in the icosapent ethyl as compared to the placebo group.

Table 6. Most Frequent Treatment-Emergent Adverse Events: $\geq 5\%$ in Either Treatment Group and Significantly Different (Safety Population)

Preferred Term ¹ , n (%)	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P-value ²
Diarrhea	367 (9.0%)	453 (11.1%)	0.0017
Edema peripheral	267 (6.5%)	203 (5.0%)	0.0024
Constipation	221 (5.4%)	149 (3.6%)	0.0001
Atrial fibrillation	215 (5.3%)	159 (3.9%)	0.0030
Anemia	191 (4.7%)	236 (5.8%)	0.0286

Note: A treatment-emergent adverse event (TEAE) is defined as an event that first occurs or worsens in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. For each subject, multiple TEAEs of the same Preferred Term will be counted only once within each Preferred Term. TEAEs are listed in descending order of icosapent ethyl frequency. Percentages are based on the number of subjects randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints are not included.

1 All adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 20.1).

2 Fishers Exact test.

7.3 Adverse Events of Special Interest

An overview of prespecified TEAEs of special interest is presented in [Table 7](#). No statistically significant differences between the icosapent ethyl and placebo groups were observed in hepatic disorders or abnormal glucose control. A statistically significantly higher incidence of bleeding TEAEs occurred in the icosapent ethyl group (11.8%) than in the placebo group (9.9%; $p=0.0055$).

An overview of prespecified SAEs of special interest is presented in [Table 8](#). No statistically significant differences between the icosapent ethyl and placebo groups were observed in hepatic disorders or abnormal glucose control. Bleeding related SAEs were low overall but trended toward significance in the icosapent ethyl group (2.7%) versus the placebo group (2.1%; $p=0.0605$), the incidences of serious GI bleeding and serious CNS bleeding were low overall and similar between treatment groups.

Table 7. Pre-Specified TEAEs of Special Interest (Safety Population)

	Icosapent Ethyl (N=4089) n (%)	Placebo (N=4090) n (%)	P-value⁴
Hepatic Disorders ¹	221 (5.4)	201 (4.9)	0.3180
Bleeding-Related Disorders ²	482 (11.8)	404 (9.9)	0.0055
Gastrointestinal Bleeding	127 (3.1)	116 (2.8)	0.4747
Central Nervous System Bleeding	20 (0.5)	12 (0.3)	0.1619
Other Bleeding	376 (9.2)	312 (7.6)	0.0108
Abnormal Glucose Control ³	621 (15.2)	630 (15.4)	0.8059

Abbreviations: AE = adverse event; excl = excluding; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = Standardized MedDRA Query; TEAE = treatment-emergent adverse event.

Note: A TEAE was defined as an event that first occurred or worsened in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. For each patient, multiple TEAEs of the same preferred term were counted only once within each preferred term.

1 Hepatic disorders were identified by the Hepatic Disorder SMQ (MedDRA v20.0).

2 Bleeding-related disorders were identified by the SMQs of “Gastrointestinal haemorrhage,” “Central Nervous System haemorrhages and cerebrovascular conditions,” and “Haemorrhage terms (excl laboratory terms).”

3 Glucose control AEs were identified based on the risk of impaired glucose control as defined in the Investigator’s Brochure.

4 The p-value was based on Fisher’s exact test.

Table 8. Pre-specified SAEs of Special Interest (Safety Population)

	Icosapent Ethyl (N=4089) n (%)	Placebo (N=4090) n (%)	P-value⁴
Hepatic Disorders ¹	16 (0.4%)	12 (0.3%)	0.4575
Bleeding related disorders ²	111 (2.7%)	85 (2.1%)	0.0605
Gastrointestinal bleeding	62 (1.5%)	47 (1.1%)	0.1496
Central nervous system bleeding	14 (0.3%)	10 (0.2%)	0.4236
Other bleeding	41 (1.0%)	30 (0.7%)	0.1925
Abnormal Glucose control ³	46 (1.1%)	38 (0.9%)	0.3832

Abbreviations: AE = adverse event; excl = excluding; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = Standardized MedDRA Query; TEAE = treatment-emergent adverse event.

Note: A TEAE was defined as an event that first occurred or worsened in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. For each patient, multiple TEAEs of the same preferred term were counted only once within each preferred term.

1 Hepatic disorders were identified by the Hepatic Disorder SMQ (MedDRA v20.0).

2 Bleeding-related disorders were identified by the SMQs of “Gastrointestinal haemorrhage,” “Central Nervous System haemorrhages and cerebrovascular conditions,” and “Haemorrhage terms (excl laboratory terms).”

3 Glucose control AEs were identified based on the risk of impaired glucose control as defined in the Investigator’s Brochure.

4 The p-value was based on Fisher’s exact test.

7.3.1 Bleeding

The bleeding event of hemorrhagic stroke was a prespecified adjudicated endpoint event (an efficacy endpoint). Occurrences of hemorrhagic stroke that were not positively adjudicated were counted as TEAEs or SAEs, per seriousness criteria. A summary of TEAE and SAE bleeding events is presented in [Table 9](#) and [Table 10](#), along with positively adjudicated endpoints of hemorrhagic stroke, as a comprehensive compilation of all documented post randomization occurrences of these bleeding events.

Table 9. Summary of All Bleeding Related Adverse Events (Including Hemorrhagic Stroke; Safety Population)

	Icosapent Ethyl (N=4089) n (%)	Placebo (N=4090) n (%)	P-value²
Bleeding Related Disorders¹	494 (12.1%)	412 (10.1%)	0.0039
Gastrointestinal Bleeding	127 (3.1%)	116 (2.8%)	0.4747
CNS Bleeding	20 (0.5%)	12 (0.3%)	0.1619
Hemorrhagic Stroke	13 (0.3%)	10 (0.2%)	0.5407
Other Bleeding	376 (9.2%)	312 (7.6%)	0.0108

¹ Bleeding-related disorders are identified by the standardized MedDRA queries of "Gastrointestinal haemorrhage," "Central Nervous System haemorrhages and cerebrovascular conditions," and "Haemorrhage terms (excl laboratory terms)."

² Fishers Exact test.

Table 10. Summary of Serious Bleeding Related Adverse Events (Including Hemorrhagic Stroke; Safety Population)

	Icosapent Ethyl (N=4089) n (%)	Placebo (N=4090) n (%)	P-value²
Bleeding Related Disorders¹	123 (3.0%)	95 (2.3%)	0.0549
Gastrointestinal Bleeding	62 (1.5%)	47 (1.1%)	0.1496
CNS Bleeding	14 (0.3%)	10 (0.2%)	0.4236
Hemorrhagic Stroke	13 (0.3%)	10 (0.2%)	0.5407
Other Bleeding	41 (1.0%)	30 (0.7%)	0.1925

¹ Bleeding-related disorders are identified by the standardized MedDRA queries of "Gastrointestinal haemorrhage," "Central Nervous System haemorrhages and cerebrovascular conditions," and "Haemorrhage terms (excl laboratory terms)."

² Fishers Exact test.

The incidence of any bleeding event was not significantly different between the icosapent ethyl group and the placebo group for patients on anti-coagulant or anti-platelet therapy; 93.9% (464/494) of icosapent ethyl bleeding events versus 93.0% (383/412) of placebo bleeding events. This implies 93% of non-serious and serious bleeding cases were associated with concomitant medications well known to increase bleeding tendency; comparing the two groups suggests treatment may increase overall bleeding by less than about one percentage point. Put into clinical terms, one would need to treat >100 patients on an anti-coagulant or anti-platelet therapy with icosapent ethyl over 6 years to experience one additional case of bleeding, irrespective of whether the bleeding is non-serious or serious. To the extent this largely involves non-serious and/or readily-managed bleeding, this would likely prove a reasonable risk compared to the lower incidence for MACE in most cases. Similarly, the incidence of any bleeding event was not significantly different between the icosapent ethyl group and the placebo group for patients on aspirin therapy; 80.6% (398/494) of icosapent ethyl bleeding events vs. 79.1% (326/412) of placebo bleeding events.

Due to the convergence of clinical events shortly before a patient's death, direct causality of an individual bleeding event with death cannot always be determined. Bleeding-related clinical events (i.e., TEAEs, SAEs, or positively adjudicated endpoints) that occurred proximal to death (per site Investigator, CEC, or Sponsor medical assessment) are presented in [Table 11](#) and occurred in 23 (0.6%) patients in the icosapent ethyl group and 34 (0.8%) patients in the placebo group,

with no statistically significant difference between treatment groups ($p=0.18$). Sponsor medical assessment classified 20 (0.5%) patients in the icosapent ethyl group and 23 (0.6%) patients in the placebo group as having a bleeding event that likely contributed to death, with no statistically significant difference between treatment groups ($p=0.76$). Sponsor medical assessment also classified 3 (0.1%) patients in the icosapent ethyl group and 11 (0.3%) patients in the placebo group as having a bleeding event that did not likely contribute to death ($p=0.06$). None of these 57 deaths with a possible fatal association were associated with study drug per Investigator assessment; one bleeding event in each treatment group was considered possibly related to study drug per Investigator assessment.

Table 11. Bleeding Events with Possible Fatal Association (Safety Population)

	Icosapent ethyl (N=4089) n (%)	Placebo (N=4090) n (%)	P-value ¹
Any Bleeding With a Possible Fatal Association	23 (0.6)	34 (0.8)	0.18
Bleeding Likely Contributing to a Fatal Event	20 (0.5)	23 (0.6)	0.76
Bleeding Not Likely Contributing to a Fatal Event	3 (0.1)	11 (0.3)	0.06

Note: Identification of patients with a fatal event possibly associated with a bleeding event was conducted through exhaustive search of the clinical adverse events dataset and the Clinical Endpoint Committee endpoint database, as well as through comprehensive Sponsor medical review of the relevant data/source documents.

¹ The p-value was based on Fisher's exact test.

Additional analyses of all bleeding events, inclusive of AEs, SAEs, and positively adjudicated endpoint events of hemorrhagic stroke (not included in AE analyses within this section) can be found in [Appendix K](#) and a related benefit-risk assessment is provided in [Section 8](#).

Overall, the rates of adjudicated hemorrhagic stroke and the incidences of serious GI bleeding (1.5% icosapent ethyl and 1.1% placebo), serious CNS bleeding (0.3% icosapent ethyl and 0.2% placebo ([Table 10](#))), and serious anemia (0.5% icosapent ethyl and 0.5% placebo; see [Table 14](#)), were low overall and similar between treatment groups.

Bleeding rates observed with icosapent ethyl are generally lower than what has been observed in studies involving low dose aspirin use in higher CV risk patients (ASCEND Study Collaborative Group 2018), although no head-to-head studies have been conducted.

7.3.2 Atrial Fibrillation and Atrial Flutter

Although not prespecified as TEAEs of special interest, atrial fibrillation and atrial flutter were also explored *post hoc* as potential safety signals. Atrial fibrillation or atrial flutter requiring hospitalization for at least 24 hours was a prespecified adjudicated endpoint event (an efficacy endpoint). Occurrences of atrial fibrillation and/or flutter that were not positively adjudicated were counted as TEAEs or SAEs, per seriousness criteria. A summary of TEAEs and SAEs of atrial fibrillation/flutter is presented in [Table 12](#), along with positively adjudicated endpoints of atrial fibrillation/flutter requiring hospitalization of ≥ 24 hours (endpoint events adjudicated by the CEC), as a comprehensive compilation of all documented post-randomization occurrences of these atrial arrhythmias.

The incidences of atrial fibrillation/flutter TEAEs reported in the AE dataset within the clinical database (i.e., not positively adjudicated as endpoints) were statistically significantly higher in the icosapent ethyl group than in the placebo group ($p=0.0079$), while the incidences of atrial fibrillation/flutter SAEs reported in the safety/clinical dataset (i.e., meeting seriousness criteria,

but not positively adjudicated as endpoints) were similar between the icosapent ethyl and placebo groups. The incidences of positively adjudicated atrial fibrillation/flutter requiring hospitalization of ≥ 24 hours were also statistically significantly higher in the icosapent ethyl group than in the placebo group ($p=0.0037$).

Table 12. Atrial Fibrillation and Atrial Flutter AEs and Endpoints (ITT Population)

	Icosapent ethyl (N=4089) n (%)	Placebo (N=4090) n (%)	P-value
Atrial Fibrillation/Flutter TEAEs¹	236 (5.8)	183 (4.5)	0.0079
Serious Atrial Fibrillation/Flutter TEAEs ²	22 (0.5)	20 (0.5)	0.7602
Positively Adjudicated Atrial Fibrillation/Flutter Requiring ≥ 24 Hours Hospitalization³	127 (3.1)	84 (2.1)	0.0037

Abbreviations: AE = adverse event; ITT = Intention-to-Treat; MedDRA = Medical Dictionary for Regulatory Activities.

Note: Percentages were based on the number of patients in the ITT population within each treatment group (N). All AEs were coded using the MedDRA, Version 20.1. Counts of atrial fibrillation/flutter AEs and counts of positively adjudicated atrial fibrillation/flutter events are mutually exclusive.

1 Includes atrial fibrillation/flutter TEAEs and excludes positively adjudicated events. The p-value was based on Fisher's exact test.

2 Includes a subset of atrial fibrillation/flutter AEs meeting seriousness criteria. The p-value was based on Fisher's exact test.

3 Includes positively adjudicated atrial fibrillation/flutter requiring ≥ 24 hours hospitalization clinical events by the Clinical Endpoint Committee. The p-value was based on stratified log-rank test.

Additional analyses of atrial fibrillation/flutter can be found in [Appendix M](#) and a related benefit-risk assessment is provided in [Section 8](#).

Overall the incidences of atrial fibrillation or atrial flutter SAEs were not different across treatment groups, but TEAEs and adjudicated endpoints were higher with icosapent ethyl than placebo. In clinical terms, the widest difference between the treatment groups for absolute risk difference was +1.3% for TEAEs in [Table 11](#). Taking this as the conservative case, it implies if one were to treat patients meeting the enrollment criteria, one would have to treat about 77 with icosapent ethyl for 6 years to experience one additional case of atrial fibrillation and/or flutter, which could either be new-onset or a recurrence in a patient with established/managed atrial fibrillation and/or flutter. To the extent MACE is apt to have more severe clinical consequences, the modest increase in risk for atrial fibrillation would seem tolerable, given lower risk for MACE. As described below, in *post hoc* analyses inclusion of positively adjudicated atrial fibrillation or atrial flutter and serious bleeding events within broadened composites of the primary and key secondary endpoints did not alter overall study conclusions.

7.4 Deaths

Death resulting from TEAEs occurred at similar incidences in the icosapent ethyl and placebo groups. Note that SAEs leading to death and death itself were to be recorded as separate events in the safety dataset.

Total mortality and CV death were secondary efficacy endpoints, with CV death being significantly reduced and total mortality trending toward reduction (see [Figure 5](#)). A summary of all CEC-adjudicated deaths (including CV death, non-CV death, undetermined death, and total mortality) is presented in [Table 13](#).

Table 13. CEC-Adjudicated Deaths (Safety Population)

Summary of Deaths ¹ , n (%)	Icosapent ethyl (N=4089)	Placebo (N=4090)	Overall (N=8179)
Total Mortality	274 (6.7)	310 (7.6)	584 (7.1)
CV Deaths (Excluding Deaths With Undetermined Cause)	138 (3.4)	180 (4.4)	318 (3.9)
Non-CV Deaths	100 (2.4)	97 (2.4)	197 (2.4)
Deaths With Undetermined Cause	36 (0.9)	33 (0.8)	69 (0.8)

Abbreviations: CV = cardiovascular.

Note: CV deaths (excluding deaths with undetermined cause) and deaths with undetermined cause were combined as “CV deaths” for the primary efficacy analysis of CV endpoints.

1 Excludes 3 patient deaths occurring after consent withdrawal (patients (b) (6), (b) (6) and (b) (6)).

Utilizing known vital status data through 31 May 2018 (study end date) and assessed as of 06 September 2018 (database lock), total mortality was 7.3% (298/4089) and 8.3% (339/4090) in the icosapent ethyl group and the placebo group, respectively.

7.5 Other Serious Adverse Events

A summary of SAEs with an incidence $\geq 0.5\%$ in either treatment group is presented in Table 14, by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. The incidences of classes of SAEs and individual SAEs were similar between the icosapent ethyl and placebo groups. The most frequent SAE in both treatment groups was pneumonia, with similar incidences in the icosapent ethyl and placebo groups (2.6% [105/4089] and 2.9% [118/4090], respectively). Of note, the incidences of serious GI hemorrhage were similar between the icosapent ethyl and placebo groups (0.6% [26/4089] and 0.5% [20/4090], respectively), as were the incidences of serious anemia (0.5% [22/4089] and 0.5% [20/4090], respectively).

Table 14. SAEs with an Incidence $\geq 0.5\%$ in Either Treatment Group, by MedDRA System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term¹	Icosapent Ethyl (N=4089) n (%)	Placebo (N=4090) n (%)	Overall (N=8179) n (%)
Patients With at Least 1 SAE	1252 (30.6)	1254 (30.7)	2506 (30.6)
Infections and Infestations	332 (8.1)	309 (7.6)	641 (7.8)
Pneumonia	105 (2.6)	118 (2.9)	223 (2.7)
Cellulitis	36 (0.9)	28 (0.7)	64 (0.8)
Sepsis	25 (0.6)	31 (0.8)	56 (0.7)
Urinary tract infection	25 (0.6)	22 (0.5)	47 (0.6)
Neoplasms Benign, Malignant, and Unspecified (Incl Cysts and Polyps)	222 (5.4)	208 (5.1)	430 (5.3)
Prostate cancer	26 (0.6)	26 (0.6)	52 (0.6)
Cardiac Disorders	192 (4.7)	224 (5.5)	416 (5.1)
Angina pectoris	48 (1.2)	48 (1.2)	96 (1.2)
Angina unstable	41 (1.0)	53 (1.3)	94 (1.1)
Atrial fibrillation	21 (0.5)	17 (0.4)	38 (0.5)
Cardiac failure congestive	19 (0.5)	13 (0.3)	32 (0.4)
Gastrointestinal Disorders	191 (4.7)	176 (4.3)	367 (4.5)
Gastrointestinal hemorrhage	26 (0.6)	20 (0.5)	46 (0.6)
Musculoskeletal and Connective Tissue Disorders	188 (4.6)	165 (4.0)	353 (4.3)
Osteoarthritis	81 (2.0)	73 (1.8)	154 (1.9)
Respiratory, Thoracic, and Mediastinal Disorders	143 (3.5)	141 (3.4)	284 (3.5)
Chronic obstructive pulmonary disease	33 (0.8)	34 (0.8)	67 (0.8)
Acute respiratory failure	19 (0.5)	18 (0.4)	37 (0.5)
Pulmonary embolism	14 (0.3)	22 (0.5)	36 (0.4)
General Disorders and Administration Site Conditions	139 (3.4)	153 (3.7)	292 (3.6)
Chest pain	66 (1.6)	66 (1.6)	132 (1.6)
Non-cardiac chest pain	49 (1.2)	52 (1.3)	101 (1.2)
Renal and Urinary Disorders	120 (2.9)	100 (2.4)	220 (2.7)
Acute kidney injury	47 (1.1)	34 (0.8)	81 (1.0)
Nervous System Disorders	104 (2.5)	100 (2.4)	204 (2.5)
Syncope	28 (0.7)	31 (0.8)	59 (0.7)
Blood and Lymphatic System Disorders	39 (1.0)	35 (0.9)	74 (0.9)
Anemia	22 (0.5)	20 (0.5)	42 (0.5)

Abbreviations: incl = including; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event.

Note: A TEAE was defined as an event that first occurred or worsened in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. For each patient, multiple TEAEs of the same preferred term were counted only once within each preferred term. TEAEs are listed in descending order of icosapent ethyl frequency. Percentages were based on the number of patients randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints were not included. Seriousness assessed by investigators per seriousness criteria.

¹ All adverse events were coded using the MedDRA, Version 20.1.

7.6 Other Safety Findings

Treatment-emergent laboratory abnormalities considered by the Investigator to be clinically significant were to be reported as TEAEs. No individual hematology or clinical chemistry TEAEs occurred at an incidence $>3\%$ among icosapent ethyl-treated patients. All individual hematology abnormalities reported as TEAEs occurred at a low ($<1\%$) incidence. As might be expected in this

patient population, the most frequently reported clinical chemistry TEAEs overall were glucose abnormalities, with similar or lower incidences in the icosapent ethyl versus placebo groups. Findings related to clinical laboratory, ECG, vital signs, or physical examination parameters were generally similar across treatment groups.

7.7 *Post Hoc* Exploration of the Impact of Atrial Fibrillation/Atrial Flutter and Bleeding on the Primary and Key Secondary Endpoints

To explore a somewhat extreme scenario of the relative impacts of atrial fibrillation or atrial flutter and bleeding on patient outcomes, *post hoc* analyses were conducted with positively adjudicated atrial fibrillation/flutter and bleeding SAEs added to the composites of the primary and key secondary endpoints. As shown in [Table 15](#), despite inclusion of atrial fibrillation/flutter endpoints and/or bleeding SAEs in the primary and key secondary endpoints, the primary plus risk and key secondary plus risk endpoints are still substantially reduced. For example, for the most extreme analyses of including both atrial fibrillation or atrial flutter endpoints and bleeding SAEs in the primary and key secondary endpoint composites, the primary+risk (HR of 0.830; $p<0.0001$) and key secondary+risk (HR of 0.855; $p=0.0042$) endpoints remain significantly reduced. More specific to atrial fibrillation/flutter, stroke, MI, cardiac arrest, and sudden cardiac death can be serious sequelae associated with atrial fibrillation/flutter, so we also explored the composite endpoint of positively adjudicated atrial fibrillation/flutter, stroke, MI, cardiac arrest, and sudden cardiac death, which suggests overall CV benefit despite inclusion of atrial fibrillation or atrial flutter (HR of 0.789; $p<0.0001$). While positively adjudicated atrial fibrillation/flutter and bleeding SAEs are clinically important, they are typically not considered as clinically consequential as the other MACE events represented within these analyses. These *post hoc* analyses are thus heavily biased against icosapent ethyl with the equal statistical consideration of these events and the components of the primary and key secondary endpoints.

Table 15. Summary of *Post Hoc* Analyses of the Primary+ Risk and Key Secondary+ Risk Composite Endpoints (ITT Population)

Endpoint	Icosapent Ethyl (N=4089)	Placebo (N=4090)	HR (95% CI)	P-value	Rate/1000 pt yrs	
					Icosapent Ethyl	Placebo
Primary + AFib/Aflutter	785 (19.2%)	946 (23.1%)	0.803 (0.731, 0.883)	<0.0001	49.0	60.7
Key Secondary + Afib/Aflutter	552 (13.5%)	660 (16.1%)	0.818 (0.731, 0.916)	0.0005	33.1	40.3
Primary + Serious Bleeding	775 (19.0%)	950 (23.2%)	0.785 (0.714, 0.863)	<0.0001	48.2	61.0
Key Secondary + Serious Bleeding	539 (13.2%)	664 (16.2%)	0.789 (0.704, 0.884)	<0.0001	32.1	40.6
Primary + Afib/Aflutter + Serious Bleeding	850 (20.8%)	992 (24.3%)	0.830 (0.757, 0.910)	<0.0001	53.5	64.2
Key Secondary + Afib/Aflutter + Serious Bleeding	625 (15.3%)	715 (17.5%)	0.855 (0.768, 0.952)	0.0042	37.8	44.1
Afib/Aflutter + MI + Stroke + Cardiac Arrest + Sudden Cardiac Death	491 (12.0%)	609 (14.9%)	0.789 (0.701, 0.889)	<0.0001	29.4	37.2

Notes: All components presented on the table except serious bleeding are adjudicated by CEC

The number of subjects with event (n) is the number of subjects with the event in the ITT Population within each treatment group (N). Rate per 1000 patient years (pt-yrs) is $1000 \times n/\text{pt-yrs}$ subjects at-risk.

Log-Rank test statistic and p-value are reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe

7.8 Overall Safety Findings

Over 4.9 years median duration of study follow-up in REDUCE-IT, icosapent ethyl 4 g/day was generally well tolerated. The nature and type of AE findings are consistent with the broader omega-3 literature or current icosapent ethyl labeling, and can be appropriately conveyed to clinicians and patients.

8 BENEFIT-RISK DISCUSSION

CVD remains the most common cause of morbidity and mortality globally, accounting for an estimated 31.5% (17 million) of all global deaths in 2013 (Roth 2017), despite increased use of statins and other therapies that target reduction of LDL-C. Public health and healthcare costs are burdened by the clinical need for treatments that effectively lower CV risk including in statin-treated patients, and yet investment in the multi-year, multi-hundred million dollar outcomes trials that are required to demonstrate CV reduction have been rare. Failures outnumber successes while significant residual CV risk persists. Reducing CV events in at-risk patients beyond available therapies is a public health priority that likely contributed toward the current application being designated for priority review by the FDA.

REDUCE-IT was a multi-national, prospective, randomized, double-blind, placebo-controlled, parallel group study designed to evaluate the effect of 4 g/day icosapent ethyl (2 g BID) for preventing CV events in statin-treated patients with controlled LDL-C (≤ 100 mg/dL), moderately elevated residual TG levels (≥ 135 mg/dL), and other CVD risk factors. REDUCE-IT enrolled 8179 patients globally, who were followed for a median of 4.9 years, resulting in 35,014 patient years collected.

REDUCE-IT provides robust and consistent evidence for CV risk reduction with icosapent ethyl in statin-treated patients with well-controlled LDL-C, as demonstrated by statistically significant reductions in the primary and key secondary composite endpoints, in each individual component of these endpoints, in the prespecified testing hierarchy, and in tertiary, exploratory, and *post hoc* CV endpoints, with findings generally consistent across subgroups.

Icosapent ethyl 4 g/day was generally well tolerated, with few observed safety imbalances between the treatment groups. Events such as serious bleeding and serious or adjudicated cases of atrial fibrillation/flutter occurred at relatively low rates; in context of observed benefits, we believe these imbalances can be effectively communicated to clinicians and patients.

8.1 Icosapent Ethyl Effectively Reduces the Risk of Cardiovascular Events

The REDUCE-IT primary endpoint was the time from randomization to the first occurrence of any component of the composite of the following clinical events: CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization. A primary endpoint event occurred in 17.2% of patients in the icosapent ethyl group, as compared to 22.0% of patients in the placebo group (HR of 0.752 [95% CI: 0.682 to 0.830; $p=0.00000001$]; RRR of 24.8%; ARR of 4.8%; and NNT of 21).

The key secondary endpoint was the time from randomization to the first occurrence of the composite of CV death, nonfatal MI, or nonfatal stroke (i.e., hard MACE endpoint). A key secondary endpoint event occurred in 11.2% of patients in the icosapent ethyl group as compared to 14.8% of patients in the placebo group (HR of 0.735 [95% CI: 0.651 to 0.830; $p=0.0000006$]; RRR of 26.5% ARR of 3.6%; and NNT of 28).

Significant reductions with icosapent ethyl were observed in each of the individual components of the primary and key secondary endpoints, including a 20% RRR in CV death (HR of 0.803 [95% CI: 0.657 to 0.981; $p=0.0315$]).

The effects of icosapent ethyl were highly consistent across the prespecified testing hierarchy, including statistically significant reductions in CV death, fatal or nonfatal MI, and fatal or nonfatal stroke.

Also consistent with the primary and key secondary endpoint findings, clinically meaningful reductions were observed in the tertiary and exploratory endpoints of total (i.e., all occurrences of) primary endpoint events and total key secondary endpoint events. A clinically meaningful lower risk in the icosapent ethyl group versus the placebo group was also observed across other tertiary and exploratory endpoints, including: All coronary revascularizations and individually for emergent, urgent, and elective revascularizations; cardiac arrests; sudden cardiac deaths; and ischemic strokes.

As exploratory analyses representing subsets of patients, subgroup analyses were not powered for significance, and therefore should not be overly relied upon to substantiate individual subgroup efficacy conclusions. Nonetheless, such exploratory subgroup analyses can be informative for hypothesis-generating efforts, and subgroup analyses of the primary and key secondary endpoints demonstrated generally consistent benefit of icosapent ethyl treatment across prespecified subgroups.

REDUCE-IT was not designed to validate changes in biomarkers as surrogates for CV risk reduction, but REDUCE-IT analyses suggest baseline TG levels have little to no impact on the CV risk reduction observed with icosapent ethyl, and on-treatment TG levels or TG reductions have limited impact. Therefore, while TG lowering likely contributed to the observed risk reduction with icosapent ethyl in REDUCE-IT, TG does not appear to be the sole or primary driver of the observed 25% relative risk reduction.

8.2 Adequacy of the Control Group

The selection of an appropriate placebo for use in the study of icosapent ethyl was thoroughly examined before and after each Phase 3 icosapent ethyl clinical trial, including within the SPA processes for each study and at the FDA advisory committee review of the ANCHOR study results in October 2013 ([Appendix C](#)). Mineral oil was chosen as the best choice to mimic the color and consistency of icosapent ethyl. Mineral oil has been used as a laxative at high doses (typically 15–30 g/day) for over 100 years, including extensive use in pediatric populations. The safety of mineral oil is generally inferred from a long history of use with limited adverse effects.

Per design as a CV outcomes study, REDUCE-IT hierarchical primary and secondary analyses focused on CV events, with biomarkers collected as single measures with large spans of time between measurements to support tertiary, exploratory, and *post hoc* analyses. We performed extensive literature searches regarding mineral oil and regarding biomarker changes observed in statin-treated patients, then we conducted a series of *post hoc* analyses to explore a potential mineral oil effects (or lack thereof) within REDUCE-IT ([Appendix D](#)), and we inquired of the FDA if they were aware of any available information we might be overlooking. The supposition that the light mineral oil used in REDUCE-IT does not exert clinically meaningful effects on medication (including statin) efficacy or absorption, biomarkers, outcomes, or safety, agrees with conclusions from prior FDA reviews, and is supported by multiple lines of evidence. Contrary to the lack of evidence for a hypothetical placebo impact on CV risk, clinical and preclinical studies provide extensive data supporting cardioprotective effects of EPA ([Appendix E](#)). While based on these various sources of evidence we do not agree that placebo influenced the REDUCE-IT results, even

if we are wrong, such potential influence cannot reasonably be estimated to account for a substantial portion of overall robust and consistent REDUCE-IT findings, including a 25% RRR in the primary endpoint that is consistent with the observed risk reduction in the JELIS study, which did not administer a mineral oil placebo. Taken together, these various analyses and comparisons are inconsistent with a placebo-mediated effect significantly overestimating the REDUCE-IT results, but rather support a conclusion that icosapent ethyl provided substantial and consistent risk reduction in statin-treated patients.

8.3 Icosapent Ethyl is Safe and Well-Tolerated

Over 4.9 years median duration of study follow-up in REDUCE-IT, icosapent ethyl 4 g/day was generally well tolerated, with the nature and type of AE findings consistent with the broader omega-3 literature or current icosapent ethyl labeling. The proportions of patients with AEs were similar between the icosapent ethyl and placebo groups, respectively, including TEAEs, severe TEAEs, study drug-related TEAEs, SAEs, study drug-related SAEs, TEAEs leading to study drug withdrawal, SAEs leading to study drug withdrawal, and SAEs leading to death. Baseline medications reflected the CV risk of enrolled patients, including antithrombotic use, and the percentages of patients taking different medications were similar between treatment groups.

A statistically significant higher incidence of total adverse bleeding events was observed with icosapent ethyl compared to placebo, while serious bleeding events were low and trended toward statistical significance in the icosapent ethyl versus the placebo group. The rates of adjudicated hemorrhagic stroke, and the incidences of GI bleeding, serious CNS bleeding, and serious anemia, were low overall and similar between treatment groups. Bleeding rates observed with icosapent ethyl are generally lower than what has been observed in studies involving low dose aspirin, although no head-to-head studies have been conducted.

A statistically significant higher incidence of atrial fibrillation/flutter TEAEs was observed with icosapent ethyl, while the incidence of atrial fibrillation/flutter SAEs was similar between treatment groups. Atrial fibrillation/flutter requiring hospitalization ≥ 24 hours was an adjudicated endpoint that occurred at a higher incidence with icosapent ethyl than placebo. The observed increase in atrial fibrillation/flutter in REDUCE-IT is consistent with trends observed for other omega-3 fatty acids. Atrial arrhythmias can contribute to congestive heart failure (CHF), but there were no changes in newly emergent CHF. Stroke, MI, cardiac arrest, and sudden cardiac death are potential clinical outcomes related to atrial fibrillation/flutter, and yet a substantially lower risk of these events was observed with icosapent ethyl group than placebo. Inclusion of positively adjudicated atrial fibrillation or atrial flutter and serious bleeding events with the composites of the primary and key secondary endpoints in *post hoc* analyses did not alter the overall study conclusions.

The nature and type of AE findings within REDUCE-IT are consistent with the broader omega-3 literature or current icosapent ethyl labeling, and they can be appropriately conveyed to clinicians and patients.

8.4 Eicosapentaenoic Acid (EPA) Unique Mechanisms of Action

A broad array of scientific literature has explored the mechanisms of action of EPA, the active metabolite of icosapent ethyl, and many of these mechanisms differ from other therapies, including individual or mixed omega-3 fatty acid products. EPA is comprised of 20 carbons and five double

bonds, which is different from other omega-3 fatty acid molecules, such as another common long-chain omega-3 fatty acid DHA that consists of 22 carbons and six double bonds; these differences can have substantial impact on biological function. The active ingredient of Vascepa, icosapent ethyl, was granted NCE status by FDA, with its single active molecule considered by the agency to be a different active ingredient than the previously approved, multiple-constituent, primarily omega-3, fatty acid product Lovaza (omega-3 ethyl esters).

The science related to CV risk reduction with omega-3 fatty acids is complex, with a lack of benefit observed in CV outcome studies that administered low-dose (<1 g/day) omega-3 fatty acid mixtures in statin-treated patients, and no outcome studies available that administered higher dose omega-3 fatty acid mixtures or DHA-only. The totality of evidence suggests that EPA may impact multiple stages along atherosclerotic processes, resulting in reduced development, slowed progression, and increased stabilization of atherosclerotic plaque. Importantly, administration in a stable form and, while based on hypothesis-generating and/or *post hoc* analyses, achieving substantially increased blood EPA concentrations appear necessary for an observed CV benefit in statin-treated patients. While additional data may become available regarding possible CV benefit of higher dose omega-3 fatty acid mixtures, the clinical and preclinical data strongly support that the relative clinical efficacy and safety of different omega-3 fatty acids cannot be presumed to be equivalent, and therefore such results will not alter the evidence for EPA-only therapy. Finally, while mechanisms of action are of clinical and scientific interest, they do not need to be fully elucidated for clear demonstration of clinical benefit, such as observed in the REDUCE-IT study.

9 EXTERNAL REVIEW OF THE REDUCE-IT RESULTS

The REDUCE-IT results have been published in *The New England Journal of Medicine* (Bhatt 2019(a); Bhatt 2019(b); [Appendix F]) and the *Journal of the American College of Cardiology* (Bhatt 2019(c), Bhatt 2019(d)), and presented as late-breaking clinical trial presentations at the AHA in 2018 and the ACC in 2019. REDUCE-IT has been extensively evaluated in editorials and other forums, and has been noted as the *NEJM Journal Watch Cardiology 2018* number one cardiology story, the *AHA Top 10 Most Important Studies for 2018*, and among the *ACC 2018 Top Clinical Trials*.

The following clinical treatment guidelines and position statements have been updated based on the REDUCE-IT results. Common to each of these updates was that icosapent ethyl should be used in high-risk statin-treated patients with TG levels ≥ 135 mg/dL.

- In March 2019 the American Diabetes Association updated its guidelines with a Level A recommendation – their highest level – in both secondary prevention patients and primary prevention patients with elevated TG levels (American Diabetes Association 2019).
- In August 2019 the AHA recognized the results of REDUCE-IT and recommended directing medical care away from unproven fish oil dietary supplements and to prescription drug therapy in patients with elevated TG levels (AHA 2019).
- In September 2019 the ESC and EAS also updated their guidelines in 2019 with a Level B (Class IIa) recommendation to administer icosapent ethyl therapy in high risk primary and secondary prevention patients with elevated TG despite statin therapy (ESC/EAS 2019).
- In September 2019 the NLA issued a position statement recommending icosapent ethyl (Vascepa) for ASCVD risk reduction in the population studied in REDUCE-IT. The NLA recommendation was issued as a Class I, Level B-R (STRONG) recommendation, its highest designation, for icosapent ethyl (NLA 2019).

In September 2019, the independent drug watchdog group, ICER, presented its analysis which found icosapent ethyl to be medically compelling and cost effective across all of the metrics typically reviewed by ICER, concluding that compared to optimal medical management alone, icosapent ethyl reduced the risk of a composite outcome of CV death, stroke, MI, coronary revascularization, or unstable angina in patients with established CVD or with diabetes and additional risk factors.

A reference list of REDUCE-IT publications to date, updated guidelines, and the ICER report are provided in [Appendix F](#).

10 OVERALL CONCLUSIONS

REDUCE-IT provides robust and consistent evidence that icosapent ethyl 4 g/day resulted in significant reduction of major adverse CV events, including CV death and a range of prespecified CV endpoints, in statin-treated patients with controlled LDL-C (≤ 100 mg/dL), but elevated residual TG levels (≥ 135 mg/dL) and other CV risk factors. Icosapent ethyl 4 g/day was generally well tolerated, with the nature and type of AE findings consistent with long-term treatment options for CV event management.

The CV risk reduction achieved in REDUCE-IT is consistent with the multifactorial and unique effects of EPA observed in clinical and preclinical studies that go beyond lipid modification, including beneficial effects at various stages along atherosclerotic processes. REDUCE-IT findings are also consistent with the results of JELIS, which administered isolated and stable EPA at a dose that achieved high blood levels of EPA and reported a 19% RRR in a patient population that was 80% primary prevention, 69% women, and that had relatively normal TG levels (Yokoyama 2007).

The benefit-risk profile of Vascepa demonstrated in REDUCE-IT supports icosapent ethyl 4 g/day as a beneficial treatment beyond statin treatment to reduce CV events in patients with elevated TG levels and other CV risk factors, and supports label expansion. The Sponsor is seeking an expansion of the current label to include information on CV risk reduction in an appropriate statin-treated population:

To reduce the risk of cardiovascular death, myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization as an adjunct to statin therapy in adult patients with elevated triglyceride levels (TG ≥ 135 mg/dL) and other risk factors for cardiovascular disease.

The proposed indication language was constructed to reflect the essentials of REDUCE-IT: how icosapent ethyl therapy was given (i.e., as an adjunct to statin therapy), the population studied (i.e., statin-treated with TG ≥ 135 mg/dL and other CV risk factors), and the CV events that were reduced by icosapent ethyl (i.e., CV death, MI, stroke, etc.). Such an indication is intended to summarize the REDUCE-IT findings to clinicians and patients in concise, accessible, and informative language, with an appreciation that clinicians can identify appropriate high-risk patients based on information available within the icosapent ethyl package insert and the published results of REDUCE-IT. Any such label will include additional information regarding clinical results, limitations of use, and safety, to ensure appropriate balance to support informed treatment decisions.

Approval of icosapent ethyl for CV risk reduction would increase access to this therapy and thereby provide an opportunity to lower CV risk beyond what can be achieved with LDL-C lowering therapies alone. There are approximately 5 to 15 million people in the US who meet the REDUCE-IT inclusion criteria. Based on the REDUCE-IT results, if these patients were treated with icosapent ethyl, the number of primary endpoint events could be reduced by more than 150,000 to 450,000 per year (Bhatt 2019(c); Fan 2019). Such reduction in CV events not only reduces pain and suffering, it also increases productivity. Also, the costs of treating CV events are high, particularly when including rehabilitation for patients who experience debilitating CV events such as stroke. Icosapent ethyl is cost-effective and, therefore, has the potential to lower healthcare costs. New therapy adoption requires time and education; potentially helping even a fraction of at-

risk patients like those who participated in REDUCE-IT warrants prompt approval of a CV risk reduction indication for icosapent ethyl.

Amarin is beholden to the 8175 patients who participated over multiple years in the REDUCE-IT study; it is through their contribution that we are seeking an expanded indication for icosapent ethyl. Amarin is appreciative of the review of this committee and looks forward to discussing the REDUCE-IT data and its potential to improve CV outcomes in the upcoming EMDAC meeting. Over a period of more than 10 years Amarin has successfully completed the development program for icosapent ethyl that was collaboratively designed and conducted through the SPA agreement process with the FDA. The unmet medical need is high and the REDUCE-IT results support a new therapy to address some of this need. We are seeking the support of this committee to recommend approval of icosapent ethyl for CV risk reduction so that it is readily available as an adjunct to statin therapy to help high CV risk patients.

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APPENDIX A: REDUCE-IT INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria

Patients were eligible for inclusion in the study if they met the following criteria:

1. The original protocol stipulated a lower end of qualifying fasting TG level of ≥ 135 mg/dL (1.53 mmol/L), reflecting a 10% allowance due to the variability in TG levels and a target lower end qualifying fasting TG level of ≥ 135 mg/dL¹ (1.69 mmol/L), and an upper TG level limit of < 500 mg/dL (5.64 mmol/L). Protocol Amendment 1 (16 May 2013) increased the lower end of fasting TG levels from ≥ 135 mg/dL to ≥ 200 mg/dL (2.26 mmol/L) to increase the proportion of patients enrolled with TG levels at or above 200 mg/dL.
2. LDL-C > 40 mg/dL (1.04 mmol/L) and ≤ 100 mg/dL (2.60 mmol/L) while on stable therapy with a statin (with or without ezetimibe) for at least 4 weeks prior to the LDL-C and TG baseline qualifying measurements for randomization.
 - Stable therapy was defined as the same daily dose of the same statin for at least 28 days before the lipid qualification measurements (TG and LDL-C) and, if applicable, the same daily dose of ezetimibe for at least 28 days before the lipid qualification measurements (TG and LDL-C). Patients who had their statin therapy or use of ezetimibe initiated at Visit 1, or had their statin type, statin dose, and/or ezetimibe dose changed at Visit 1, needed to go through a stabilization period of at least 28 days since initiation/change and have their qualifying lipid measurements (TG and LDL-C) after the washout period (at Visit 1.1).
 - Statins may have been administered with or without ezetimibe.

NOTE: If patients qualified at the first qualification visit (Visit 1) for TG and LDL-C, and met all other inclusion/exclusion criteria, they may have been randomized at Visit 2. If patients did not qualify at the first qualifying visit (Visit 1), a second re-qualifying visit (Visit 1.1) was allowed. For patients requiring stabilization and/or washout of medications, the second re-qualifying visit (Visit 1.1) was conducted after the stabilization/washout period.
3. Either having established CVD (per protocol “CV Risk Category 1”) or at high risk (per protocol “CV Risk Category 2”). The CV risk categories were defined as follows:
 - **“CV Risk Category 1” (Established CVD; Secondary Prevention Cohort):** defined as men and women ≥ 45 years of age with one or more of the following:
 - Documented coronary artery disease; one or more of the following primary criteria must have been satisfied:

¹ The protocol specified TG levels of ≥ 150 mg/dL with an allowed 10% variance. Thus, subjects with TG levels ≥ 135 mg/dL were enrolled.

- Documented multi-vessel coronary artery disease ($\geq 50\%$ stenosis in at least two major epicardial coronary arteries, with or without antecedent revascularization).
- Documented prior myocardial infarction.
- Hospitalization for high-risk non-ST-segment elevation acute coronary syndrome, with objective evidence of ischemia: ST-segment deviation or biomarker positivity.
- Documented cerebrovascular or carotid disease; one of the following primary criteria must have been satisfied:
 - Documented prior ischemic stroke.
 - Symptomatic carotid artery disease with $\geq 50\%$ carotid arterial stenosis.
 - Asymptomatic carotid artery disease with $\geq 70\%$ carotid arterial stenosis per angiography or duplex ultrasound.
 - History of carotid revascularization (catheter-based or surgical).
- Documented peripheral arterial disease; one or more of the following primary criteria must have been satisfied:
 - Ankle brachial index < 0.9 with symptoms of intermittent claudication.
 - History of aorto-iliac or peripheral arterial intervention (catheter-based or surgical).
- **“CV Risk Category 2” (High-Risk; Primary Prevention Cohort):** defined as patients with:
 - Diabetes mellitus (Type 1 or Type 2) requiring treatment with medication.
 - Men and women ≥ 50 years of age.
 - One or more of the following at Visit 1 (additional risk factor for CVD):
 - Men ≥ 55 years of age or women ≥ 65 years of age.
 - Cigarette smoker or stopped smoking within 3 months before Visit 1.
 - Hypertension (blood pressure ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic) or on antihypertensive medication.
 - HDL-C ≤ 40 mg/dL for men or ≤ 50 mg/dL for women.
 - hsCRP > 3.00 mg/L (0.3 mg/dL).
 - Renal dysfunction: creatinine clearance > 30 and < 60 mL/min (> 0.50 and < 1.00 mL/sec).
 - Retinopathy, defined as any of the following: non-proliferative retinopathy, pre-proliferative retinopathy, proliferative retinopathy, maculopathy, advanced diabetic eye disease, or a history of photocoagulation.
 - Micro- or macroalbuminuria. Microalbuminuria was defined as either a positive Micral or other strip test (may have been obtained from medical records), an albumin/creatinine ratio ≥ 2.5 mg/mmol or an albumin excretion rate on timed collection ≥ 20 mg/min all on at least two successive occasions; macroalbuminuria, defined as Albustix or other dipstick evidence of gross proteinuria, an

albumin/creatinine ratio ≥ 25 mg/mmol or an albumin excretion rate on timed collection ≥ 200 mg/min all on at least two successive occasions.

- Ankle brachial index < 0.9 without symptoms of intermittent claudication (patients with ankle brachial index < 0.9 with symptoms of intermittent claudication were included in CV Risk Category 1).

Note: Patients with diabetes and CVD, as defined above, were eligible, based on the CVD requirements and were to be included in CV Risk Category 1. Only patients with diabetes and no documented CVD, as defined above, required at least one additional risk factor as listed, and were to be included in CV Risk Category 2.

4. Women were required to meet all 3 of the following criteria:
 - Not pregnant.
 - Not breastfeeding.
 - Not planning on becoming pregnant during the study.
5. Women of child-bearing potential were required to have a negative urine pregnancy test before randomization. Women were to be considered not of child-bearing potential if they met one of the following criteria, as documented by the Investigator:
 - Had a hysterectomy, tubal ligation or bilateral oophorectomy prior to signing the informed consent form.
 - Were post-menopausal, defined as ≥ 1 year since their last menstrual period or had a follicle-stimulating hormone level in a menopausal range.
6. Women of child-bearing potential were required to agree to use an acceptable method of avoiding pregnancy from Screening to the end of the study, unless their sexual partner(s) was/were surgically sterile or the woman was abstinent.
7. Understood the study procedures, was willing to adhere to the study schedules, and agreed to participate in the study by giving informed consent prior to screening.
8. Agreed to follow and maintain a physician recommended diet through the duration of the study.

Exclusion Criteria

Patients were to be excluded from the study if they met any of the following criteria:

1. Severe (New York Heart Association class IV) heart failure.
2. Any life-threatening disease expected to result in death within the next 2 years (other than CVD).
3. Active severe liver disease (evaluated at Visit 1): cirrhosis, active hepatitis, alanine aminotransferase or aspartate aminotransferase $> 3 \times$ the upper limit of normal, or biliary obstruction with hyperbilirubinemia (total bilirubin $> 2 \times$ upper limit of normal).
4. Glycated hemoglobin $> 10.0\%$ (or > 86 mmol/mol International Federation of Clinical Chemistry units) at Screening (Visit 1). If patients failed this criterion at Visit 1, they may have had their antidiabetic therapy optimized and been retested at Visit 1.1.

5. Poorly controlled hypertension: blood pressure ≥ 200 systolic mmHg or ≥ 100 mmHg diastolic (despite antihypertensive therapy).
6. Planned coronary intervention (such as stent placement or heart bypass) or any non-cardiac major surgical procedure. Patients may have been (re)evaluated for participation in the study (starting with Visit 1.1) after their recovery from the intervention/surgery.
7. Known familial lipoprotein lipase deficiency (Fredrickson Type 1), apolipoprotein C-II deficiency, or familial dysbetalipoproteinemia (Fredrickson Type 3).
8. Participation in another clinical study involving an investigational agent within 90 days prior to Screening (Visit 1). Patients were not to participate in any other investigational medication or medical device study while participating in this study. (Participation in a registry or observational study without an additional therapeutic intervention was allowed.)
9. Intolerance or hypersensitivity to statin therapy.
10. Known hypersensitivity to any ingredients of the study product or placebo (Protocol Amendment 2); known hypersensitivity to fish and/or shellfish.
11. History of acute or chronic pancreatitis.
12. Malabsorption syndrome and/or chronic diarrhea (Note: patients who underwent gastric/intestinal bypass surgery were considered to have malabsorption and were not eligible; patients who underwent gastric banding were eligible).
13. Non-study drug-related, non-statin, lipid-altering medications, supplements or foods:
 - Patients were excluded if they received niacin >200 mg/day or fibrates during screening (after Visit 1) and/or planned to receive them during the study; patients who were taking niacin >200 mg/day or fibrates during the last 28 days before Visit 1 were required to have a washout of at least 28 days after their last use and have their qualifying lipids measured (TG and LDL-C) after the washout period (Visit 1.1).
 - Patients were excluded if they received any omega-3 fatty acid medications (prescription medicines containing EPA and/or DHA) during screening (after Visit 1) and/or planned to receive during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who received omega-3 fatty acid medications during the last 28 days before Visit 1 (except patients in the Netherlands) were required to have a washout period of at least 28 days after their last use and have their qualifying lipids measured (TG and LDL-C) after the washout period (at Visit 1.1).
 - Note for patients in the Netherlands only: patients being treated with omega-3 fatty acid medications containing EPA and/or DHA were excluded; no washout was allowed.
 - Patients were excluded if they used dietary supplements containing omega-3 fatty acids (e.g., flaxseed, fish, krill, or algal oils) during the screening period (after Visit 1) and/or planned to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who were taking >300 mg/day omega-3 fatty acids (combined amount of EPA and DHA) within 28 days before Visit 1 (except patients in the

Netherlands) were required to have a washout period of at least 28 days since their last use and have their qualifying lipid measurements (TG and LDL-C) after the washout period (at Visit 1.1).

- Note for patients in the Netherlands only: patients being treated with dietary supplements containing omega-3 fatty acids of >300 mg/day EPA and/or DHA were excluded; no washout was allowed.
- Patients were excluded if they used bile acid sequestrants during the screening period (after Visit 1) and/or planned to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who were taking bile acid sequestrants within 7 days before Visit 1, were required to have a washout period of at least 7 days since their last use and have their qualifying lipid measurements (TG and LDL-C) after the washout period (at Visit 1.1).
- Patients were excluded if they used proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors during the screening period (after Visit 1) and/or planned to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients could not have taken a PCSK9 inhibitor within 90 days prior to their screening visit.

14. Other medications (not indicated for lipid alteration):

- Treatment with tamoxifen, estrogens, progestins, thyroid hormone therapy, systemic corticosteroids (local, topical, inhalation, or nasal corticosteroids were allowed), or human immunodeficiency virus-protease inhibitors that were not stable for ≥ 28 days prior to the qualifying lipid measurements (TG and LDL-C) during screening. To be eligible for participation in the study, patients who were not taking a stable dose of these medications within 28 days before Visit 1 were required to have a stabilization period of at least 28 days since their last dose change and have their qualifying lipid measurements (TG and LDL-C) after the washout period (at Visit 1.1).
- Patients were excluded if they used cyclophosphamide or systemic retinoids during screening (after Visit 1) and/or planned to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who were taking these medications within 28 days before Visit 1 were required to have a washout period of at least 28 days since their last use and have their qualifying lipid measurements (TG and LDL-C) after the washout period (at Visit 1.1).

15. Known to have acquired immunodeficiency syndrome; patients who were human immunodeficiency virus-positive without acquired immunodeficiency syndrome were allowed.

16. Requirement for peritoneal dialysis or hemodialysis for renal insufficiency or creatinine clearance < 30 mL/min (0.50 mL/sec).

17. Unexplained creatine kinase concentration $> 5 \times$ upper limit of normal or creatine kinase elevation due to known muscle disease (e.g., polymyositis, mitochondrial dysfunction) at Visit 1.

18. Any condition or therapy that, in the opinion of the Investigator, might have posed a risk to the patient or made participation in the study not in the patient's best interest.
19. Drug or alcohol abuse within the previous 6 months, and unable/unwilling to abstain from drug abuse and excessive alcohol consumption during the study or drinking 5 units or more for men or 4 units or more for women in any one hour (episodic excessive drinking or binge drinking). Excessive alcohol consumption was defined on average of >2 units of alcohol per day. A unit of alcohol was defined as a 12-ounce (350 mL) beer, 5-ounce (150 mL) wine, or 1.5-ounce (45 mL) of 80-proof alcohol for drinks.
20. Mental/psychological impairment or any other reason to expect patient difficulty in complying with the requirements of the study or understanding the goal and potential risks of participating in the study (evaluated at Visit 1).

APPENDIX B: CLINICAL ENDPOINT COMMITTEE (CEC): ADJUDICATION PROCESS AND CLINICAL EVENTS DEFINITIONS

Adjudication Process

The CEC was responsible for adjudicating the primary, secondary, and tertiary efficacy outcome events as defined in the CEC Charter. Investigator-reported potential clinical endpoints were automatically imported for adjudication into an IBM Watson Health (formerly Merge Healthcare) database. For the adjudication process, the contract research organization Endpoint Management team created complete electronic packets with required documents from all available records related to the event. All source documents were blinded of all patient identifiers. Each adjudication packet underwent initial medical review by the CEC to determine if sufficient information was available from source documentation to allow for adjudication. Requests for additional documentation were directed to staff at the contract research organization Endpoint Management team, who sought to resolve any deficiency to the best of the Investigator's ability.

Each packet identified, by medical review, as ready for assessment was assigned to two physicians on the CEC for adjudication. The physician reviewers independently reviewed the cases assigned to them. If both adjudicators agreed, the event adjudication was considered complete and the adjudication results were entered into the appropriate Adjudicator electronic case report form by the CEC member. If there was a discrepancy in event adjudication between the physician reviewers, the reviewers discussed the case until they reached consensus or agreed that they were unable to reach final consensus. If consensus was reached, the final event adjudication was entered into the appropriate Adjudicator electronic case report form, reflecting this consensus. If consensus could not be reached, the case was presented to the CEC Chairman for review. The Chairman then completed an independent review of the adjudication package and the Chairman's decision was the final determination. His/her adjudication was entered into the appropriate Adjudicator electronic case report form.

Two cardiologists reviewed all CV events and all deaths, with the exception of death due to stroke. One cardiologist and one neurologist reviewed all cerebrovascular events, including deaths due to stroke.

All adjudications were documented, within the event review packet, with respect to the supporting endpoint criteria that were met. For cases that set precedence, details were recorded in a working conventions guide for reviewers.

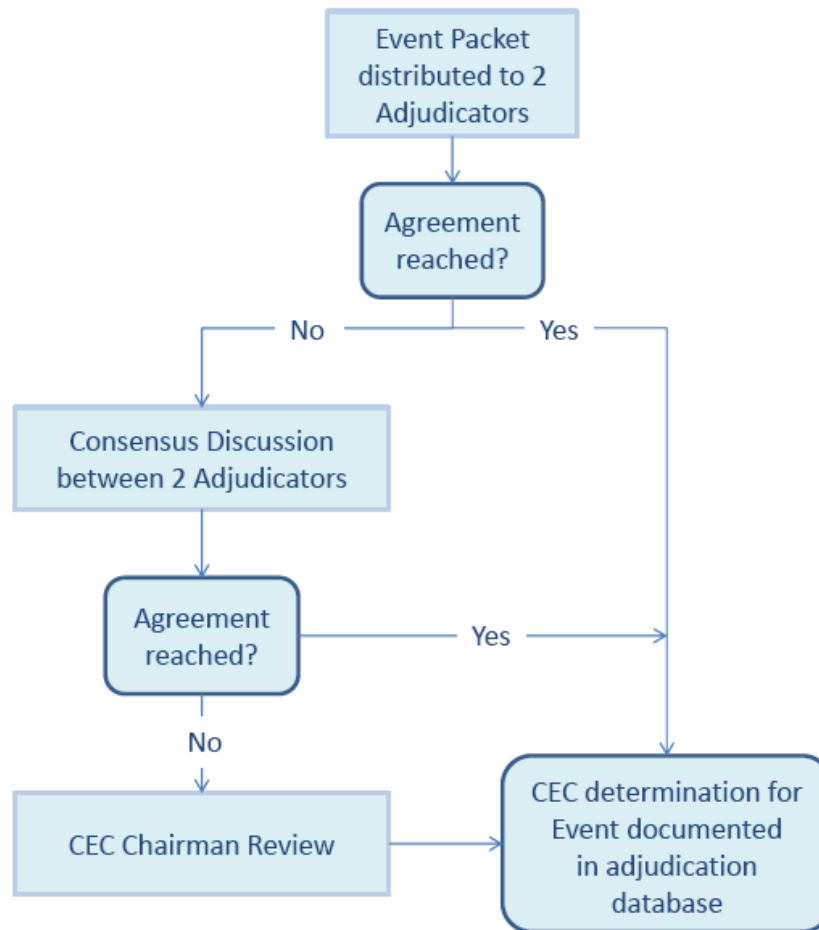
All ECGs obtained during the study were to be sent to the CEC for review and assessment of potential silent MI. As outlined in the CEC Charter Section 4.5, each ECG was read by one of the cardiologists on the CEC (designated as ECG reviewers) for evidence of pathologic Q-waves. If such Q-waves were found, that ECG reviewer then reviewed all of the patient's prior ECGs (beginning with the baseline visit in this study). If no prior evidence of such pathologic Q-waves was observed, then this ECG was flagged as indicative of new silent MI. For a new silent MI to be counted, the pathologic Q-waves needed to be present on the patient's final ECG in study.

ECGs meeting those criteria (potential silent MI with manifestation on the patient's final ECG in the study) were then submitted for adjudication using the standard adjudication process. Two cardiologist adjudicators then reviewed those cases to rule out clinical (symptomatic)

manifestation of MI within the 1 year prior to the patient's first ECG indicative of potential silent MI. If no clinical manifestation of MI was present within that 1-year period prior to the patient's first ECG indicative of potential silent MI, then the CEC adjudicators would confirm the silent MI designation. The onset date for positively adjudicated silent MIs correspond to the date of the first (post-baseline) visit with the confirmed pathologic Q-waves.

The CEC endpoint adjudication process is presented in the [Figure 12](#).

Figure 12. Clinical Endpoint Committee Adjudication Process



Abbreviations: CEC = Clinical Endpoint Committee.

Clinical Endpoint Definitions

Clinical endpoint definitions can be found within the REDUCE-IT protocol provided in the Supplementary Materials associated with the primary results publication in the New England Journal of Medicine (Bhatt 2019(a)).

APPENDIX C: VASCEPA (ICOSAPENT ETHYL) CAPSULES REGULATORY HISTORY WITH FDA

Key Dates and Documents

Date	Occurrence
07-14-2008	Pre-Investigational New Drug (IND)/End-of-Phase 2 meeting with the Division
01-16-2009	Amarin submits request for an SPA review for the MARINE study
03-19-2009	Amarin submits request for an SPA review for the ANCHOR study
05-01-2009	Amarin and the Division enter into an SPA agreement for the MARINE study
07-06-2009	Amarin and the Division enter into an SPA agreement for the ANCHOR study
11-11-2010	Amarin submits request for an SPA review for the REDUCE-IT study
04-13-2011	Type A meeting with the Division to discuss the design of the REDUCE-IT outcomes study
08-05-2011	Amarin and the Division enter into an SPA agreement for the REDUCE-IT study
09-25-2011	Amarin submits NDA 202057 for FDA review; NDA contains data for both MARINE and ANCHOR studies
11-21-2011	First patient screened in REDUCE-IT
11-28-2011	First patient randomized in REDUCE-IT
12-08-2011	FDA issues Day 74 letter accepting NDA 202057 for review
07-26-2012	Amarin receives approval for NDA 202057 based on MARINE efficacy plus ANCHOR and MARINE safety findings
02-21-2013	Amarin submits ANCHOR sNDA (S-005) after reaching 50% enrollment of the patients in the REDUCE-IT CV outcomes study
05-01-2013	FDA issues Day 74 letter accepting the sNDA application for the Vascepa “ANCHOR indication,” without reference to issues with prior trials, or any reference to a new substantial scientific issue that raises a public health concern pertaining to the indication being sought in the sNDA
05-16-2013	REDUCE-IT protocol amendment 1 SPA re-agreement with FDA and finalized/signed
10-16-2013	The Division holds an advisory committee meeting with the EMDAC. EMDAC voted 9-2 against approval based on the following question: “Taking into account the described efficacy and safety data for Vascepa, do you believe that its effects on the described lipid/lipoprotein parameters are sufficient to grant approval for co-administration with statin therapy for the treatment of patients with mixed dyslipidemia and coronary heart disease (CHD) or CHD risk equivalent prior to the completion of REDUCE-IT?”
10-29-2013	The Division rescinds the ANCHOR SPA Agreement because “the results from the ACCORD-Lipid and AIM-HIGH trials, as well as the publicly presented results from the HPS2-THRIVE trial [fenofibrate and niacin products], fail to support the hypothesis that a triglyceride-lowering drug significantly reduces the risk for cardiovascular events among statin-treated patients.”
04-27-2015	Amarin received Complete Response letter in response to the ANCHOR sNDA noting that “Given the current level of uncertainty regarding the benefits of drug-induced changes in lipid/lipoprotein parameters on CV risk among statin-treated patients with residually high TG (200-499 mg/dL), you will need to provide evidence that Vascepa reduces the risk of major adverse CV events in patients at high risk for cardiovascular disease, at LDL-C goal on statin therapy, with residually high TG. We anticipate that the final results from the REDUCE-IT trial could be submitted to satisfy this deficiency.”
03-01-2016	CEC charter v1 submitted to FDA (email)
06-29-2016	REDUCE-IT protocol amendment 2 SPA re-agreement with FDA
07-08-2016	REDUCE-IT protocol amendment 2 finalized/signed
07-08-2016	REDUCE-IT SAP finalized

08-04-2016	Last patient in REDUCE-IT randomized
09-09-2016	First REDUCE-IT DMC interim efficacy review
08-09-2017	Final signed REDUCE-IT CEC charter v2
08-11-2017	Second REDUCE-IT DMC interim efficacy review
03-07-2018	Pre-sNDA meeting between Amarin and FDA to discuss REDUCE-IT sNDA
05-31-2018	Last REDUCE-IT patient last visit
08-15-2018	REDUCE-IT statistical analysis plan addendum finalization
09-06-2018	REDUCE-IT study database lock
09-06-2018	REDUCE-IT study database unblinding
09-25-2019	REDUCE-IT topline results press release submitted to FDA
03-28-2019	REDUCE-IT sNDA submitted to FDA
05-24-2019	FDA issues Day 60 Filing Communication letter accepting the REDUCE-IT sNDA application for the Vascepa CV risk reduction indication without reference to issues with the placebo or trial conduct, or any reference to a new substantial scientific issue that raises a public health concern pertaining to the indication being sought in the sNDA. Priority review granted with a 09-28-2019 Prescription Drug User Fee Act (PDUFA) goal date.
08-08-2019	FDA issues notice to Amarin that it plans to hold an advisory committee meeting, tentatively scheduled for 11-14-2019 (after the PDUFA date), in connection with its review of the sNDA
09-11-2019	Review Extension – Efficacy Supplement Major Amendment letter received from FDA extending the user fee goal date from 09-28-2019 to 12-28-2019 in response to Sponsor's request for clarity on PDUFA date
11-14-2019	REDUCE-IT Endocrinologic and Metabolic Drug Advisory Committee meeting
12-28-2019	Extended PDUFA goal date

I. Phase 3 clinical studies of Vascepa and FDA review leading up to REDUCE-IT

1. The Division of Metabolism and Endocrinology Products of FDA (DMEP or the Division) approved Vascepa for use as a treatment in adults with very high (≥ 500 mg/dL) TG levels in July 2012. Patients with very high, also known as severe, HGT are at increased risk of pancreatitis, the primary clinical treatment concern, and secondarily, CVD. Roughly two to three million adults in the US have very high TG levels.

2. Division approval of Vascepa is based primarily on the successful results from the MARINE study of Vascepa in the approved patient population. In considering this approval, the Division also reviewed the successful results from the ANCHOR study of Vascepa. ANCHOR safety data is reflected in current Vascepa labeling.

3. Amarin sought a label expansion from the Division for Vascepa efficacy data in 2013 but was denied in 2015. ANCHOR efficacy data is not in Vascepa labeling.

4. ANCHOR assessed Vascepa use in patients with high TG levels (≥ 200 mg/dL and < 500 mg/dL) who were also on statin therapy for elevated LDL-C levels, which condition is referred to as mixed dyslipidemia or persistent high TGs. It is estimated that over 25 million adults in the US have elevated TG levels ≥ 200 mg/dL and that more than 50 million adults in the US have elevated TG levels ≥ 150 mg/dL.

5. The ANCHOR study met all primary and secondary endpoints. The EMDAC that assessed the clinical trial in October 2013 acknowledged the clinical success of the ANCHOR trial, as did the Division. However, based on a supporting 9-2 vote of the EMDAC convened in 2013,

the Division rescinded an agreement with Amarin to approve expansion of an indication based on the TG-lowering effect demonstrated in the ANCHOR study. It was determined that the proposed TG-lowering indication was targeted, ostensibly, to reduce CV risk reduction in patients studied in ANCHOR (with persistent high TGs) (as opposed to pancreatitis risk, which was the focus in MARINE). The Division determined that a substantial scientific issue essential to determining the effectiveness of Vascepa in the studied population was identified after testing began. Specifically, after prior agreement to use TG-lowering as a surrogate for CV risk reduction in the studied patient population, the Division determined the following:

“the results from the ACCORD-Lipid and AIM-HIGH trials, as well as the publicly presented results from the HPS2-THRIVE trial [fenofibrate and niacin products], fail to support the hypothesis that a triglyceride-lowering drug significantly reduces the risk for cardiovascular events among statin-treated patients.”

6. Accordingly, the Division communicated to Amarin in a complete response letter in April 2015 that there were insufficient data to conclude that drug-induced changes in serum TGs demonstrated in ANCHOR could be recognized by the FDA as a valid surrogate for the purpose of regulatory approval of a drug targeted at CV risk reduction by virtue of lowering TG levels in the studied patient population. The Division’s review and analysis of final positive results from the REDUCE-IT CV outcomes were thus cited in the complete response letter to Amarin as the best path to an FDA-approved label expansion for Vascepa beyond the MARINE population:

“Given the current level of uncertainty regarding the benefits of drug-induced changes in lipid/lipoprotein parameters on CV risk among statin-treated patients with residually high TG (200-499 mg/dL), you will need to provide evidence that Vascepa reduces the risk of major adverse CV events in patients at high risk for cardiovascular disease, at LDL-C goal on statin therapy, with residually high TG. We anticipate that the final results from the REDUCE-IT trial could be submitted to satisfy this deficiency.”

II. The Examination of Mineral Oil Placebo from Prior FDA Reviews of Vascepa

7. The same placebo, comprised of light liquid paraffin oil, or mineral oil, was agreed with the Division and used in each of the MARINE, ANCHOR and REDUCE-IT clinical trials of Vascepa. Mineral oil was selected as the appropriate placebo to mimic the color and consistency of Vascepa. No suitable other option existed for choice of placebo; sugar, corn oil and olive oil would all have been detected as being different in color, taste, odor or texture. Evidence continues to support that the use of mineral oil in REDUCE-IT was inert and did not impact the successful results of the study (see [Appendix D](#) for Control Group Response Analysis).

Examination of mineral oil placebo in MARINE

8. As noted, the Division approval of Vascepa in 2012 was based on both the MARINE and ANCHOR trials for consistency of results and review of safety data. Consideration of external data regarding characteristics of mineral oil was also assessed by the Division before its approval. An overview of FDA assessment of MARINE clinical data was provided by the

Division as follows in connection with its review of ANCHOR data (Note: AMR101 research code identifier for Vascepa that is used within clinical studies):

“During the review of the MARINE data, the Division noted that several lipid parameters (including TG) increased from baseline to week 12 in the placebo group, treated with mineral oil. The available literature regarding potential effects of mineral oil was considered. Similar increases in TG levels observed in the placebo groups from the Lovaza (omega-3 EE) clinical trials of hypertriglyceridemic patients were noted, and these trials did not use a mineral oil placebo. Because no strong evidence for biological activity of mineral oil was identified, ultimately it was concluded that the between-group differences likely provided the most appropriate descriptions of the treatment effect of AMR101 and that whatever factor(s) led to the within-group changes over time in the placebo group were likely randomly distributed to all treatment groups. Taken together, along with the statistical robustness in primary and sensitivity analyses of AMR101 4g/day on TG lowering, the Division concluded that AMR101 4g/day is an effective TG-lowering agent for patients with severe hypertriglyceridemia. AMR101 was approved for the following treatment indication on July 26, 2012: Treatment of Severe Hypertriglyceridemia VASCEPA™ (icosapent ethyl) is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia.”

Examination of mineral oil placebo in ANCHOR

9. During the October 16, 2013 EMDAC meeting held by the Division as part of its review of the ANCHOR sNDA, a discussion was held regarding observed, nominally statistically significant changes in the placebo group from baseline of certain lipid parameters in an adverse direction, while on background statin therapy. The discussion was based on questions raised by the Division in FDA’s briefing book and at the meeting about the possibility that the mineral oil placebo in the ANCHOR trial (the same as that used in MARINE and then at use in the REDUCE-IT trial) might not be biologically inert and might be viewed as artificially exaggerating the clinical effect of Vascepa when measured against placebo in the ANCHOR trial.

10. It was ultimately concluded by the EMDAC and the Division that the between-group differences likely provided the most appropriate descriptions of the treatment effect of Vascepa and that whatever factor(s) led to the within-group changes over time in the placebo group were likely randomly distributed to all treatment groups.

11. In the April 2015 complete response letter from the Division issued in connection with the Amarin sNDA related to the ANCHOR study, there was no suggestion by the Division of a concern with the mineral oil placebo being biologically active or interfering with the statin-treated patient population in the ANCHOR study. From May 2015 through March 2016, in connection with litigation in federal court between Amarin and FDA and a related settlement agreement that ultimately allowed Amarin to promote the results of the ANCHOR study to doctors, FDA did not dispute the veracity of the ANCHOR trial data or seek to require that Amarin include any qualification related to the mineral oil placebo in promotional materials reflecting ANCHOR data.

Examination of mineral oil placebo in connection with the REDUCE-IT SPA agreement and FDA's continual monitoring of the study

12. On August 5, 2011, Amarin entered into an SPA agreement with the Division for REDUCE-IT that covered the clinical trial and placebo among other matters.

13. Early in the course of the REDUCE-IT trial, the Division directed the DMC for REDUCE-IT to periodically review unblinded lipid data to monitor for signals that the placebo might not be inert. Over several years, after each quarterly unblinded safety analysis and review meeting, the DMC recommended to continue the REDUCE-IT study as planned without modification. Each of these DMC recommendations was shared with the Division. Amarin was blinded to such analyses during the study. The DMC summary within their final closed session meeting minutes reflect that the biomarker changes observed within the REDUCE-IT placebo group cannot explain the “very potent and consistent [REDUCE-IT] results”, which support that icosapent ethyl “provides novel and important value over and above standard and even aggressive lipid management”.

14. In August 2016, Amarin announced an amendment to the REDUCE-IT SPA agreement with the Division that reaffirmed the Division's concurrence on key elements of REDUCE-IT. In this amended REDUCE-IT SPA agreement, the Division agreed that, based on the information submitted to the agency, the critical elements of the revised REDUCE-IT protocol and analysis plans adequately address the objectives necessary to support a regulatory submission. In this August 2016 re-agreement of the SPA for REDUCE-IT, the Division expressed no concerns to Amarin about the use of mineral oil in REDUCE-IT. Key new elements of that amendment included matters as detailed as the following:

- Finalization of details of the statistical analysis plan covering both final and interim efficacy analyses;
- Addition of a second prespecified interim efficacy analysis at approximately 80% of the 1,612 primary CV events targeted for completion of the study without mandatory study stopping rules; and
- Expansion to over 30 the number of prespecified secondary and tertiary endpoints in an effort to more fully capture the broad potential clinical effects of Vascepa and the diversity of the patient population being studied.

APPENDIX D: CONTROL GROUP RESPONSE ANALYSES

Executive Summary

The selection of an appropriate placebo for use in the study of icosapent ethyl was thoroughly examined before and after each Phase 3 icosapent ethyl clinical trial, including within the SPA processes for each study and at the FDA advisory committee review of the ANCHOR study results in October 2013 ([Appendix C](#)). The same placebo comprised of light liquid paraffin oil (pharmaceutical grade mineral oil) was proposed and accepted, examined and selected again as the best choice to mimic the color and consistency of icosapent ethyl, and because light mineral oil is not extensively absorbed and not known to interact with the absorption or activity of drugs based on literature review and preclinical and clinical data. Mineral oil has been used as a laxative at high doses (typically 15–30 g/day) for over 100 years, including extensive use in pediatric populations. The safety of mineral oil is generally inferred from a long history of use with limited adverse effects. Some parties have raised questions regarding the relatively small biomarker changes in the placebo group of REDUCE-IT and speculated if light mineral oil may have influenced these changes, and thus resulted in an overestimation of the treatment effect observed in REDUCE-IT.

Per design as a CV outcomes study, REDUCE-IT hierarchical primary and secondary analyses focused on CV events, with biomarkers collected as single measures with large spans of time between measurements to support tertiary, exploratory, and *post hoc* analyses. The design of REDUCE-IT recognized that the reported clinical effects of icosapent ethyl extend beyond lipid modification and therefore, were not expected to be defined by changes within specific biomarkers. Amarin completed the studies defined within the FDA-agreed development program for icosapent ethyl, including the REDUCE-IT study, and conducted a series of *post hoc* analyses to explore a potential mineral oil effect (or lack thereof) within REDUCE-IT. The supposition that the light mineral oil used in REDUCE-IT does not exert clinically meaningful effects on medication (including statin) efficacy or absorption, biomarkers, outcomes, or safety, agrees with conclusions from prior FDA reviews. It is also supported by multiple lines of evidence including observed event rate agreement with REDUCE-IT design predictions, extensive literature reviews (EPA mechanisms of action, mineral oil, and impact of biomarker changes on CV risk), Amarin nonclinical and clinical studies, independent REDUCE-IT DMC review, and observed event rate and biomarker comparisons with statin-treated patients across other CV outcome studies. This supposition is also supported by *post hoc* REDUCE-IT data analyses (e.g., off drug, statin type, regression to the mean, diarrhea, lack of correlation between placebo biomarker changes and outcomes, and biomarker covariate-adjusted analyses). Contrary to the lack of evidence for a hypothetical placebo impact on CV risk, a range of clinical and preclinical studies provide data supporting cardioprotective effects of EPA ([Appendix E](#)). While based on these various sources of evidence we do not agree that placebo influenced the REDUCE-IT results, even if we are wrong, such potential influence cannot reasonably be estimated to account for a substantial portion of overall robust and consistent REDUCE-IT findings, including a 25% RRR in the primary endpoint that is consistent with the observed risk reduction in the JELIS study, which did not administer a mineral oil placebo. Taken together, these various analyses and comparisons are inconsistent with a placebo-mediated effect significantly overestimating the REDUCE-IT results, but rather support a conclusion that icosapent ethyl provided substantial and consistent risk reduction in statin-treated patients.

Introduction and Background

Biomarker Considerations

CV outcomes may or may not correlate with therapeutically modified biomarker changes and therefore, CV outcomes studies such as REDUCE-IT are needed for unequivocal demonstration of CV benefit for individual therapies. The REDUCE-IT protocol was design to test the CV benefit of icosapent ethyl in high-risk patients, and did not include biomarkers within the primary or secondary endpoint definitions, per FDA and Sponsor discussions that biomarkers were considered of peripheral value for interpretation of outcomes effects. Therefore, biomarkers in REDUCE-IT were collected as single measures with large spans of time between measurements to support tertiary, exploratory, and *post hoc* analyses, but are insufficient to support conclusive interpretation of the prespecified primary or secondary outcome measures. Had REDUCE-IT been a biomarker-focused trial, such as the previous MARINE and ANCHOR studies, more frequent biomarker sampling would have been performed with replicate measurements. This is because biomarkers have inherent variability and the precision of individual timepoint measures are diminished with infrequent and singular measurements. This is particularly true for patients with elevated TG levels, for whom such variability extends to biomarkers beyond TG. For example, intra-individual LDL-C levels can vary in healthy adults by approximately 2% to 12% (Demacker 1982; Hegsted 1987; Mjøs 1979; Shumak 1993; Speechley 1995; Takahashi 2010; Tolonen 2005), and patients with elevated TG levels have even larger LDL-C variability, such as the 23% to 29% variability in LDL-C observed in the AFCAPS/TexCAPS study (Clearfield 2002). Even greater fluctuations are possible within individual patients, on the order of several-fold increases (Reed 2000; Sathyapalan 2008; Sathyapalan 2010). These LDL-C increases despite statin stabilization have been postulated to be due to a number of possible factors including a decrease in patient drug and life style compliance with time, physiological compensation mechanisms whereby the body attempts to counteract a statin-induced decrease in cholesterol (known as, physiological escape phenomenon), regression to the mean (particularly in studies with low baseline LDL-C), and increased intra-individual variability with time.

Accordingly, for trials in which biomarkers are a primary focus, study designs incorporate replicate measures that are collected in close proximity, supporting a more representative averaged biomarker estimate for each timepoint (e.g., multiple measures for baseline or in-study timepoints). Therefore, caution should be used in interpreting relatively small differences in biomarkers that fall within the range of intra-patient variability noted above, for both within-group and between-group comparisons. Other likely confounders, such as regression to the mean, were anticipated during early FDA review and discussion of REDUCE-IT design, which influenced the exclusion of biomarker analyses from the prespecified hierarchical primary and secondary endpoint analyses.

Mineral Oil as Placebo

Light mineral oil was chosen as placebo to mimic the colorless icosapent ethyl capsules to ensure appropriate blinding, and because extensive literature reviews and preclinical and clinical data suggest that light mineral oil is not extensively absorbed and not known to interact with the absorption or activity of drugs, including statins. Mineral oil has been used as a laxative at high doses (typically 15–30 g/day) for over 100 years, including extensive use in pediatric populations. The safety of mineral oil is generally inferred from a long history of use with limited adverse effects.

Speculation has been made regarding the appropriateness of mineral oil as an inactive placebo based on small changes observed in some, but not all, biomarkers in the MARINE and ANCHOR studies, which included the same 4 g/day light mineral oil placebo. These findings were reviewed by FDA and discussed at an Advisory Committee meeting in 2013. In the FDA briefing book for the 2013 ANCHOR EMDAC meeting, FDA summarized its assessment of MARINE and mineral oil as placebo by stating that "[b]ecause no strong evidence for biological activity of mineral oil was identified, ultimately it was concluded that the between-group differences likely provided the most appropriate descriptions of the treatment effect of [icosapent ethyl] and that whatever factor(s) led to the within-group changes over time in the placebo group were likely randomly distributed to all treatment groups." Based on the MARINE and ANCHOR studies, the FDA concluded that icosapent ethyl 4g/day is an effective TG-lowering agent for patients with severe hypertriglyceridemia. In addition, in the April 27, 2015 complete response letter to the Sponsor, FDA did not cite any concern with respect to the reliability of the clinical results from the ANCHOR clinical study.

Mineral Oil

Mineral Oil Quality and Characteristics

Based on general safety and toxicology, in 2015 the European Commission amended European Union regulations to add pharmaceutical grade mineral oils to the list of substances/active ingredients that do not pose a risk ("Annex IV" of Directive No. 396/2005; "Annex IV" amendment through Directive No. 2015/1608) if they meet the high standards of pharmaceutical compendia (United States Pharmacopeia [USP], European Pharmacopeia [Ph. Eur.], etc.).

The light mineral oil used in the Sponsor's nonclinical and clinical studies, including REDUCE-IT, is a pharmaceutical grade light mineral oil that meets pharmaceutical compendia standards, and consists of a mixture of straight chain saturated hydrocarbons ranging approximately from 16 to 24 carbons ([Table 16](#)). The placebo capsule fill consisted only of light mineral oil with 0.2% alpha tocopherol added for similarity to icosapent ethyl capsules. No emulsifying agent or surfactant was added to the capsule fill. The placebo capsule formulation listed in the table below has been the same across the SPA-agreed development program, including the previously completed and reviewed MARINE and ANCHOR studies ([Appendix C](#)).

The placebo material used in REDUCE-IT is purified by the supplier/manufacturer to meet the standards of the USP and Ph. Eur., and the requirements of regional health authorities, including FDA. The material is virtually free of all aromatic hydrocarbons, unsaturated hydrocarbons, and other related impurities, and is manufactured and packaged under cGMP. These processes and standards differ substantially from those applying to lesser technical or food grade mineral oils (21 US CFR 178.3620).

Table 16. Placebo Capsule Formulation

Component	Unit Quantity mg/capsule	Function	Reference to Standard
Capsule Fill			
Light Mineral Oil (Paraffin, light liquid)	932 ¹	Filler	NF, Ph. Eur.
All-rac- α -tocopherol	1.86	Antioxidant	USP, Ph. Eur.
Capsule Shell^[1]			
Gelatin	285	Capsule shell material	NF, Ph. Eur.
Noncrystallizing Sorbitol Solution (Sorbitol Liquid, Non-Crystallizing)	80	Plasticizer	NF, Ph. Eur.
Glycerin (Glycerol)	45	Plasticizer	USP, Ph. Eur.
Purified Water	38	Solvent	USP, Ph. Eur.
Maltitol Solution	29	Plasticizer	NF, Ph. Eur.

For the Placebo Capsules, ethyl-EPA is replaced with Light Mineral Oil such that the volumes are the same.

¹ Capsule shell quantities represent a nominal "dry shell" formula weight containing approximately 8% water, and is identical to the shell formula used for icosapent ethyl drug product.

Abbreviations: NF = National Formulary; Ph. Eur. = European Pharmacopeia; USP = United States Pharmacopeia.

Mineral Oil Literature Review

Literature reviews support the conclusion that light mineral oil does not exert clinically meaningful effects on medication (including statin) or nutrient absorption or efficacy, changes in lipids or other biomarkers, or changes in patient safety. Of note, there are critical distinctions between the pharmaceutical grade light mineral oil utilized in REDUCE-IT versus technical/industrial grade mineral oils, and such distinctions are important when determining relevant available data.

Literature searches found no clear clinical evidence for direct effects, or possible inhibition of medication absorption or efficacy, including statins. Clinical studies show no consistent or conclusive changes in plasma lipids with administration of mineral oil (Table 17).

Similarly, clinical studies have demonstrated no convincing signal in other biomarkers, such as fatty acid levels (da Silva 2008; Horrobin 1991; McDaniel 2010; Paixao 2017; Tan 2018; Yang 1999), inflammatory markers and related genes (Abdolahi 2019; Abdolahi 2018; Abdolahi 2017; Agh 2017; Bahadori 2010; Gharekhani 2014; Jamilian 2018; Lotfi-Dizaji 2019; Mazaherioun 2017; Mejia-Montilla 2018; Mirmasoumi 2018; Mohammadi 2012; Soveyd 2018), or other analytes (Hosseini 2013; Nogueira 2016; Mazaherioun 2017; Mortazavi 2018; Mozaffari-Khosravi 2015; Razavi 2017; Rondanelli 2010; Tan 2018).

No safety signals arose across the studies noted above, in a broader group of studies that also administered mineral oil (see reference list at the end of this appendix) or in high-dose nonclinical studies conducted by the Sponsor. Many of the references noted above and published in or before 2013 were reviewed with FDA through the 2013 EMDAC meeting for ANCHOR, with observations of biomarkers moving in different directions across studies in which mineral oil was administered. Subsequently published data continues to support the lack of mineral oil effect on lipids or other biomarkers, or on patient safety.

As further detail, we identified 79 studies that administered mineral oil. Many studies made no comment regarding the efficacy or safety of mineral oil, which implies the general acceptance of mineral oil as safe. A subset of these studies reported effects on some biomarkers, and the findings are summarized in Table 17. Citations for these studies are provided at the end of this appendix; the subset of references included in Table 17 are in bold text.

Because of the established history of mineral oil use, and because it was the best-suited placebo for studies of icosapent ethyl, the FDA agreed the development and regulatory program for icosapent ethyl did not require any additional mineral oil-specific testing.

Table 17. Summary of Clinical Studies That Administered Mineral Oil and Reported On-Study Biomarker Levels

Author (year)	n*	Dose, Type†	Patient Population	Statins	Duration of Tx	Change in Mineral Oil Placebo Group					
						TC	Non-HDL-C	LDL-C	TG	HDL-C	hsCRP
Bhatt (2019)	4090	4 g/day LLP	≥45 years with established CVD or ≥50 years with DM and ≥1 additional CV risk factor	Required; 63.0% moderate intensity; 30.0% high intensity	Median 4.9 years	NR	+5.1%; P<0.001	+10.2%; P<0.001	-6.5%; P<0.001	+5.7%; P<0.001	+29.9%; P<0.001
Golzari (2019)	18	2 g/day edible paraffin	DM for ≥1 year, 35-50 years, antidiabetic therapy ≥3 months	NR	8 weeks	~ +19.8 mg/dL [‡] ; NS	NR	~ +3 mg/dL [‡] ; NS	~ +6.8 mg/dL [‡] ; NS	~ +0.3 mg/dL [‡] ; NS	NR
Abdolahi (2018)	57	Paraffin oil (80 mg or 2500 mg)	Episodic migraine	NR	2 months	NR	NR	NR	NR	NR	-0.45 [§] ; NS
Mejia-Montilla (2018)	85	Paraffin oil capsule	Women with POS and vitamin D deficiency	NR	12 weeks	~ -3.5 mg/dL [‡] ; NS	NR	~ +1.8 mg/dL [‡] ; NS	~ +0.9 mg/dL [‡] ; NS	~ -1.7 mg/dL [‡] ; NS	NR
Mirmasoumi (2018)	30	1 g/day, liquid paraffin	Women with POS	NR	12 weeks	+5.7 mg/dL	NR	+2.8 mg/dL	+9.7 mg/dL	+1.0 mg/dL	+0.2 mg/L
Mortazavi (2018)	23	4 g/day edible paraffin	Male 45-55 years with CVD and ≥50% occlusion in one coronary artery	NR	8 weeks	-13.45 mg/dL	NR	+9.43 mg/dL	-21.59 mg/dL	+3.81 mg/dL	+0.68 mg/L
Ramezani (2018)	20	4 soft gel edible paraffin capsules/ day	CVD	NR; no fibrates	8 weeks	-3.90 mg/dL; NS	NR	+8.70 mg/d; NS	-16.82 mg/dL; NS	+9.35 mg/dL; NS	NR
Agh (2017)	21	Edible paraffin	Men w/ CAD; ≤50% recent stenosis; BMI ≤30 kg/m ² ; no warfarin.	Statin therapy in 92% of patients	8 weeks	-13.45 mg/dL	NR	+9.42 mg/dL	-21.69 mg/dL	+9.11 mg/dL	+0.81 mg/L
Paixao (2017)	22	2 g/day, mineral oil	Breast cancer patients	NR	30 days	~ -3 mg/dL [‡] ; NS	NR	~ -4.5 mg/dL [‡] ; NS	~ -20 mg/dL [‡] ; NS	~ +1 mg/dL [‡] ; NS	+17.2 mg/dL; P=0.0245
Razavi (2017)	30	1 g/day + 500 mg once every 2 weeks, liquid paraffin	Gestational DM	NR	6 weeks	NR	NR	NR	NR	NR	+0.9 mg/L
Mazaherioun (2017)	44	2.7 g edible paraffin	Men > 30 years, BMI 25-40 kg/m ² with T2DM	NR	10 weeks	~ -16 mg/dL [‡] ; NS	NR	~ +1.6 mg/dL [‡] ; NS	~ +5 mg/dL [‡]	~ -1.7 mg/dL [‡] ; NS	NR
Nogueira (2016)	28	1 g, mineral oil	Non-alcoholic steatohepatitis	NR	6 months	No significant change	NR	NS	NS	NS	NS
Gholamhosseini (2015)	31	Edible paraffin ^{††}	Men with CVD	84% in placebo group on statin	8 weeks	-1.54%	NR	+6.9%	-19.82%	+3.96%	NR
Gharekhani (2014a,b)	20	Dose “6 capsule,” paraffin oil	Hemodialysis patients	NR	4 months	NR	NR	NR	NR	NR	+4.96 mg/L
Hosseini (2013)	35	5 mL/day, mineral oil	T2DM	NR	2 months	+2.75%; NS	NR	+2.96%; NS	+6.0%; NS	+3.9%; NS	NR
Ballantyne (2012)	227	4 g/day, LLP	TG ≥200 and <500 mg/dL; LDL- C ≥40 and <100 mg/dL	Required	12 weeks	+9.1%	+9.8%	+8.8%	+5.9%	+4.8%	+17.1%
Ghorbanighajjo (2012)	43	1-g paraffin pearl in the fasted state	Adult females with RA on stable therapy ≥2 months	Excluded patients taking lipid lowering drugs	3 months	NR	NR	NR	NR	~ -0.4 mg/dL [‡] ; NS	NR

Author (year)	n*	Dose, Type†	Patient Population	Statins	Duration of Tx	Change in Mineral Oil Placebo Group					
						TC	Non-HDL-C	LDL-C	TG	HDL-C	hsCRP
Lemos (2012)	60	2 g/day mineral oil +7 mg/day of α - tocopherol	Terminal renal failure undergoing chronic hemodialysis	NR	120 days	~ -3.4 mg/dL [‡] NS	NR	~ -5.8 mg/dL [‡] NS	$\sim +20.5$ mg/dL [‡] NS $P=0.05$	$\sim +0.6$ mg/dL [‡] NS	~ -0.7 mg/L [‡] NS
Mohammadi (2012)	31	2 g/day, liquid paraffin	Women with POS	NR	8 weeks	~ -1 mg/dL [‡] NS	NR	No change	~ -6 mg/dL [‡] NS	$\sim +0.4$ mg/dL [‡] NS	~ -0.14 mg/dL [‡] NS
Bays (2011; 2013)	75	4 g/day, LLP	TG ≥ 500 mg/dL and ≤ 2000 mg/dL	Allowed	12 weeks	+7.7%	+7.8%	-3.0%	+9.7%	0%	+33.3%
Fogaca (2011)	11	NA, paraffin	Alcohol-dependent patients	NR	90 days	No change	NR	No change	NR	No change	NR
Rocha Filho (2011)	38	2 g/day mineral oil [§]	Women with PMS	NR	10 days	~ -0.1 mmol/L [‡] NS	NR	NR	NR	NR	NR
Bahadori (2010)	9	paraffin wax placebo	Active RA	NR	20 weeks	No change	NR	No change	NR	No change	No change
Allain (2009)	8	3 g/day, paraffin oil	Healthy volunteers	NR	6 weeks	NR	NR	No change	No change	No change	NR
Emsley (2008)	33	2 g/day, medicinal liquid paraffin	Schizophrenia	NR	12 weeks	No change	NR	No change	~ -0.2 mmol/L [‡] NS	~ -0.1 mmol/L [‡] NS	NR
De Truchis (2007)	62	2 g/day, paraffin oil	HIV on antiviral; TG >200 - <1000 mg/dL	Allowed	8 weeks	+5.7%	NR	NR	+1.0%	+8.97% NS	NR
Kabir (2007)	14	3 g/day, paraffin oil	Type 2 DM; w/o HTG	Allowed (n=5)	8 weeks	~ -0.1 mmol/L [‡] NS	NR	No change	$\sim +0.1$ mmol/L [‡] NS	$\sim +0.1$ mmol/L [‡] NS	NR
Peet (2002)	6	4 g/day; liquid paraffin	Schizophrenia; on clozapine	NR	12 weeks	NR	NR	NR	$\sim +0.6$ mmol/L [‡] NS	NR	NR
Yang (1999)	20	5 g/day, paraffin oil	Atopic dermatitis	NR	4 months	NR	NR	$\sim +0.03$ mmol/L [‡] NS	No change	$\sim +0.09$ mmol/L [‡] NS	NR
Kremer (1985)	17	1.8 g/day non- digestible paraffin wax	RA	NR	12 weeks	$\sim +0.78$ mmol/L [‡] NS	NR	NR	$\sim +0.23$ mmol/L [‡] NS	NR	NR

CAD, coronary artery disease; CV, cardiovascular; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; DM, diabetes mellitus; hsCRP, high sensitivity C-reactive protein; HTG, hypertriglyceridemia; LLP, light liquid paraffin; LDL-C low-density lipoprotein cholesterol; Non-HDL-C, non-high-density lipoprotein cholesterol; NR, not reported; NS, not significant; POS, polycystic ovary syndrome; PMS, premenstrual syndrome; RA, rheumatoid arthritis; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglyceride; Tx, treatment.

*n represents subjects in the mineral oil group.

†Exact and as complete information as possible per what was provided in the publication on the type and grade of mineral oil used.

‡Changes were not published by the study authors; therefore, approximated ($\sim$) changes are estimated from reported study-level summaries.

§Units not reported..

MARINE and ANCHOR Analyses

Biomarker changes in patients taking light mineral oil are also inconsistent within single studies, such as, within the Sponsor's Phase 3 MARINE and ANCHOR trials. In MARINE, patients could optionally be on statin therapy, with the statin-treated cohort being statin-stabilized prior to baseline. Statin-stabilized MARINE patients receiving placebo (n = 18) experienced an 8% median decrease from baseline in LDL-C, whereas there was no change in LDL-C within the placebo-treated cohort without statin therapy (n = 57). This greater drop in LDL-C in statin-treated than non-statin-treated patients suggests light mineral oil did not have independent effects or interfere with statin absorption or efficacy.

In ANCHOR all patients were statin-stabilized at baseline and an overall 9% median increase from baseline in LDL-C was observed in placebo patients, but there was no increase in LDL-C in placebo patients within the highest baseline LDL-C tertile. These variable LDL-C changes across ANCHOR placebo patients again suggest that light mineral oil did not have independent effects or interfere with statin absorption or efficacy.

In addition, not all biomarkers moved in the same direction with light mineral oil placebo across the Sponsor's three Phase 3 trials. For example, LDL-C increased from baseline in the ANCHOR and REDUCE-IT studies but decreased in the placebo group of the MARINE study, and MARINE statin-treated patients receiving placebo observed an even greater decrease than other patients receiving placebo, as noted above.

Therefore, biomarker changes across and within studies do not support lipid effects of light mineral oil placebo.

REDUCE-IT DMC Review

FDA requested that the Sponsor direct the REDUCE-IT independent DMC to consider the ANCHOR biomarker results as they reviewed unblinded REDUCE-IT placebo data. The Sponsor complied and the DMC actively met this request across the remainder of the study, including within subsequent quarterly meetings. The DMC employed several analytical approaches to explore for possible placebo effects over the course of the study; they explored changes in LDL-C and TG levels, and potential relationships of these changes with CV outcomes and safety parameters, but found no relationship between placebo group LDL-C or TG changes and outcomes. The DMC also noted within Closed Session minutes at various stages of the study (e.g., at the second interim analysis meeting) that the icosapent ethyl and placebo event rate curves for the primary prevention subgroup took time to separate, and the DMC concluded that "in the primary prevention group, there is no substantial outcome difference in any specific measure. If there were harm with the light mineral oil placebo, one would anticipate observing an increase rate of outcome(s) in the placebo group relative to the active study drug... [which] supports no measurable harm being done in the placebo group." The DMC further commented "that while a small physiological effect of mineral oil may be possible, it does not appear harmful. It is also unlikely to explain the observed effect of active study drug in the secondary prevention group." In addition, the DMC noted that the increase in lipids in the placebo group could be impacted by regression to the mean, randomness, diet, or other medications. Finally, the DMC also requested and reviewed periodic mineral oil updates from the Sponsor based on publicly available or non-blinded information, such as periodic literature reviews.

During the two preplanned interim analyses and other meetings, the DMC deliberated about stopping for overwhelming efficacy, weighing the relative societal impact of a fuller dataset against patient access to a beneficial therapy. Across the study and within the final Closed Session meeting minutes "the DMC unanimously recommended continuing the study without any intervention or modification." They also "considered various hypotheses that could explain these very potent and consistent results but have not found any that could explain the results nor that would suggest a safety issue for the placebo... It appears that the intervention provides novel and important value over and above standard and even aggressive lipid management."

Therefore, DMC review across the conduct of REDUCE-IT found no apparent harmful effect of placebo on outcomes, with the small LDL-C differential observed between treatment groups unlikely to explain the robust observed benefit of icosapent ethyl.

REDUCE-IT Topline and *Post Hoc* Analyses Exploring Placebo

After study readout, Amarin performed *post hoc* analyses using the REDUCE-IT dataset to explore if there was evidence (or lack thereof) of possible mineral oil effects that might overestimate CV outcomes.

REDUCE-IT Topline Biomarker Analyses

In support of tertiary, exploratory, and *post hoc* analyses, data related to biomarkers was collected and findings include reductions in lipid, lipoprotein and inflammatory biomarkers with icosapent ethyl compared to placebo, including TG, LDL-C, and non-HDL-C from baseline to one year, and apoB and hsCRP from baseline to two years ([Table 18](#)). As noted above and discussed in more detail below, biomarker samples were collected infrequently at single points in time and that were not intended to be relied upon to assess the primary or secondary outcome results of REDUCE-IT. Furthermore, patients throughout the study were being treated in accordance with current practice of medicine with multiple other drugs, patient diet and exercise were not controlled and, as discussed further below, regression to the mean was anticipated for LDL-C and related biomarkers due in large part to the enrollment criteria of the study. The most notable and expected change in the study was the 386% increase in EPA levels in patients in the icosapent ethyl group from baseline to one year.

Table 18. Plasma Biomarker Changes from Baseline to Year 1 or 2 (ITT Population)

Biomarker	Icosapent ethyl (N=4089) Median			Placebo (N=4090) Median			Median Between Group Difference at Year 1 or 2 ⁴		
	Baseline	Year 1,2 ⁴	Change from Baseline	Baseline	Year 1,2 ⁴	Change from Baseline	Absolute Change from Baseline ¹	% Change from Baseline ¹	% Change P-value ²
			Baseline			Baseline	Baseline ¹	Baseline ¹	
EPA (µg/mL)	26.1	144.0	112.6	26.1	23.3	-2.9	114.9	385.8	<0.0001
TG (mg/dL)	216.5	175.0	-39.0	216.0	221.0	4.5	-44.5	-19.7	<0.0001
LDL-C (mg/dL) ³	74.0	77.0	2.0	76.0	84.0	7.0	-5.0	-6.6	<0.0001
LDL-C (Hopkins) (mg/dL)	85.8	85.3	-1.1	86.7	95.8	9.3	-9.6	-11.4	<0.0001
non-HDL-C (mg/dL)	118.0	113.0	-4.0	118.5	130.0	12.0	-15.5	-13.1	<0.0001
apo B (mg/dL) ⁴	82.0	80.0	-2.0	83.0	89.0	6.0	-8.0	-9.7	<0.0001
HDL-C (mg/dL)	40.0	39.0	-1.0	40.0	42.0	1.5	-2.5	-6.3	<0.0001
hsCRP (mg/L) ⁴	2.2	1.8	-0.2	2.2	2.8	0.5	-0.9	-39.9	<0.0001
Log hsCRP (mg/L) ^{4,5}	0.8	0.6	-0.1	0.8	1.0	0.3	-0.4	-22.5	<0.0001

Abbreviations: apo B = apolipoprotein B; EPA = eicosapentaenoic acid; HDL-C = high-density lipoprotein-cholesterol; hsCRP = high-sensitivity C-reactive protein; ITT = intention-to-treat; LDL-C = low-density lipoprotein-cholesterol; TG = triglycerides.

1 Based on Hodges-Lehmann estimation.

2 P-value from Wilcoxon rank-sum test.

3 Preparative ultracentrifugation measurements for LDL-C were analyzed, unless these values were missing. If the LDL-C preparative ultracentrifugation values were missing, then alternative LDL-C values were used, with the highest priority given to the direct LDL-C measurement. If no measurements were available, approximations were used, first by the Friedewald calculation (only for patients with TG <400 mg/dL), and finally by the calculation published by Johns Hopkins University investigators.

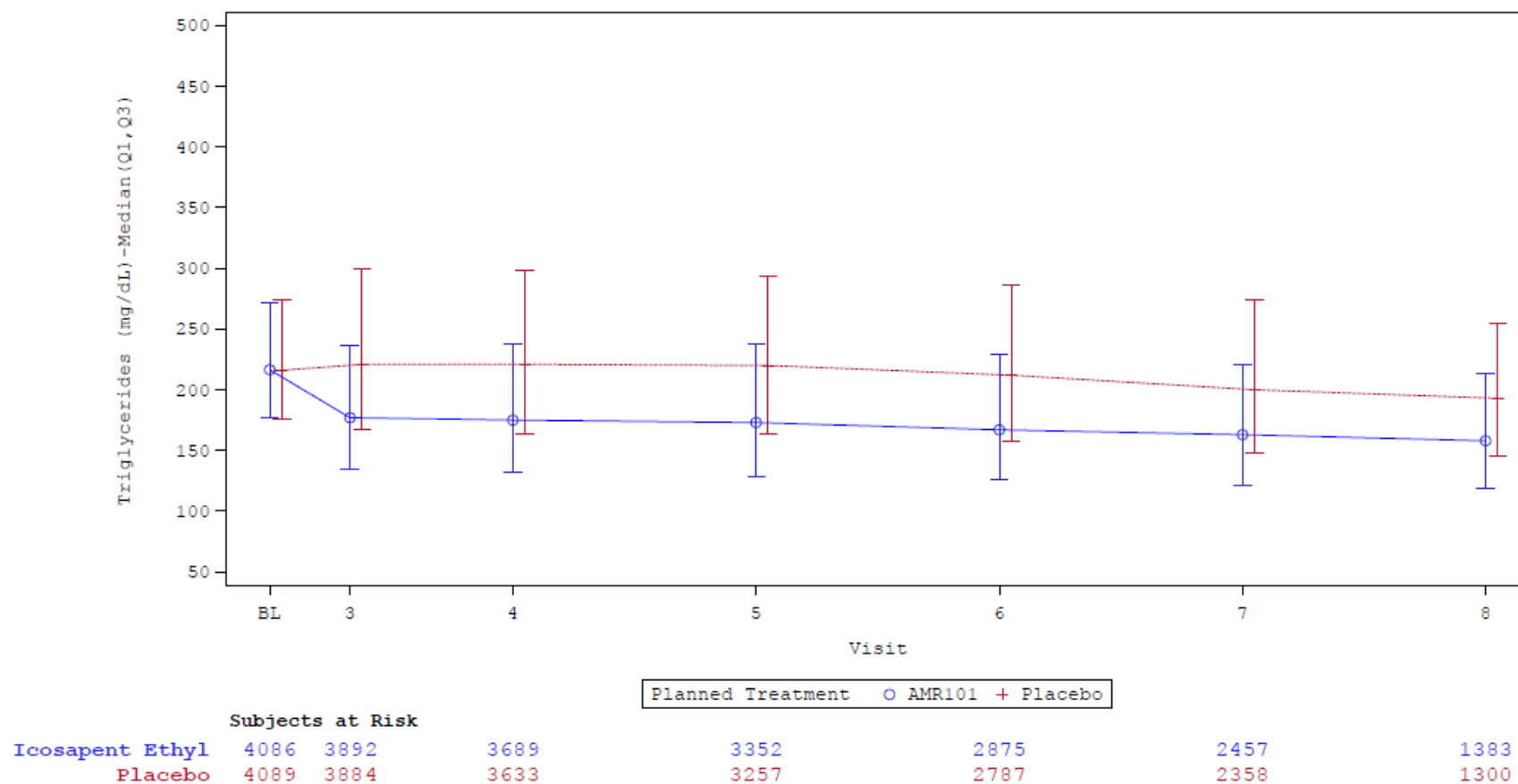
4 Apo B, hsCRP, and log hsCRP were measured at Year 2; all other biomarkers presented were measured at Year 1.

5 "Log" denotes log.

In the icosapent ethyl group, median percent decreases from baseline in TG were observed at each time point, with the difference from placebo being significant across time points (Figure 13).

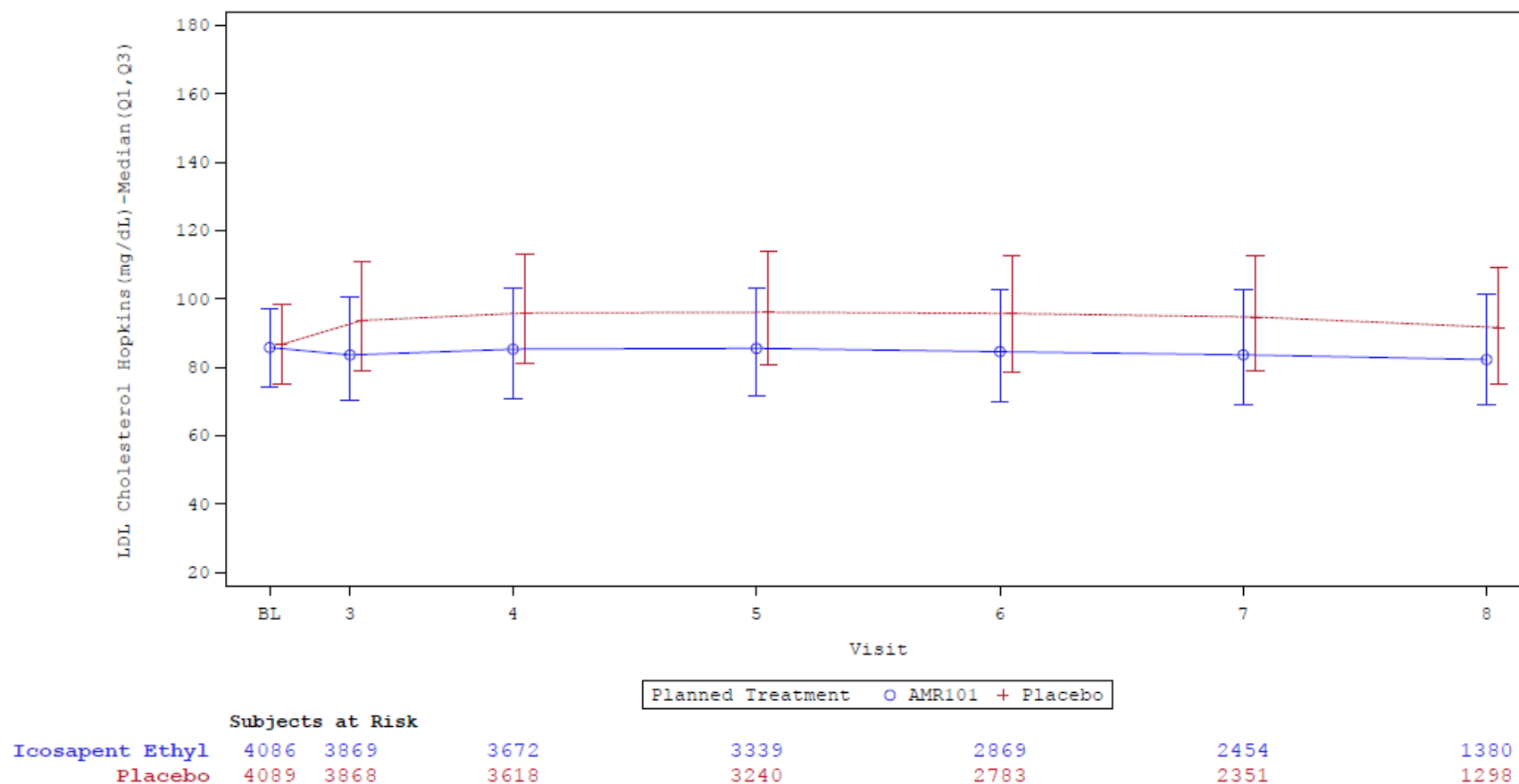
Median percent decreases from baseline were observed with icosapent ethyl at each time point in Hopkins approximated LDL-C (published Johns Hopkins University method [Martin 2013]), with differences from placebo being significant across time points (Figure 14).

Figure 13. Median Triglycerides Over Time (ITT Population)



Abbreviations: ITT = Intention-to-Treat; Q1 = 25th percentile; Q3 = 75th percentile

Figure 14. Median LDL-C (Hopkins Approximation) Over Time (ITT Population)



Abbreviations: ITT = Intention-to-Treat; LDL-C = low-density lipoprotein-cholesterol; Q1 = 25th percentile; Q3 = 75th percentile

Analyses of Biomarker Changes after Permanent Discontinuation of Study Drug

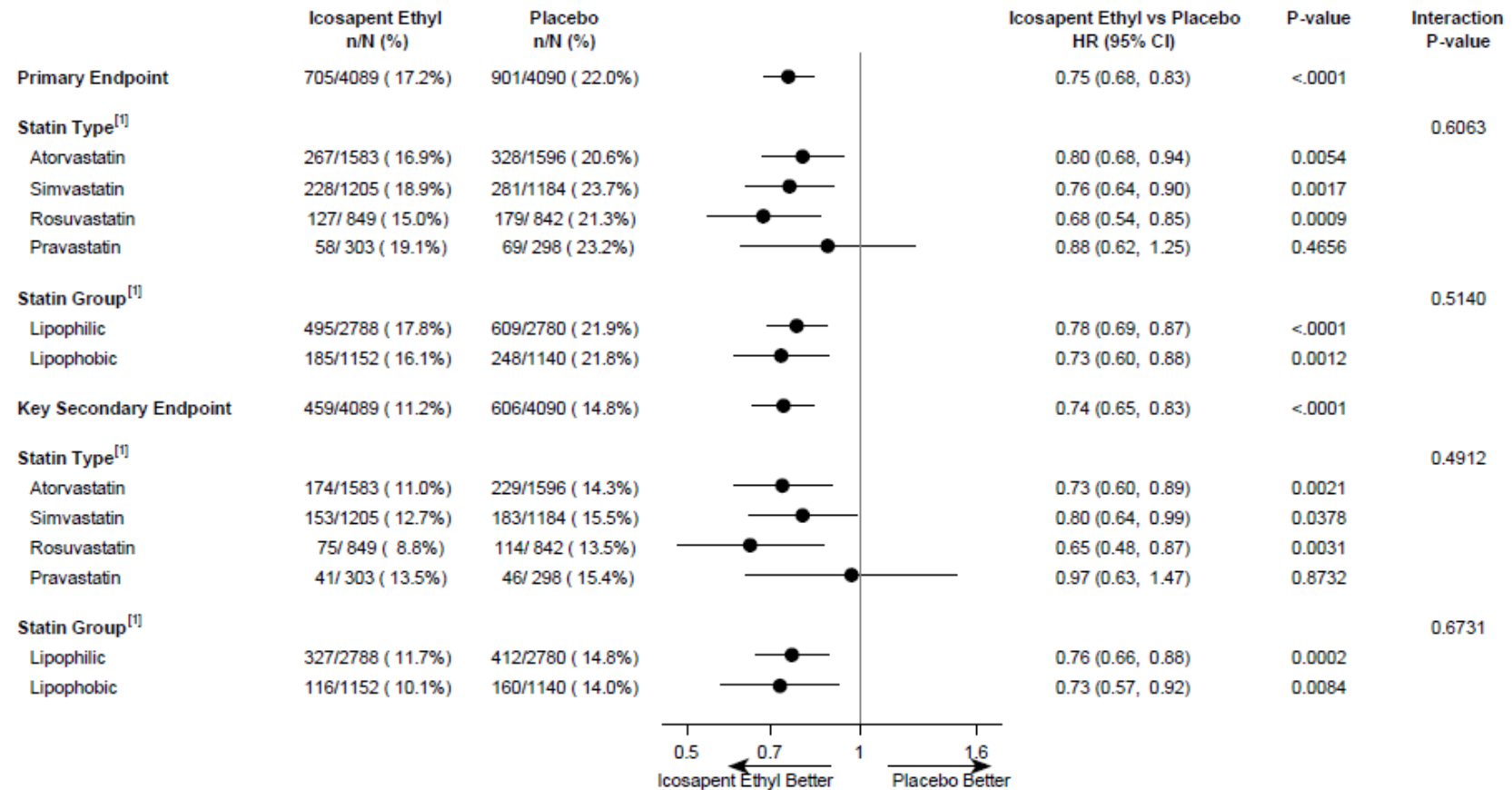
Post hoc analyses examining percent change in TG, LDL-C, and hsCRP after permanent discontinuation of study drug (off drug in study [ODIS]) were conducted. Evaluation of TG icosapent ethyl or placebo after ODIS showed inconsistent mean increases or decreases, generally in the range of ± 0 to 40 mg/dL. LDL-C showed generally small and inconsistent mean increases or decreases, primarily in the range ± 0 to 5 mg/dL. Measurements of hsCRP were limited to randomization, one-year, and end of study visits, and hsCRP levels showed wide variability at individual visits and in hsCRP changes between visits, with standard deviations and interquartile ranges that were much greater in magnitude than the related means or medians. For all three biomarkers, the associated standard deviations were large, indicating substantial variability and suggesting limited confidence in the precision of these change estimates. Collectively, these *post hoc* LDL-C, TG, and hsCRP analyses showed no consistent patterns after discontinuation of either study drug and provide limited insight into potential effects of study drug discontinuation.

Analyses by Statin Type, Including Consideration of Lipophilicity/Lipophobicity

Amarin further explored the theoretical impact of mineral oil on the absorption or efficacy of different types of statin. Primary and key secondary endpoint analyses and LDL-C changes from baseline were investigated by individual statin type (atorvastatin, simvastatin, rosuvastatin, or pravastatin) at baseline, and then by grouping these statins into lipophilic (i.e., hydrophobic; simvastatin, atorvastatin) and lipophobic (i.e., hydrophilic; rosuvastatin, pravastatin) categories. [Figure 15](#) presents the outcome results for the primary and key secondary endpoints across the individual statins and the lipophilic versus lipophobic groups. These analyses suggest no meaningful differences in the primary or key secondary endpoints across all statins and groups. A similar lack of difference was observed in LDL-C changes from baseline to one year across the individual statin types and the lipophilic versus lipophobic statin categories ([Table 19](#)).

If mineral oil were theoretically impacting the absorption or efficacy of statins, this could be expected to impact individual statins, and particularly lipophilic versus lipophobic statins differently, but no differences were observed in the primary or key secondary outcomes or in LDL-C changes from baseline across individual or lipophilic versus lipophobic statins, and therefore, the hypothetical scenario of mineral oil-induced statin malabsorption or decreased efficacy is not supported by these data.

Figure 15. Primary and Secondary Composite Endpoints by Baseline Statin Medication Type: ITT Population



Note: Lipophobic includes rosuvastatin, pravastatin; Lipophilic includes atorvastatin, simvastatin.

[1] 119 subjects with more than 1 statin medication (among the list of the 4: atorvastatin, simvastatin, rosuvastatin, or pravastatin) at baseline are excluded from the analyses.

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Data Cutoff Date: 06SEP2018

Table 19. Summary of LDL-C (Derived) (mg/dL) One Year Changes by Baseline Statin Medication Type

Baseline Statin Subgroup	Visit	Icosapent Ethyl					Placebo					Between Group Difference		
		Observed Values (n)	Median Observed Values	Median Absolute Change from Baseline	Median % Change from Baseline	Median % Change P-value	Observed Values (n)	Median Observed Values	Median Absolute Change from Baseline	Median % Change from Baseline	Median % Change P-value	Median Absolute Change from Baseline ¹	Median % Change from Baseline ¹	Median % Change P-value ³
Atorvastatin	Baseline	1446	74.0				1418	75.0						
	Year 1	1446	78.0	3.3	4.7	<0.0001	1418	84.0	8.0	10.7	<0.0001	-4.0	-5.8	<0.0001
Simvastatin	Baseline	1078	76.0				1043	76.0						
	Year 1	1078	77.0	1.0	1.1	<0.0001	1043	84.0	7.0	10.2	<0.0001	-6.0	-8.3	<0.0001
Rosuvastatin	Baseline	769	71.0				757	74.0						
	Year 1	769	76.0	2.0	3.0	<0.0001	757	82.0	7.0	9.5	<0.0001	-5.0	-6.4	<0.0001
Pravastatin	Baseline	259	79.5				259	78.0						
	Year 1	259	79.0	1.0	1.5	0.0065	259	87.0	8.0	10.0	<0.0001	-7.0	-8.4	0.0003
Lipophobic Statin ⁴	Baseline	1028	74.0				1016	75.0						
	Year 1	1028	78.0	2.0	2.5	<0.0001	1016	83.0	7.0	9.8	<0.0001	-5.0	-6.9	<0.0001
Lipophilic Statin ⁴	Baseline	2524	74.5				2461	76.0						
	Year 1	2524	77.0	2.0	3.1	<0.0001	2461	84.0	7.5	10.4	<0.0001	-5.0	-7.0	<0.0001

Note: 119 subjects with more than 1 statin medication (among the list of the 4: atorvastatin, simvastatin, rosuvastatin, pravastatin) at baseline are excluded from the table.

¹ Based on Hodges-Lehmann Estimation

² P-Value from Wilcoxon rank-sum test

³ p-value from Wilcoxon Signed-Rank test

⁴ Lipophobic includes rosuvastatin, pravastatin; Lipophilic includes atorvastatin, simvastatin

Regression to the Mean Analysis

Based on the design of the REDUCE-IT study and observations from other studies, it was understood in advance of commencing REDUCE-IT that regression to the mean was expected for LDL-C and related biomarkers. The REDUCE-IT inclusion criteria (e.g., LDL-C ≤ 100 mg/dL) and a single qualifying value for each biomarker may have contributed to a regression-to-the-mean phenomenon and the observed LDL-C increase from baseline in the placebo group. Over time, regression to the mean would predict increases from baseline in LDL-C, and the lower the LDL-C at baseline, the more likely it might be expected to rise with time. In support of this hypothesis, LDL-C increases observed at one year in the REDUCE-IT placebo group were more substantial in the lowest baseline LDL-C tertile, than in the middle tertile, and LDL-C decreased in the highest tertile (Table 20). This trend in placebo patient LDL-C changes across baseline LDL-C tertiles provides support for a regression to the mean contribution to the observed LDL-C rise in the placebo group. As presented further below, increases in LDL-C after statin stabilization are observed in 79% of recent historical study curves (34 of 43 curves), and the LDL-C changes observed in the statin-stabilized REDUCE-IT placebo group fall within the range of changes from comparator studies (see Figure 28 and Figure 29 below). Interestingly, a similar, but blunted pattern was also observed across baseline LDL-C tertiles within the icosapent ethyl group, suggesting that icosapent ethyl may have minimized, but not negated, the underlying impact of a possible regression to the mean phenomenon as might be expected; icosapent ethyl, while not primarily an LDL-C lowering therapy, has been shown to modestly lower LDL-C levels.

These results are consistent with ANCHOR study analyses where all patients were statin-stabilized and an overall 9% median increase from baseline in LDL-C was observed in placebo patients, but without increase in LDL-C in placebo patients with the highest baseline LDL-C tertile.

Similar results were observed for hsCRP. REDUCE-IT did not include specific hsCRP inclusion criteria for all patients, although hsCRP >3 mg/L could be an additional risk factor for qualification within the primary prevention patient cohort. While this may only force hsCRP level high in some patients, we explored REDUCE-IT on-study hsCRP changes in patients with hsCRP >3 or ≤ 3 mg/L at baseline (Table 21). About a third (37%) of REDUCE-IT patients with available hsCRP measurements at baseline and two years had baseline hsCRP levels >3 mg/L at baseline. Placebo patients with baseline hsCRP >3 mg/dL experienced a median decrease in hsCRP of 0.16 mg/L from baseline to Year 2, while placebo patients with baseline hsCRP ≤ 3 mg/L experienced a median increase of 0.58 mg/L. This differential response between patients with high versus low baseline hsCRP levels is supportive of underlying drivers such as regression to the mean, and not supportive of a placebo-mediated effect on hsCRP changes in REDUCE-IT, which would be postulated to induce similar changes in hsCRP regardless of baseline level.

Table 20. LDL-C Change at 1 Year: Possible Within-study Regression to the Mean (ITT Population)

Baseline LDL-C (Derived; mg/dL)	Icosapent ethyl (N=4089) Median			Placebo (N=4090) Median			Median Between Group Difference at Year 1		
	Baseline	Year 1	Absolute Change from Baseline	Baseline	Year 1	Absolute Change from Baseline	Absolute Change from Baseline	% Change from Baseline	% Change p-value
All Patients (ITT)	74.0	77.0	2.0	76.0	84.0	7.0	-5.0	-6.6	<0.0001
By Tertile									
≤67 mg/dL	58.0	64.0	8.0	58.0	69.0	12.0	-5.0	-8.9	<0.0001
>67 - ≤84 mg/dL	76.0	78.0	2.0	76.0	84.0	8.0	-6.0	-8.0	<0.0001
>84 mg/dL	96.0	93.0	-6.0	95.5	97.0	-1.0	-5.0	-4.7	<0.0001

Table 21. hsCRP (mg/L) Change at Year 2 from Baseline by Baseline hsCRP Category (ITT Population)

		Icosapent Ethyl (N=4089) Median (Q1, Q3)			Placebo (N=4090) Median (Q1, Q3)			Median Between Group Difference at Year 2 ¹ (95% CI)			
	n	Baseline	Year 2	Change from Baseline	n	Baseline	Year 2	Change from Baseline	Change from Baseline	% Change from Baseline	% Change p-value ²
All Patients (ITT)	3322	2.10 (1.05, 4.34)	1.79 (0.86, 4.01)	-0.18 (-1.21, 0.69)	3229	2.09 (1.04, 4.40)	2.79 (1.30, 5.80)	0.47 (-0.42, 2.09)	-0.85 (-0.95, -0.76)	-39.91 (-43.86, -35.98)	<0.001
By Baseline hsCRP											
≤3 mg/L	2076	1.27 (0.75, 1.92)	1.15 (0.63, 2.16)	-0.02 (-0.47, 0.68)	2040	1.26 (0.75, 1.93)	1.81 (1.00, 3.47)	0.58 (0.00, 1.85)	-0.62 (-0.69, -0.55)	-50.93 (-56.45, -45.50)	<0.001
>3 mg/L	1246	5.41 (3.97, 8.37)	3.89 (2.10, 6.97)	-1.69 (-3.79, 0.73)	1189	5.55 (4.05, 8.82)	5.80 (3.24, 9.27)	-0.16 (-2.66, 2.70)	-1.55 (-1.89, -1.21)	-24.76 (-29.85, -19.72)	<0.001

¹ Based on Hodges-Lehmann Estimation.

² P-Value from Wilcoxon rank-sum test.

Additionally, screening to randomization values were compared, providing LDL-C values closer in time and prior to study drug administration. LDL-C estimated by Friedewald and Hopkins equations are available per protocol across on-site visits and therefore, the analyses are provided separately using each estimation method. [Table 22](#) and [Table 23](#) compare LDL-C values from the last available screening visit (Visit 1 or 1.1) with the randomization visit (Visit 2); [Table 22](#) presents LDL-C Friedewald values, [Table 23](#) LDL-C Hopkins values. Both tables include LDL-C levels for the ITT population, as well as the subpopulations defined by screening tertile. Similar to the on-study tertile analyses above, the screening to randomization analyses suggest increases in LDL-C for patients in the lowest screening LDL-C tertile, with lesser increases or decreases in LDL-C in the middle and upper tertiles. For example, Friedewald LDL-C increased by a median of 3.00 mg/dL in placebo patients within the lowest screening LDL-C tertile, by 1.00 mg/dL in the middle tertile, and decreased 2.00 mg/dL in the highest tertile. The same trend is observed from lowest to highest screening LDL-C tertile in the icosapent ethyl group (+4.00, 0.00, and -2.00 mg/dL, respectively), and also with LDL-C Hopkins for both the placebo (+2.06, -0.22, -2.26 mg/dL, respectively) and icosapent ethyl (+2.53, -0.39, -2.83 mg/dL, respectively) groups.

Table 22. LDL-C Change at V2 (Randomization Visit) from Screening (Friedewald Method; ITT Population)

	Icosapent ethyl (N=4089) Median			Placebo (N=4090) Median			Median Between Group Difference at Baseline		
	Visit 1/1.1	Visit 2	Absolute Change from Screening	Visit 1/1.1	Visit 2	Absolute Change from Screening	Absolute Change from Screening	% Change from Screening	% Change p-value ¹
All Patients (ITT)	73.0	73.0	1.0	74.0	75.0	1.0	0.0	0.36	0.4415
By LDL-C Screening Tertile									
≤65 mg/dL	56.0	59.0	4.0	56.0	58.0	3.0	1.0	1.84	0.0655
>65 - ≤82 mg/dL	74.0	74.0	0.0	74.0	75.0	1.0	-1.0	-1.23	0.1287
>82 mg/dL	90.0	89.0	-2.0	91.0	89.0	-2.0	0.0	0.04	0.9240

Tertiles are based on the latest of Screening (Visit 1) and Follow-up Screening (Visit 1.1) observations and among subjects with both screening and Visit 2 (Randomization Visit) LDL-C values not missing.

¹ P-Value from Wilcoxon rank-sum test.

Table 23. LDL-C Change at V2 (Randomization Visit) from Screening (Hopkins Method; ITT Population)

	Icosapent ethyl (N=4089) Median			Placebo (N=4090) Median			Median Between Group Difference at Baseline		
	Visit 1/1.1	Visit 2	Absolute Change from Screening	Visit 1/1.1	Visit 2	Absolute Change from Screening	Absolute Change from Screening	% Change from Screening	% Change p-value ¹
All Patients (ITT)	85.70	85.23	0.14	86.81	86.35	-0.12	0.13	0.20	0.5640
By LDL-C Screening Tertile									
≤78.19 mg/dL	69.57	71.29	2.53	70.08	70.87	2.06	0.57	0.88	0.1789
>78.19 - ≤93.93 mg/dL	86.31	86.00	-0.39	86.34	85.87	-0.22	-0.25	-0.31	0.6006
>93.93 mg/dL	101.42	99.82	-2.83	101.93	100.29	-2.26	-0.42	-0.40	0.4698

Tertiles are based on the latest of Screening (Visit 1) and Follow-up Screening (Visit 1.1) observations and among subjects with both screening and Visit 2 (Randomization Visit) LDL-C values not missing.

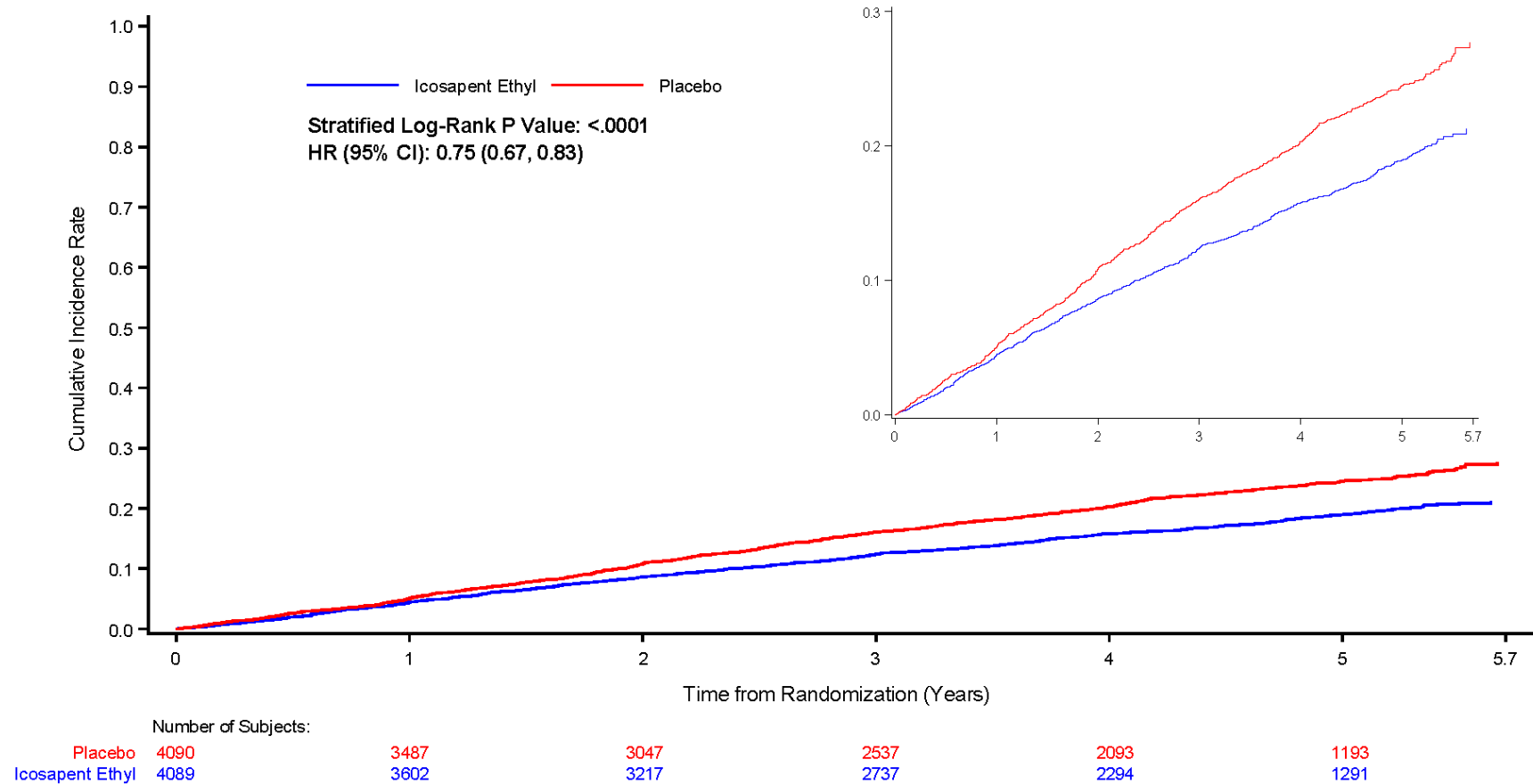
¹ P-Value from Wilcoxon rank-sum test.

These pre-randomization trends in LDL-C changes (Table 22 and Table 23) are consistent with the post-randomization trends presented in Table 20, despite a shorter time interval (≤ 28 days per protocol) between screening and randomization visits. The pre-randomization trend of greater increases in LDL-C for patients with lower screening LDL-C levels is not consistent with mineral oil influences on statins, as these measurements were made prior to study drug initiation. The pre- and post-randomization tertile results are however consistent with a regression to the mean phenomenon, as anticipated during the design of the REDUCE-IT study.

Diarrhea as a Theoretical Marker of Malabsorption

Furthermore, we considered if theoretical malabsorption or decreased efficacy of statins or other compounds resulting from placebo, as noted by onset of diarrhea, correlated with changes in patient outcomes in the placebo group. Figure 16 and Figure 17 provide the primary and key secondary endpoint analyses by censoring patients at the onset date of diarrhea and suggest no substantial differences from primary analyses using the overall ITT population. Therefore, the hypothetical scenario of statin malabsorption or decreased efficacy is not supported by this data.

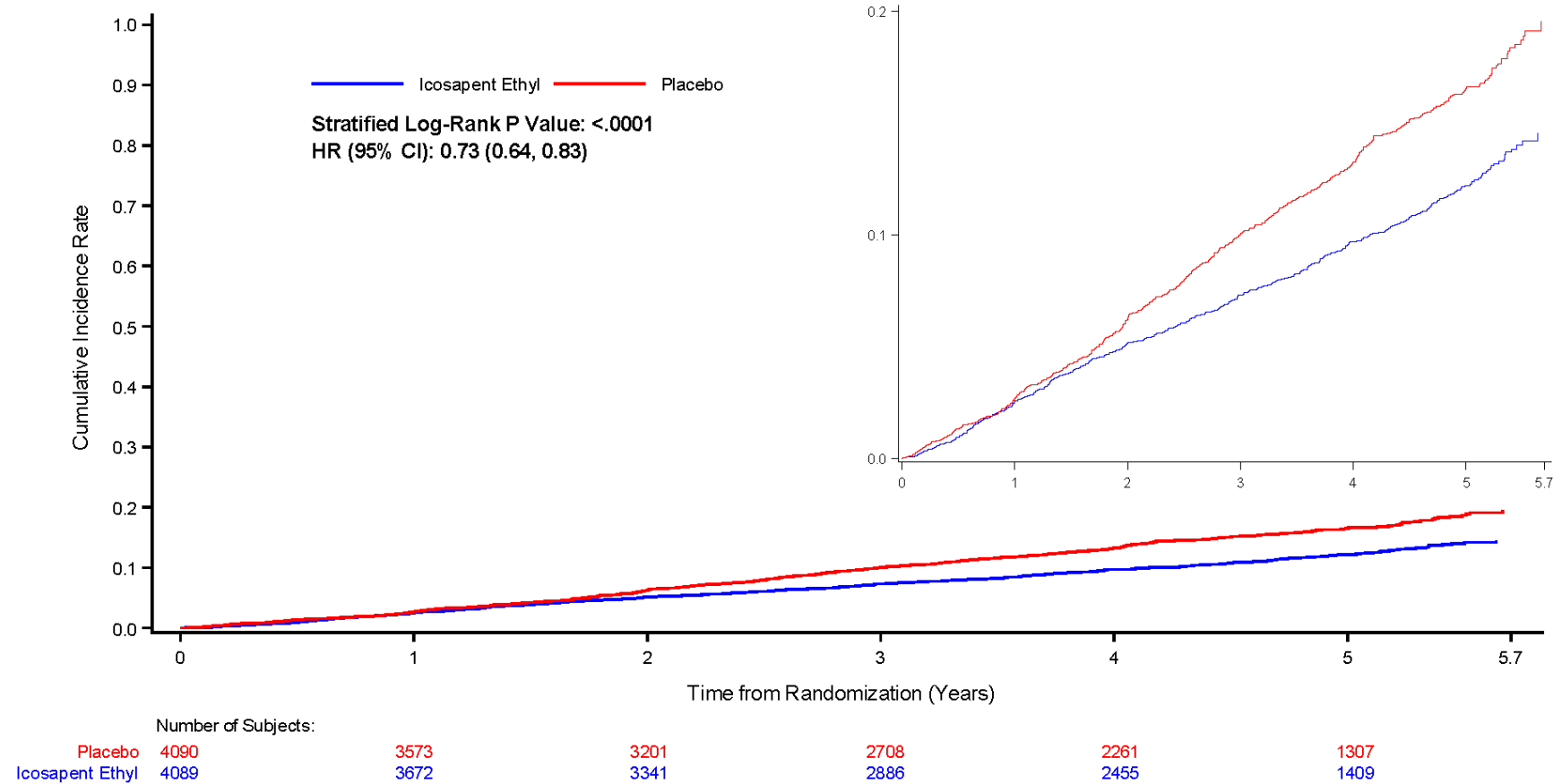
Figure 16. Time to the Primary Endpoint by Censoring Event at Onset of Diarrhea (ITT Population)



Note: Subjects with Diarrhea prior to Primary Composite Endpoint are censored at Diarrhea.

Abbreviations: AMR101 = icosapent ethyl; CI = confidence interval; HR = hazard ratio; ITT = Intention-to-Treat.

Figure 17. Time to the Key Secondary Endpoint by Censoring Event at Onset of Diarrhea (ITT Population)



Abbreviations: AMR101 = icosapent ethyl; CI = confidence interval; HR = hazard ratio; ITT = Intention-to-Treat.

Placebo Biomarker Changes Have Little to No Impact CV Outcomes

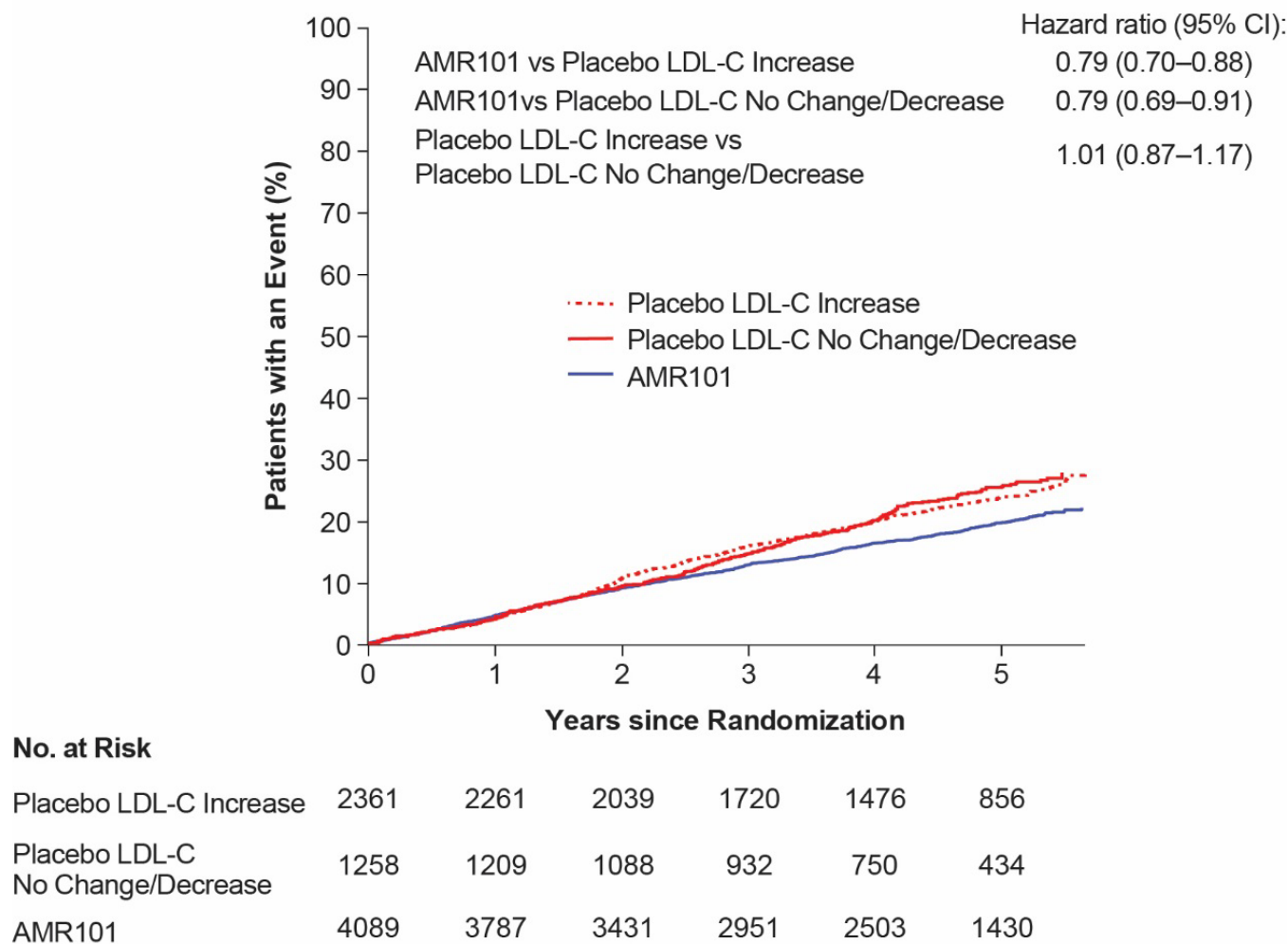
Some have speculated that if light mineral oil might have negatively affected statin absorption or efficacy, this could have resulted in an overestimation of the observed differences in outcomes between treatment groups. To explore this possibility, *post hoc* analyses were conducted comparing the effects of icosapent ethyl to placebo with respect to the primary and key secondary endpoints according to whether placebo-treated patients had any increase from baseline in biomarkers at one or two years versus placebo patients with no change or a decrease.

A Kaplan-Meier curve of time to the primary endpoint from date of randomization for icosapent ethyl versus placebo by an LDL-C increase in the placebo group, or by no change/a decrease in LDL-C in the placebo group is presented in [Figure 18](#). For the comparison of the icosapent ethyl group versus the placebo group with increases in LDL-C, the HR was 0.79 (95% CI: 0.70 to 0.88); for the placebo group with no change/a decrease in LDL-C, the HR was also 0.79 (95% CI: 0.70 to 0.91). For the comparison of placebo groups with increases in LDL-C versus no change/a decrease in LDL-C, the HR was 1.01 (95% CI: 0.87 to 1.17).

Likewise, a similar lack of effect of changes in LDL-C within the placebo group is demonstrated in the Kaplan-Meier curve of time to the key secondary endpoint from date of randomization for icosapent ethyl versus placebo by an LDL-C increase or no change/a decrease at one year in the placebo group is presented in [Figure 19](#). Thus, there was no apparent difference in the primary or key secondary endpoint event rates between the placebo group with an increase in LDL-C as compared to the group with no change/a decrease in LDL-C.

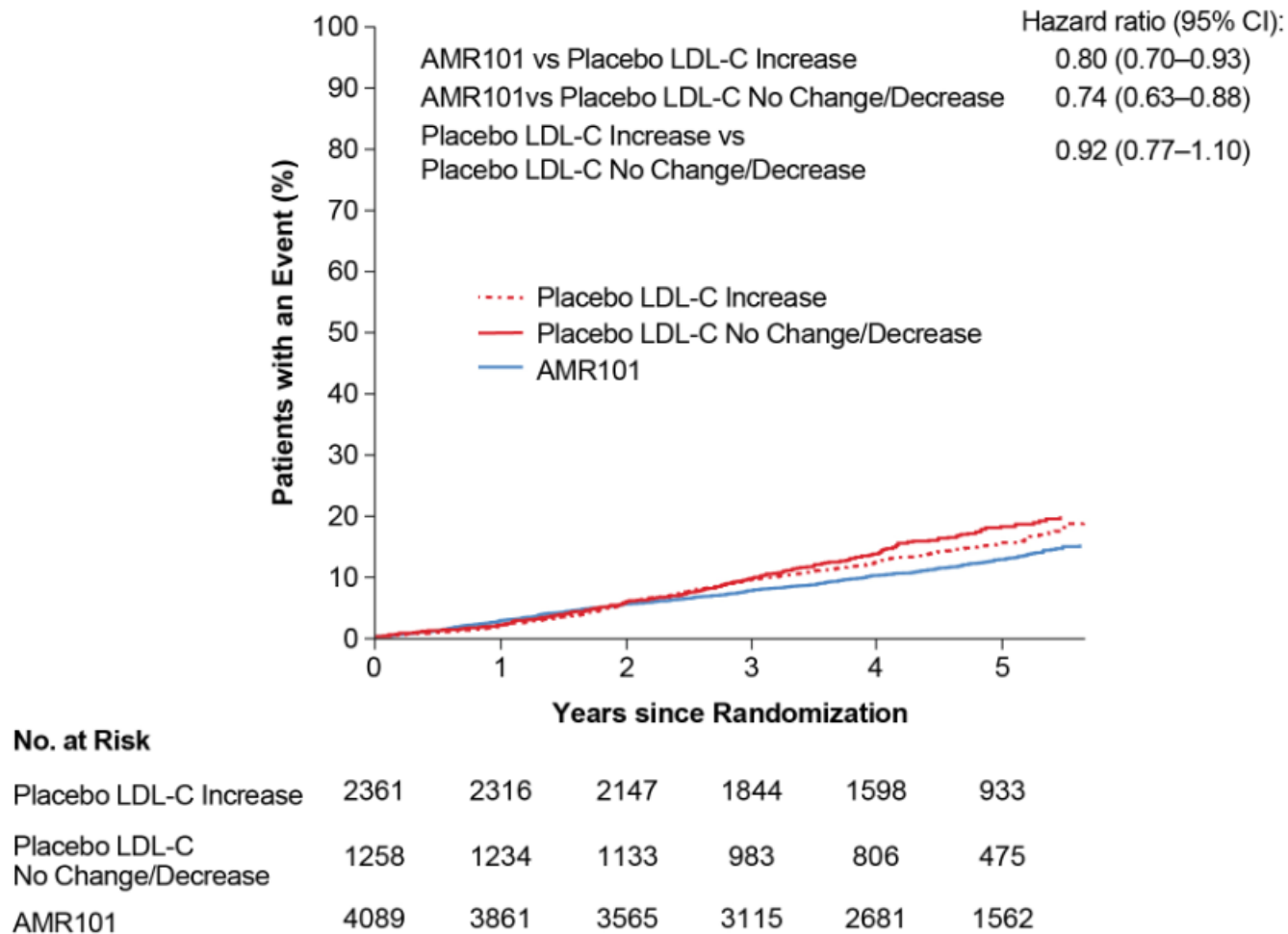
Similar analyses were conducted examining time to the primary and key secondary endpoints from date of randomization for icosapent ethyl versus placebo by increase or no change/a decrease in the placebo group of non-HDL-C, HDL-C, TG, ApoB, and hsCRP. Results and conclusions were similar to those presented for LDL-C and are summarized in [Table 24](#). Analyses were also conducted utilizing individual LDL-C measures/estimates (Derived, Ultracentrifugation, Friedewald, or Hopkins), which provide similar results and conclusions, regardless of the LDL-C measure/estimate analyzed

Figure 18. Time to the Primary Endpoint for Icosapent Ethyl Versus Placebo by an LDL-C Increase or No Change/A Decrease at 1 Year in the Placebo Group (ITT Population)



Abbreviations: AMR101 = icosapent ethyl; CI = confidence interval; ITT = Intention-to-Treat; LDL-C = low-density lipoprotein-cholesterol; no. = number; vs = versus.

Figure 19. Time to the Key Secondary Endpoint for Icosapent Ethyl Versus Placebo by LDL-C Increase or No Change/A Decrease at 1 Year in the Placebo Group (ITT Population)



Abbreviations: AMR101 = icosapent ethyl; CI = confidence interval; ITT = Intention-to-Treat; LDL-C = low-density lipoprotein-cholesterol; no. = number; vs = versus.

Table 24. Summary of Hazard Ratios and 95% Confidence Intervals for Analyses of Icosapent Ethyl vs Placebo by Biomarker Increase or No Change/Decrease in the Placebo Group (ITT Population)

	Primary Endpoint HR (95% CI)			Key Secondary Endpoint HR (95% CI)		
	Icosapent Ethyl vs. Placebo Increase ¹	Icosapent Ethyl vs. Placebo No Change/ Decrease ¹	Placebo Increase vs. Placebo No Change/ Decrease ¹	Icosapent Ethyl vs. Placebo Increase ¹	Icosapent Ethyl vs. Placebo No Change/ Decrease ¹	Placebo Increase vs. Placebo No Change/ Decrease ¹
LDL-C	0.79 (0.70, 0.88)	0.79 (0.69, 0.91)	1.01 (0.87, 1.17)	0.80 (0.70, 0.93)	0.74 (0.63, 0.88)	0.92 (0.77, 1.10)
hsCRP	0.79 (0.71, 0.89)	0.83 (0.72, 0.96)	1.05 (0.90, 1.22)	0.83 (0.71, 0.95)	0.85 (0.71, 1.02)	1.03 (0.85, 1.24)
Non- HDL-C	0.78 (0.70, 0.87)	0.81 (0.70, 0.94)	1.04 (0.89, 1.20)	0.79 (0.68, 0.90)	0.78 (0.65, 0.93)	0.99 (0.82, 1.19)
HDL-C	0.76 (0.67, 0.85)	0.85 (0.74, 0.97)	1.12 (0.97, 1.29)	0.77 (0.67, 0.89)	0.81 (0.69, 0.95)	1.05 (0.88, 1.25)
TG	0.80 (0.71, 0.90)	0.77 (0.68, 0.88)	0.97 (0.84, 1.11)	0.78 (0.67, 0.90)	0.79 (0.67, 0.92)	1.02 (0.86, 1.21)
ApoB	0.77 (0.69, 0.87)	0.87 (0.75, 1.00)	1.12 (0.96, 1.31)	0.80 (0.69, 0.93)	0.89 (0.74, 1.07)	1.11 (0.92, 1.35)

¹ Time to endpoint is 1 year for LDL-C Derived, non-HDL-C, HDL-C, and TG; 2 years for hsCRP and ApoB.

Similar analyses looking at an increase versus no change or a decrease in LDL-C or hsCRP in the icosapent ethyl group as compared to the full placebo group also suggested little to no impact on the efficacy results of LDL-C or hsCRP changes in the icosapent ethyl group (Table 25 and Table 26). Similar results were observed in the key secondary endpoint, and regardless of the LDL-C measure/estimate (Derived, Ultracentrifugation, Friedewald, Hopkins).

Table 25. Overall Summary of Primary Composite Endpoint by Placebo and Icosapent Ethyl LDL-C Derived Increase/No Change-Decrease at 1 Year (ITT Population)

Parameter	Category	HR (95% CI)
LDL-C	Icosapent Ethyl Increase vs. Icosapent Ethyl No Change/Decrease	1.06 (0.90, 1.24)
	Icosapent Ethyl Increase vs. Placebo	0.75 (0.66, 0.86)
	Icosapent Ethyl No Change/Decrease vs. Placebo	0.71 (0.62, 0.82)

Note: Excludes patients with missing LDL-C change at 1 year.

Abbreviations: CI = confidence interval; HR = hazard ratio; LDL-C = low-density lipoprotein cholesterol (Derived).

Table 26. Overall Summary of Primary Composite Endpoint by Placebo and Icosapent Ethyl hsCRP Increase/No Change-Decrease at 2 Years (ITT Population)

Parameter	Category	HR (95% CI)
hsCRP	Icosapent Ethyl Increase vs. Icosapent Ethyl No Change/Decrease	1.05 (0.89, 1.25)
	Icosapent Ethyl Increase vs. Placebo	0.73 (0.63, 0.84)
	Icosapent Ethyl No Change/Decrease vs. Placebo	0.69 (0.61, 0.79)

Note: Excludes patients with missing hsCRP change at 2 years.

Abbreviations: CI = confidence interval; hsCRP = high-sensitivity C-reactive protein; HR = hazard ratio.

Together these results suggest that the CV benefits of icosapent ethyl therapy are likely not driven by, or highly correlated with, measured LDL-C or hsCRP changes. These findings are in agreement with the broader literature, which suggests multiple benefits of EPA therapy beyond lipids/lipoproteins (see Appendix E), and that relatively small changes in LDL-C levels in statin-treated patients with LDL-C below 100 mg/dL may be less predictive of changes in CV risk, and that the CV risk predictiveness of hsCRP changes in statin-treated patients is yet to be established.

These analyses also suggest that the observed biomarker increases or decreases had little to no impact on outcomes in the placebo group or on the magnitude of benefit within the icosapent ethyl group, and the CV benefits of icosapent ethyl observed in REDUCE-IT are likely not driven by the biomarker changes in the placebo group.

REDUCE-IT Outcomes Compared to Historical CV Outcome Trials

Historical Event Rates in Placebo Groups

The original projected primary endpoint annualized event rate of 5.9% for the REDUCE-IT placebo group was derived prior to study based on data available from CV outcome trials with similar at-risk statin-treated patients and similar endpoint components as the primary endpoint in REDUCE-IT (Bhatt 2006; Braunwald 2004; Cannon 2004; Colhoun 2004; Ginsberg 2010; Patel 2008; Pedersen 2005). The actual observed annualized primary endpoint event rate for placebo patients in REDUCE-IT was 5.74%, which is in strong agreement with the projected rate.

For further perspective, the observed annualized (time-averaged) REDUCE-IT placebo group event rates for the full (mixed), primary prevention, and secondary prevention cohorts were

compared to those from the historical CV outcome studies with published event curves and reasonably comparable patient populations and endpoints (somewhat comparable expanded 5-point MACE primary endpoint or 3-point MACE key secondary endpoint). Minor variations in endpoint definitions and patient populations were reasonably allowed to facilitate adequate data capture. The trials identified were recent (published since 2000) and included complete or very high prevalence of statin use in at least one group (placebo or active), comparable hard and/or broad MACE composite endpoints, comparable patient populations, and publicly available survival curves (or available with permission). In addition to plotting the survival curves, eight key clinical baseline parameters were prospectively defined with relative weights subsequently assigned for each in relation to pooled, blinded baseline REDUCE-IT values. Individual weighting was applied to each clinical parameter comparability score, and a total proximity score was ultimately generated for each trial. Proximity scores could range from 0 (no comparability to REDUCE-IT) to 5 (strongest comparability to REDUCE IT) to appropriately account for the eight baseline parameters as compared to REDUCE-IT.

The CV outcome trial historical comparisons for the secondary prevention established CVD group, which comprised 70.7% of the REDUCE-IT study population, are presented in [Figure 20](#). The cumulative incidences (%) of broad and hard MACE events from REDUCE-IT and historical trials are presented; thicker lines represent greater proximity scores in relation to the REDUCE-IT population and individual proximity scores are provided in parenthesis after each trial name. As shown, there is a range of event rates across the CV outcome trials, the event rates for statin-treated placebo patients in REDUCE-IT lie within the range of event rates for secondary prevention statin-treated patients observed in other CV outcome trials, and the REDUCE-IT event rates were generally more comparable to studies with higher proximity scores. Thus, while patient populations and endpoints differ somewhat between trials, the event rates in REDUCE-IT for the secondary prevention placebo group are consistent with historical data.

Fewer studies were available for comparison with the REDUCE-IT primary prevention group, and primary CV prevention studies with particularly high-risk patients (e.g., advanced age, diabetes, Westernized) were lacking. All the primary prevention patients enrolled in REDUCE-IT were at least 45 years old and had elevated TG levels despite statin therapy, diabetes, and other CV risk factors. None of the studies available for comparison enrolled patients with this level of increased CV risk, including as identified by elevated TG levels. Therefore, it is not surprising that the high risk primary prevention group, which comprised 29.3% of the REDUCE-IT study population, appeared to have higher cumulative incidences of broad and hard MACE events than the comparator primary prevention studies ([Figure 21](#)). Therefore, CV outcome trial historical comparisons for the primary prevention group are considered less representative of the high risk primary population in REDUCE-IT compared to the comparative studies presented in [Figure 20](#) for the secondary prevention group.

The CV outcome trial historical comparisons for mixed (primary plus secondary) prevention are presented in [Figure 22](#). Like the secondary prevention comparison, the event rates for statin-treated placebo patients in REDUCE-IT lie within the observed event rate ranges, and these rates were comparable to those for mixed prevention statin-treated patients in other CV outcome trials.

Therefore, while patient populations and endpoints necessarily differ somewhat between trials, the event rates observed in the REDUCE-IT statin-treated placebo group were expected and are consistent with event rates for statin-treated patients from recent CV outcome studies.

Figure 20. CV Outcome Trials Historical Comparison of Broad and Hard MACE (Secondary Prevention Group)

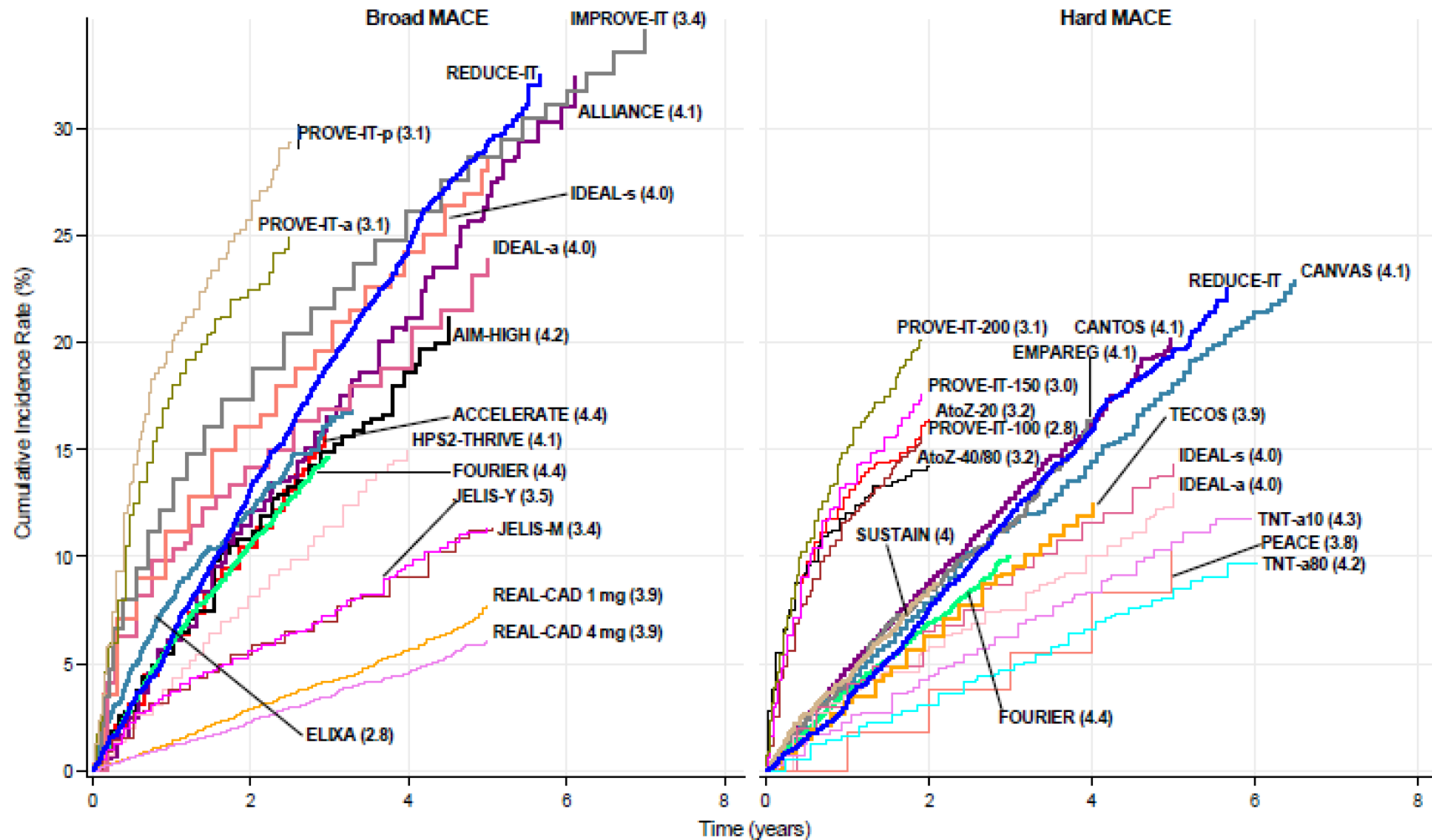


Figure 21. CV Outcome Trials Historical Comparison of Broad and Hard MACE (Primary Prevention Group)

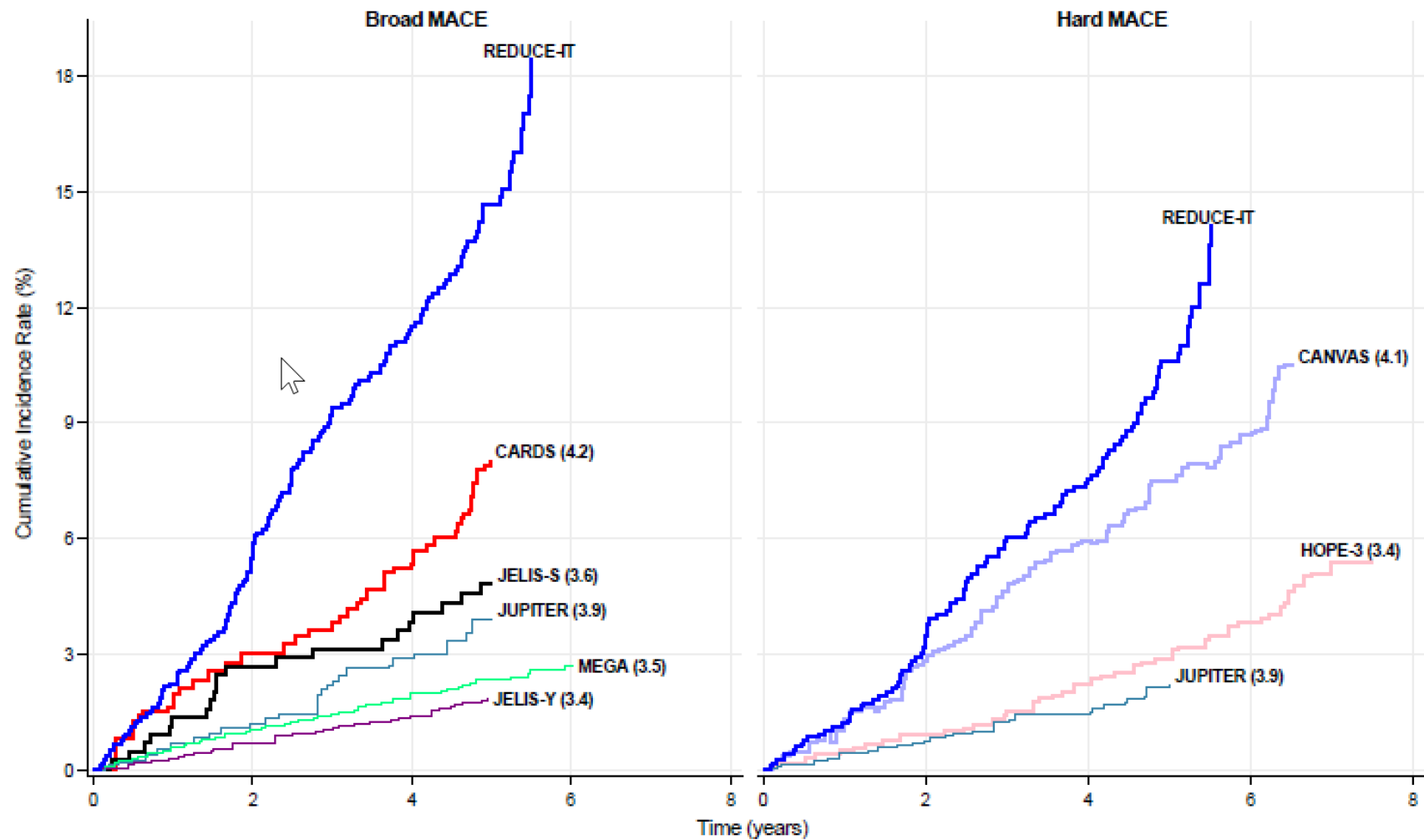
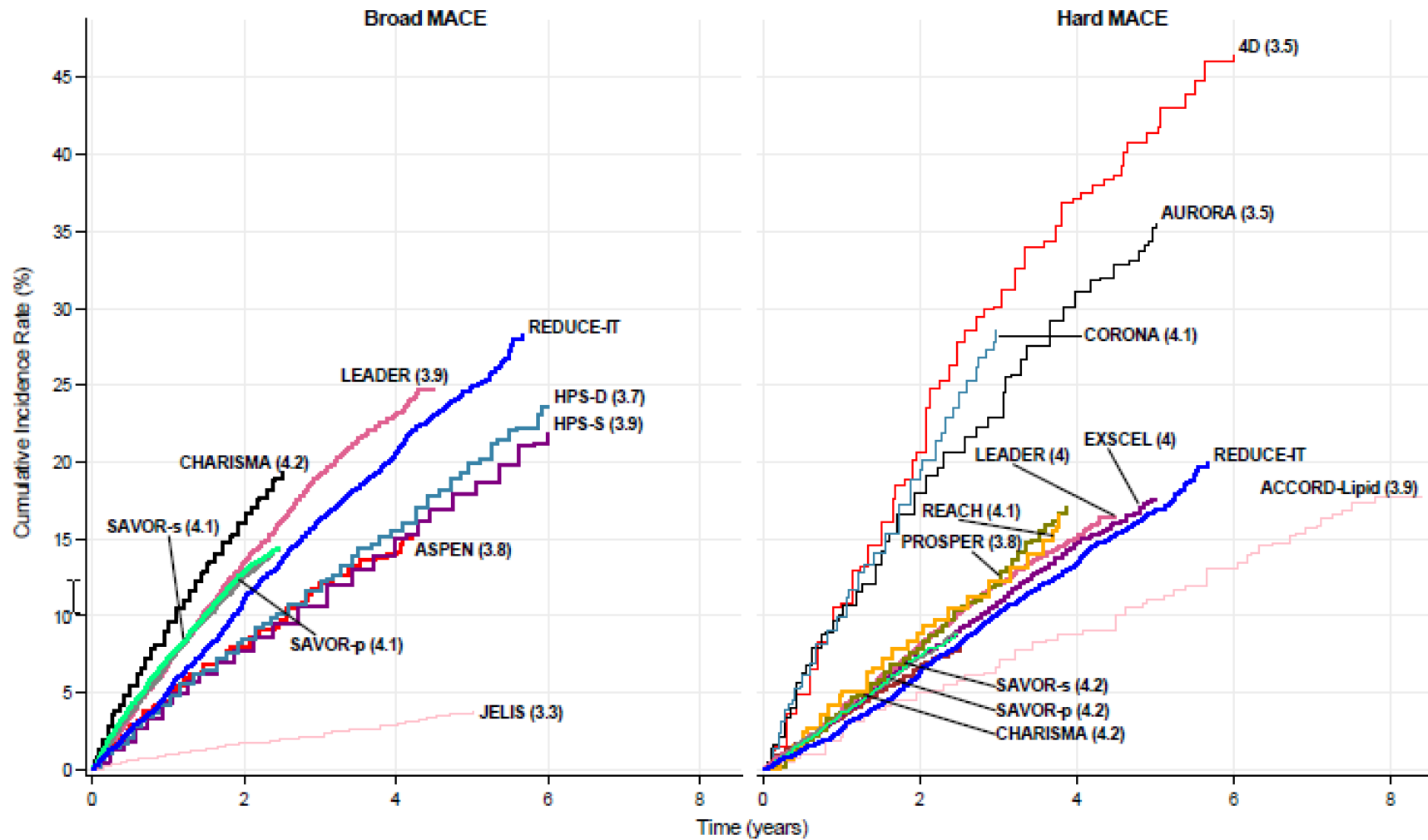


Figure 22. CV Outcome Trials Historical Comparison of Broad and Hard MACE (Mixed Prevention Group)



Meta-analyses

Cross-study meta-analyses can provide additional historical perspectives, however, there are significant underlying limitations when interpreting results and subsequent conclusions from such analyses that should be highlighted. Comparing results from a treatment arm in one randomized trial to results from a treatment arm from another randomized trial is counter to the fundamental principle of randomized trials. Randomly assigning treatment to patients allows for equal distribution of important non-random study confounders, while historical cross-study comparison eliminates the rigorous control of equal distribution of non-random confounders across treatment arms and, therefore, produces far less conclusive findings. Additionally, the composite 5-point MACE endpoints across these historical trials were not identical to each other or to the REDUCE-IT primary composite endpoint. Even across studies where the composite 5-point MACE endpoints were similarly defined, other factors such as differences in inclusion or exclusion criteria, data collection mechanisms, study governance practices, and clinical endpoint adjudication practices would materially influence results from comparator arms of different studies.

It also important to note that studies that prospectively enrolled patients (primary or secondary prevention) with elevated TG levels despite statin therapy are lacking, and therefore event rates from comparator studies within these analyses are expected to underestimate the risk of patients enrolled in the REDUCE-IT study (Bruckert 2011; Maki 2015). For example, while studies did not prospectively enroll patients with elevated TG at baseline, subgroup analyses from studies that focused on statin-treated patients suggest approximately 12-42% increases in events in patients with elevated TG compared to the full study cohorts (ACCORD-Lipid 2010; Boden 2011; Davidson 2014; Guyton 2013; Landray 2014; Saito 2008; Yokoyama 2007). This agrees with earlier studies of patients that were not required to be on statin therapy, where patients with elevated TG levels experienced approximately 16-86% higher event rates compared to the full study cohorts (BIP 2000; Manninen 1992; Rubins 1999; Scott 2005).

With such caveats in mind, presented below are five forest plots for the 5-point MACE primary endpoint. In each of these five figures, results from REDUCE-IT (RR and associated 95% CI) are presented along with corresponding results using the REDUCE-IT icosapent ethyl treatment arm, but replacing the placebo event rate results from REDUCE-IT with surrogate statin-alone historical control arm data derived from other CV outcomes trials. [Figure 23](#), [Figure 24](#), and [Figure 25](#) present meta-analyses for the 5-point MACE primary endpoint for the secondary prevention group, the primary prevention group, or the mixed prevention group, using the following six studies that were used in determining the REDUCE-IT sample size:

- Four secondary prevention studies: IDEAL, CHARISMA, PROVE-IT, and PEACE;
- Two primary prevention studies: ADVANCE, and ACCORD.

Event rate results derived from these six studies formed the basis for the REDUCE-IT sample size determination and discussion with the FDA at the study design stage and continue to be the most relevant studies for these meta-analyses. As shown in [Figure 23](#), the estimated overall RR ratio and 95% CI for the secondary prevention group are 0.67 (0.64, 0.70) from the fixed effects model, and 0.68 (0.57, 0.81) from the random effects model. For the primary prevention group ([Figure 24](#)), the estimated overall RR ratio and 95% CI are 0.83 (0.76, 0.91) from the fixed effects model, and 0.86 (0.59, 1.25) from the random effects model. For the mixed prevention group, control arm

rates were constructed using the 70% to 30% ratio (per REDUCE-IT design) to combine each of the historical secondary prevention study arms with the historical primary prevention study arms. The estimated overall RR ratio and 95% CI for the mixed prevention group are 0.68 (0.65, 0.71) from the fixed effects model, and 0.69 (0.62, 0.77) from the random effects model ([Figure 25](#)).

Sensitivity analyses were also conducted that included additional recent relevant secondary prevention studies (ELIXA, IMPROVE-IT, ACCELERATE, ALLIANCE, FOURIER, and AIM-HIGH). JELIS, REAL-CAD, and HPS2-THRIVE results were not included in this sensitivity analysis due to enrollment of patient populations sufficiently different from the patients enrolled in REDUCE-IT. No suitable additional primary prevention studies were identified for the sensitivity analyses. Results from these sensitivity analyses that broadened the historical secondary prevention comparator sets are presented in [Figure 26](#) and [Figure 27](#). Inclusion of additional studies provided consistent results with the meta-analyses based on the six studies that supported the REDUCE-IT study design, and all analyses are consistent with the primary composite efficacy findings within REDUCE-IT.

Overall historical cross-study event rate comparisons are limited by differing study designs, patient populations, and co-administered therapies (e.g. statin use, type, and dose), and do not allow for balanced distribution of important non-random study confounders across treatment groups. Therefore, while such historical comparisons can be of some utility, they produce far less conclusive findings than those produced within a randomized, well-controlled trial such as REDUCE-IT. Despite these caveats, these meta-analyses are in strong agreement with the 25% relative risk reduction observed in the primary endpoint for the full ITT population in REDUCE-IT, and further support a substantial CV benefit with icosapent ethyl therapy.

Figure 23. Meta-Analysis of Primary Composite Endpoint with Historical Controls – Secondary Prevention

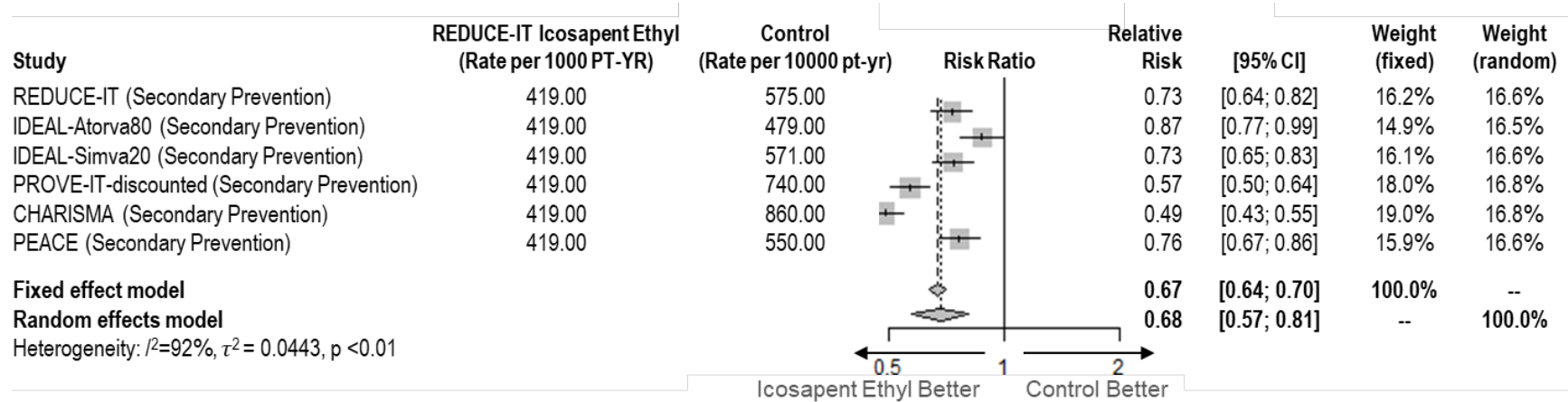


Figure 24. Meta-Analysis of Primary Composite Endpoint with Historical Controls – Primary Prevention

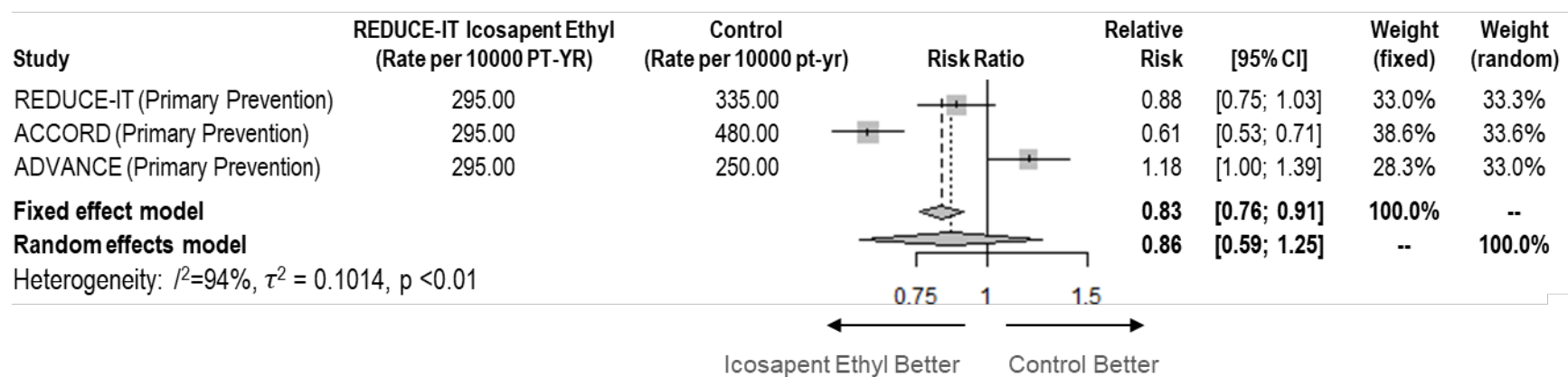


Figure 25. Meta-Analysis of Primary Composite Endpoint with Historical Controls – Primary + Secondary Preventions

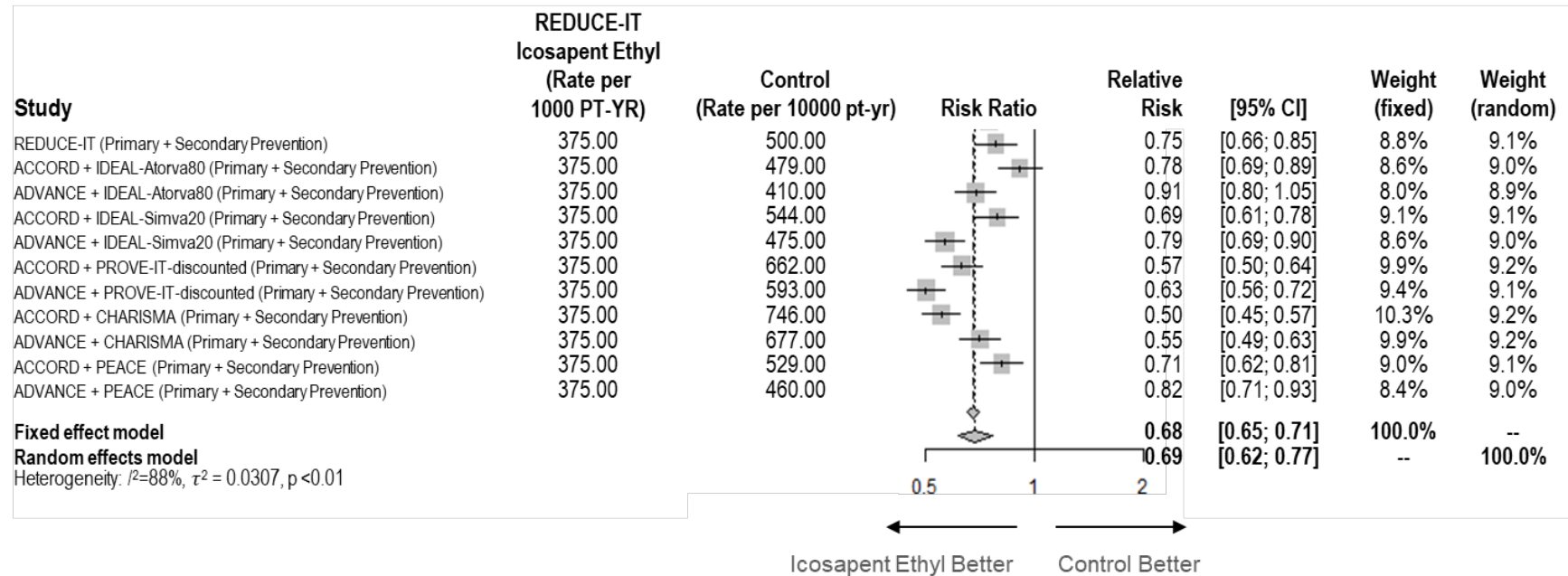


Figure 26. Meta-Analysis of Primary Composite Endpoint with Historical Controls – Secondary Prevention (Sensitivity Analysis)

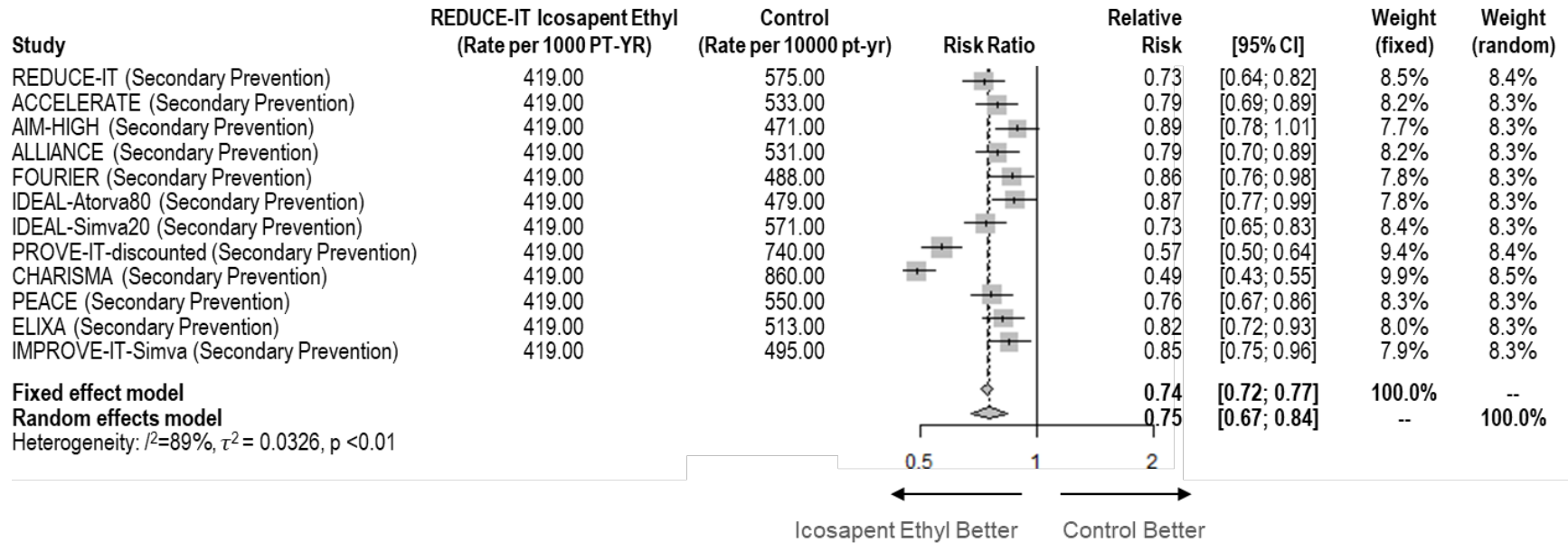
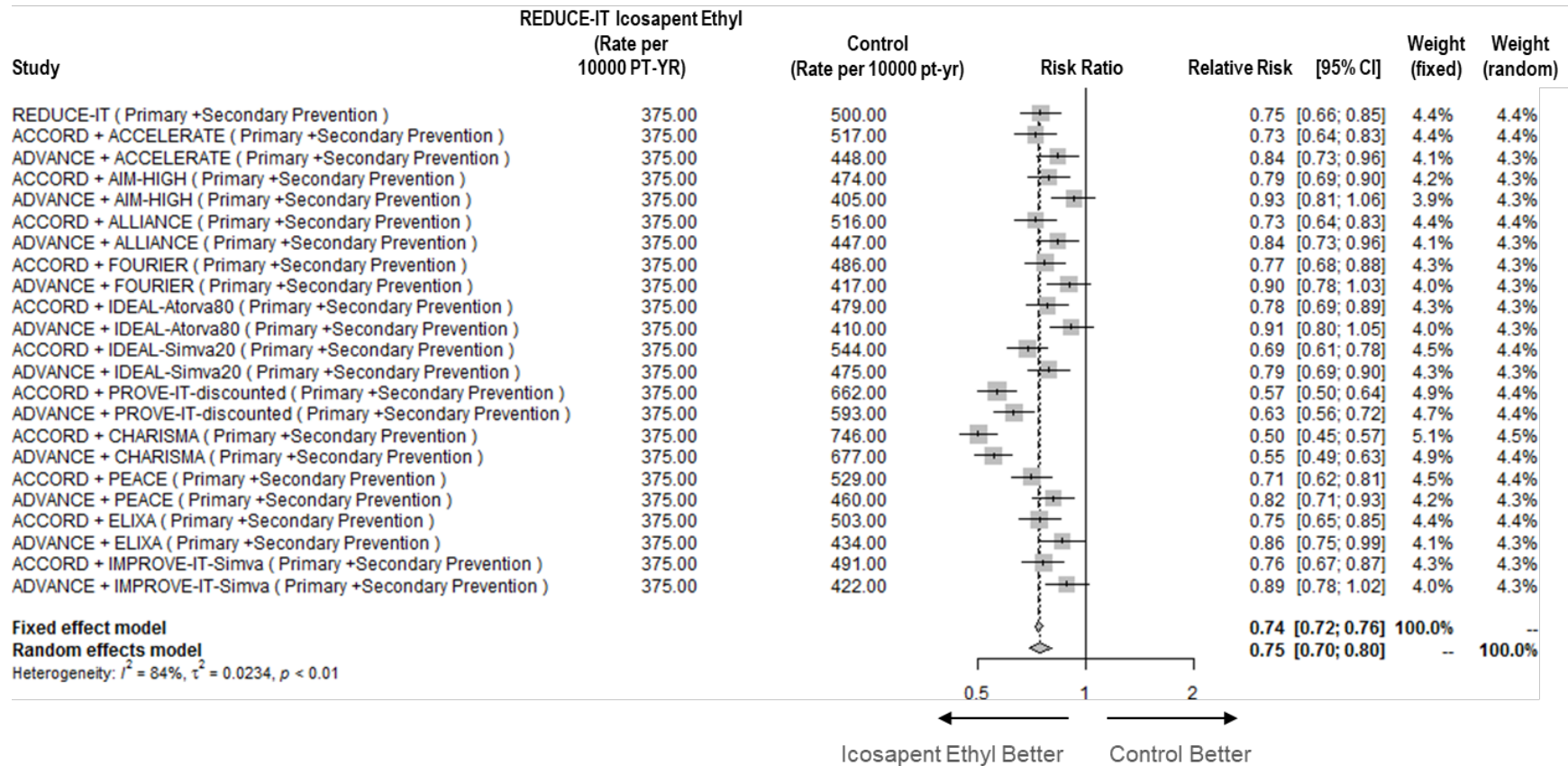


Figure 27. Meta-Analysis of Primary Composite Endpoint with Historical Controls – Primary + Secondary Preventions (Sensitivity Analysis)



REDUCE-IT Biomarker Changes as Compared to other Studies Administering Long-term Statin Therapy

LDL-C

Through extensive literature search, we did not find studies specifically focused on the long-term stability of LDL-C levels in statin-treated patients, and furthermore not with the CV risk factors used for REDUCE-IT study inclusion, but have identified numerous studies that present serial LDL-C results over time in patients stabilized on statin therapy. As discussed in previous responses, REDUCE-IT was designed with features that may differ from comparator studies, particularly those evaluating cholesterol management therapies. In addition, as a CV outcomes study, the REDUCE-IT protocol did not optimize biomarker measurements, which per FDA and Amarin discussions were considered of peripheral value for interpretation of outcomes effects and therefore, were not included in the primary or secondary endpoint analyses.

Direct measurements of LDL-C are more accurate than estimations, particularly for patients with low LDL-C or elevated TG levels. Within REDUCE-IT, the LDL-C ultracentrifugation direct measurement was available at randomization and Year 1 visits, and LDL-C ultracentrifugation measurements are the primary contributors to the LDL-C Derived value. The LDL-C Hopkins estimation was generally available across all on-site visits; the Friedewald estimation was also generally available across on-site visits, but only for patients with TG ≤ 400 mg/dL. Therefore, for the current comparison to historical studies, both REDUCE-IT LDL-C Derived (more accurate) and Hopkins (most available timepoints) are provided for comparison.

Figure 28 provides an overview of the LDL-C percent changes observed in statin-treated cohorts from recent (published since 2003) CV outcome trials and other long-term studies that reported at least two statin-treated LDL-C measurements over time (individual study citations), along with a comparison to LDL-C changes in REDUCE-IT (per LDL-C Derived and Hopkins methods). Historical mean or median values were obtained from available data tables or digitization of published LDL-C curves, and time zero was assumed to be the first available statin-stabilized timepoint. As studies inconsistently reported LDL-C values from a variety of methods, the percent changes from baseline were used for cross-study comparison to minimize the impact of differential methods on absolute values. As shown in Figure 28, increases in LDL-C after statin stabilization are observed in 79% of historical study curves (34 of 43 curves). The LDL-C changes observed in the statin-stabilized REDUCE-IT placebo group fall within the range of changes from comparator studies. It is also worth noting that study-wide mean or median levels do not convey the substantial inter- and intra-patient variability that is often observed across these studies.

The studies in Figure 28 represent a wide range of designs with differing inclusion and exclusion criteria. Absolute and percent changes in LDL-C after study entry can be significantly impacted by baseline LDL-C levels. Further, when enrollment criteria require a biomarker to be above or below a certain level for study entry, regression to the mean can occur after study entry.

REDUCE-IT inclusion criteria required LDL-C levels of >40 mg/dL and ≤ 100 mg/dL at entry, thereby forcing LDL-C values low and resulting in a placebo group median baseline of 76.0 mg/dL. In contrast, some studies included in Figure 28 forced LDL-C high for enrollment (e.g., FOURIER, ODYSSEY-LONGTERM, OSLER, SPIRE, LY3015014), where LDL-C levels would be more likely to decrease over the course of the study if impacted by a regression to the mean phenomena. Therefore, Figure 29 compares REDUCE-IT LDL-C changes to studies within

Figure 28 that also required statin-treated LDL-C below a specific threshold for study entry and reported an initial statin-stabilized LDL-C comparable to REDUCE-IT (i.e. ≤ 110 mg/dL; allowing for 10% variability from the upper limit REDUCE-IT LDL-C inclusion criterion).

Even more pronounced than Figure 28, almost all curves (7 of 8) in Figure 29 demonstrate an increase in LDL-C in statin-treated patients, and the LDL-C increases observed in REDUCE-IT are similar to that observed in some comparator studies with similar baseline LDL-C requirements. The LDL-C increases often occurred early across this subgroup of studies that forced LDL-C low at study entry, further supporting a regression to the mean phenomenon rather than longer-term underlying contributors such as disease progression or a decrease in statin therapy adherence.

These cross-study comparisons of LDL-C changes in statin-treated patients demonstrate that the LDL-C increase observed in the REDUCE-IT placebo group is similar to increases observed from comparable statin-treated groups in other long-term studies. Also, these cross-study comparisons support a regression to the mean phenomenon, in agreement with the previously discussed analyses exploring regression to the mean for LDL-C in REDUCE-IT (Table 20, Table 22, and Table 23). Overall, these historical comparisons do not support a placebo-mediated effect on LDL-C in REDUCE-IT.

Figure 28. Historical Studies: Changes in LDL-C in Statin-Stabilized Treatment Groups

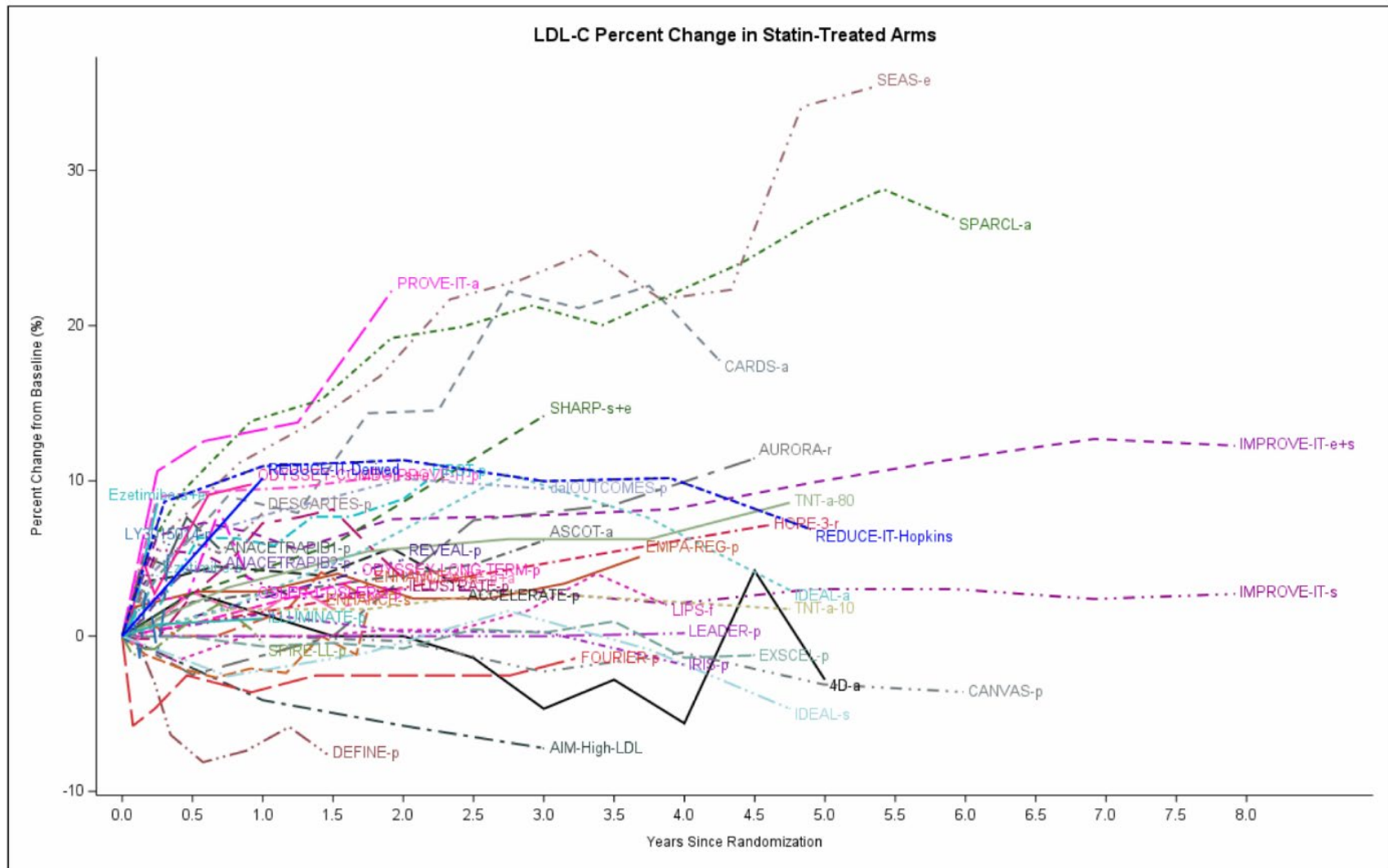
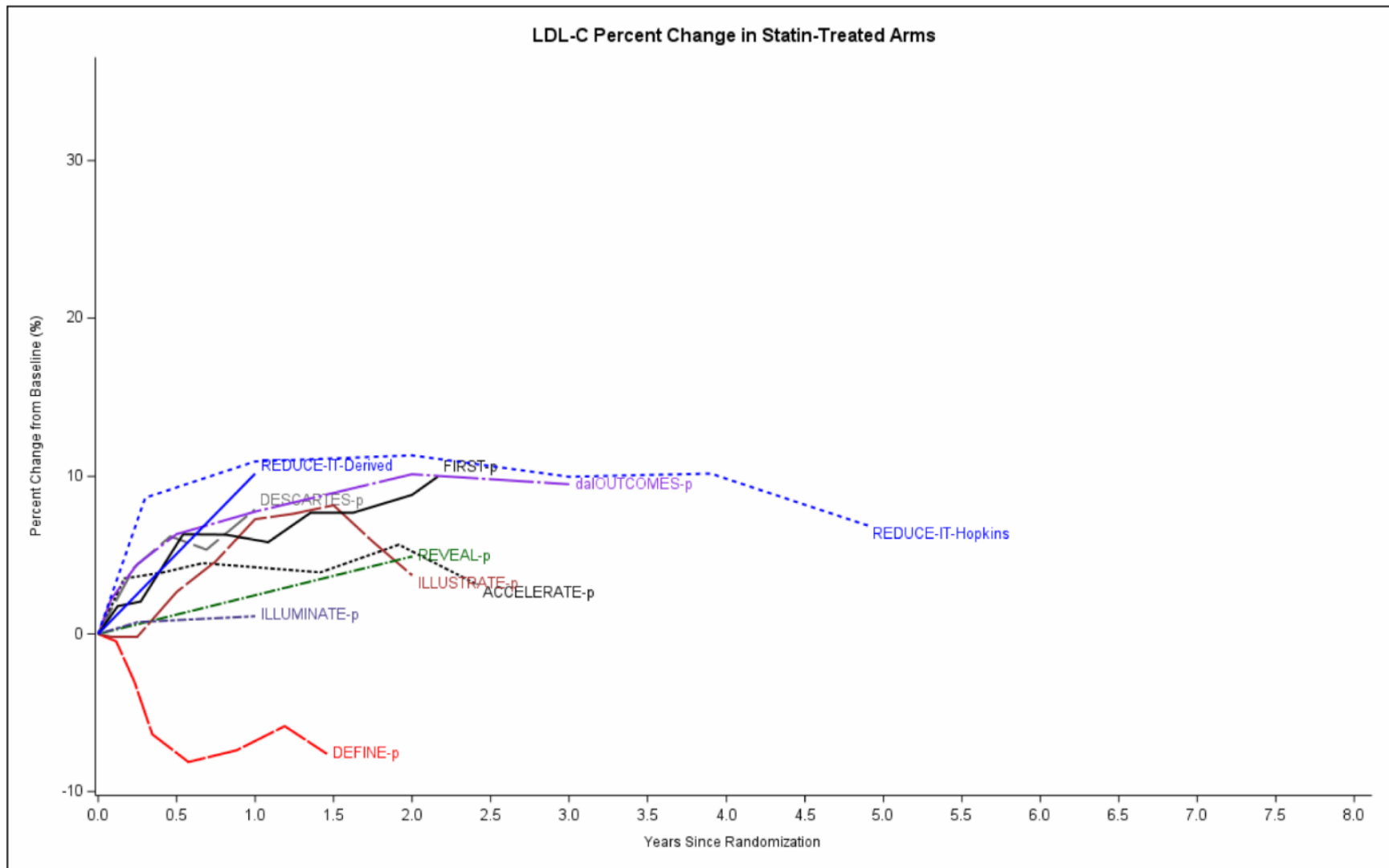


Figure 29. Historical Studies with Statin-Stabilized LDL-C Inclusion Criteria Similar to REDUCE-IT: Changes in LDL-C in Statin-Stabilized Treatment Groups



hsCRP

Similarly, we did not find studies specifically focused on the long-term stability of hsCRP levels in statin-treated patients, and furthermore not with the CV risk factors used for REDUCE-IT study inclusion. we did identify isolated studies which present serial hsCRP results over time in patients stabilized on statin therapy. Importantly, there are far fewer studies presenting hsCRP levels across time in patients stabilized on statin therapy as compared to studies presenting LDL-C measurements in statin-treated patients. Additionally, as discussed in previous responses, REDUCE-IT was designed with features that may differ from comparator studies, particularly those evaluating cholesterol or inflammation management therapies.

As discussed above, clinical trials evaluating biomarkers known to have high intra-individual variability typically employ repeat measurements over short durations of time for a more accurate average biomarker level. High intra-individual variability is especially pronounced for hsCRP (estimated standard deviation of 1-3 mg/L), which is heavily influenced by transient conditions such as minor trauma and infections (Ockene 2001). Substantial intra-individual variability for hsCRP is the reason behind the joint AHA and Center for Disease Control recommendations that hsCRP measurements be performed in metabolically stable patients without ongoing inflammation or infection, and with two measurements spaced two weeks apart which should be averaged for a more stable estimate of this biomarker (Pearson 2003). In addition, inter-individual variability can also be high across differing patient populations, for example across differing ethnic groups (ERFC 2010). Along with this high variability, clinical studies have shown that hsCRP increases in about 25-50% of statin-treated patients (Riesen 2002; Strandberg 2000; van Wissen 2002), and the changes in individual patients can be quite large, on the order of several mg/L (Strandberg 2000). As summarized by Kinlay, those patients with substantial increases in hsCRP are not necessarily non-responders to statin therapy, but likely patients with a high degree of hsCRP variability that has obscured a signal of actual hsCRP change (Kinlay 2007). How such variability and observed increases in select patients might influence specific studies, and their enrolled patient populations, is not fully understood. Due to these caveats, the single measurements of hsCRP at baseline and Year 2 in REDUCE-IT limit the conclusiveness of any observed associations or cross-study comparisons.

Some recent CV outcome studies that collected hsCRP measurements over time also included enrollment criteria that required hsCRP to be elevated at entry, and thus set these studies up for a regression to the mean phenomenon where hsCRP levels would be expected to decrease in the control arms over the course of the study. The JUPITER study selected for non-statin treated patients with hsCRP levels ≥ 2 mg/dL, who were then randomized to rosuvastatin or placebo. Within the placebo arm, hsCRP was reduced from a baseline of 4.3 mg/L to 3.5 mg/L at one year, remaining in the range of 3.3-3.5 mg/L over the course of approximately four years in study (Ridker 2008). This approximately 0.8-1.0 mg/L reduction of hsCRP in the placebo group suggests a regression to the mean phenomenon resulting from forcing hsCRP high at baseline, per study inclusion criterion. Similarly, the CANTOS study selected patients with hsCRP levels ≥ 2 mg/L despite aggressive secondary prevention strategies, who were then randomized to canakinumab or placebo; 91.1% of CANTOS patients were on statin therapy at baseline. In the placebo arm, hsCRP was reduced from 4.1 mg/L at baseline to 3.5 mg/dL at three months and continued to remain at a level between 3.4-3.6 mg/L across the approximately four years in study (Ridker 2017). These CANTOS results suggest that, despite stable statin therapy in most patients within the placebo arm, there was a rapid decrease of approximately 0.6 mg/dL in hsCRP, followed

by fairly stable levels over the approximately four-year follow-up period that were approximately 0.5-0.7 mg/dL below baseline. Such results are again supportive of a regression to the mean phenomenon rather than other confounders that may be slower to impact biomarker levels. The FOURIER study randomized statin-treated patients to evolocumab or placebo (Sabatine 2017). FOURIER did not prospectively select for patients with high hsCRP levels, but hsCRP >2 mg/L was a risk factor that could qualify a patient, along with other risk factors. At baseline, hsCRP was 1.8 mg/L in the statin-treated placebo group and was reduced by 0.2 mg/dL at 48 weeks. Of note, a subgroup analysis split patients into those with baseline hsCRP levels <1, 1-3, or >3 mg/L (Bohula 2018). In placebo patients across these subgroups, hsCRP change from baseline to 48 weeks was essentially zero in patients with baseline hsCRP <1 mg/L (baseline = 0.6 mg/L; change = -0.01 mg/L), hsCRP was reduced by 0.2 mg/L in patients with baseline hsCRP of 1-3 mg/L (baseline = 1.7 mg/L), and was decreased 2.0 mg/L in patients with baseline hsCRP levels >3 mg/L (baseline = 5.4 mg/dL). These FOURIER results suggest that, despite stable statin therapy in patients within the placebo arm, there was a decrease of approximately 2.0 mg/L in hsCRP in patients with hsCRP >3 mg/dL at baseline. This trend of a relatively large reduction in patients with hsCRP >3mg/dL, a lesser reduction in patients with baseline hsCRP 1-3 mg/dL, and no reduction for patients with hsCRP <1 mg/L, is again supportive of a regression to the mean phenomenon rather than other confounders. It is particularly noteworthy that both JUPITER and CANTOS started with similar baseline hsCRP levels slightly above 4 mg/L, and both observed similar reductions of approximately 0.5-1.0 mg/L by the first published timepoint and across the following timepoints, and that the FOURIER subgroup with baseline hsCRP levels >3 mg/L (median hsCRP baseline of 5.4 mg/dL) demonstrated an even greater decrease in hsCRP of 2.0 mg/dL; together again supporting a regression to the mean phenomenon may be occurring with similar impact regardless of background statin therapy. Within their discussion of the CIRT trial (which did not show a change in hsCRP or events with methotrexate), investigators noted that prior methotrexate research in the context of arthritis flairs had reported reductions in hsCRP and suggested that such reduction may have been due to high baseline hsCRP and subsequent regression to the mean (Ridker 2019). Each of these studies (or discussion) support a susceptibility of hsCRP to modulations outside of treatment-induced changes, which is consistent with the hsCRP changes observed within the placebo arms of JUPITER, CANTOS, and FOURIER.

We found limited other studies that included statin therapies and serial on-treatment hsCRP levels. The few studies we identified did not force hsCRP low or high at entry, and they reported fairly consistent statin-stabilized hsCRP levels over time, with relatively small increases or decreases. These trials include PRINCE (Albert 2001), ASAP (vanWissen 2002), dal-OUTCOMES (Schwartz 2012), PROVE-IT (Ridker 2005), AURORA (Fellstrom 2009), ODYSSEY COMBO (Cannon 2015), HOPE-3 (Yusef 2016), and J-STARS (Kitawaga 2017).

Overall, there are far fewer comparator studies for hsCRP than for LDL-C in statin-treated patients. Available data across studies suggest that intra-individual hsCRP levels are highly variable, and that increases in hsCRP levels are observed in approximately 25-50% of statin-treated patients; how such variability and increases might influence specific studies and patient populations is not fully understood. If accurate hsCRP levels are needed, investigators should employ repeat measures over short durations of time in metabolically stable patients. Per discussions with FDA, REDUCE-IT was designed as a CV outcomes study and, therefore, such design parameters were not employed, as hsCRP and other biomarkers were only measured to support tertiary, exploratory, and *post hoc* analyses. Furthermore, it was agreed that biomarkers such as hsCRP would not be relied upon to assess the CV outcomes results of REDUCE-IT. Results from studies that forced

hsCRP high at entry suggest that regression to the mean likely results in an early and sustained change in hsCRP of approximately 0.5-1.0 mg/L (including in statin-treated patients), which supports this biomarker being susceptible to changes in placebo groups that are not mediated through a placebo-specific effect, but rather by other underlying influences that do not appear to be overcome by statin therapy. This is also in agreement with the previously discussed analyses exploring regression to the mean in REDUCE-IT ([Table 21](#)). Ultimately, there is too little available data on hsCRP changes in comparable patient populations under similar treatment conditions to fully understand how the REDUCE-IT results fit into the limited hsCRP landscape, but these historical comparisons do not support a placebo-mediated increase in hsCRP in REDUCE-IT. In addition, as presented earlier, hsCRP changes in the placebo group appear to have no impact on outcomes ([Table 24](#)), and hsCRP changes in the icosapent ethyl arm appear to have only limited impact ([Table 26](#); see also [Table 27](#) below).

Theoretical Predicted Impact of Biomarker Changes on CV Outcomes and Related Post Hoc Covariate-Adjusted Analyses

LDL-C Studies and CV Risk Predictiveness

Median LDL-C levels at baseline and one year, along with within-group and between-group changes from baseline to one year were provided using different direct methods (e.g., in [Table 18](#)). LDL-C was directly measured by ultracentrifugation at randomization (Visit 2) and one year (Visit 4); ultracentrifugation was the preferential method utilized within the LDL-C Derived values. LDL-C could also be estimated by the Hopkins calculation (or by the Friedewald calculation for patient visits with TG $\leq$ 400 mg/dL) from the lipid panel collected at each on-site visit (randomization, four months, one year, and annually thereafter). LDL-C by ultracentrifugation (preferentially used to support the LDL-C Derived values) represents the most accurate measurement of LDL-C, but with limited visits available; the LDL-C Hopkins estimation was generally available across all on-site visits and regardless of TG levels, but with less accuracy compared to direct measurement methods (particularly for patients with low LDL-C). Therefore, [Table 18](#) presents both LDL-C Derived and LDL-C Hopkins values.

In comparative trials, within-group changes from baseline can be informative, but placebo-corrected values are considered the most accurate representation of drug effects as this approach appropriately accounts for potential confounders, such as underlying disease progression, changes in medication compliance, or regression to the mean phenomena. Considering the increased accuracy of LDL-C ultracentrifugation versus the LDL-C Hopkins estimation method, and of placebo-corrected data versus within-group comparisons, the more appropriate and complete representation of LDL-C changes across the study is provided by LDL-C Derived values, which at Year 1 show a change from baseline of +2.0 mg/dL in icosapent ethyl and +7.0 mg/dL in placebo groups, for a placebo-corrected difference of -5.0 mg/dL with icosapent ethyl. The corresponding Hopkins estimations show a change from baseline of -1.1 mg/dL in icosapent ethyl and +9.3 mg/dL in placebo groups, for a placebo-corrected difference of -9.6 mg/dL with icosapent ethyl. REDUCE-IT inclusion criteria required LDL-C below 100 mg/dL and the LDL-C changes in the REDUCE-IT placebo group appear to be influenced by a regression to the mean phenomenon.

As presented in [Appendix E](#), EPA has multiple effects on lipoprotein metabolism observed across studies (with differing placebos/controls); many of these effects are unique to EPA (e.g., in comparison to DHA) and they include reduced production and faster clearance of TG, decreased

production of VLDL particles, and increased clearance of apoB-containing particles (e.g., see Dunbar 2019; Fialkow 2016; Ishida 2013; Oscarsson 2017). This recent EPA literature argues that the between-group differences observed in LDL-C within REDUCE-IT are driven by a modest beneficial LDL-C-lowering effect of icosapent ethyl, as opposed to a placebo-mediated effect. In addition, the LDL-C increase observed in the REDUCE-IT placebo group is similar to increases observed within other comparable modern statin-treated populations over longer treatment times (Figure 29) and is also consistent with other expected phenomena such as regression to the mean.

The predictive nature of treatment-naïve LDL-C levels for CV risk has been well established on a population basis, although with limitations on a patient-level basis (Sniderman 2001). In addition, treatment-induced reductions in LDL-C that target increases in LDL receptor availability have consistently demonstrated CV risk reduction in treatment-naïve patients. In such treatment-naïve patients at a population level, CV-related risk reductions of approximately 19-23% per mmol/L (39 mg/dL) reduction in LDL-C have been observed across meta-analyses of randomized controlled trials, which equates to about 0.49-0.59% reduction in risk per 1 mg/dL reduction in LDL-C (e.g., CTT Collaborators 2005; Konstantinos 2018; Kizer 2010; Robinson 2005; Silverman 2016). Importantly, population-level analyses are limited in their ability to account for the variable nature of LDL-C and, therefore, suffer from regression dilution bias that can overestimate the risk reduction associated with relative changes in LDL-C. Patient-level meta-analyses address this bias, but are less prevalent; one available patient-level meta-analysis predicts a HR of 1.13 for each 32 mg/dL increase in LDL-C (Beekholdt 2012), which equates to 0.41% change in risk per 1 mg/dL change in LDL-C. Therefore, for hypothetical exploration through entertaining this correlation for the illustrative purposes of calculating a change in risk that we do not see evidence to be valid under the totality of the circumstances, the 5 mg/dL LDL-C difference in change from baseline between treatment groups observed in REDUCE-IT would only amount to a 2.0% risk difference per the patient-level meta-analysis, and a 2.4-2.9% risk difference per the less accurate population-level meta-analyses. As noted above, this hypothetical 2.0% risk difference is heavily reliant on data from studies in which statin-naïve LDL-C baseline levels were much higher. The risk difference with a statin-treated baseline LDL-C of 75 mg/dL may be lower, where it is less definitively established how relative changes within statin-stabilized patients fall on these predictive curves.

As noted above, it is not clear if changes in LDL-C in statin-treated patients fall on the same predictive curves as statin-naïve patients, particularly once LDL-C is well controlled, such as in REDUCE-IT, with a statin-treated median baseline LDL-C of 76 mg/dL in the placebo group. Multiple investigators have found the predictive strength of changes in LDL-C to be substantially attenuated in statin-treated patients. For example, in analyses of the AFCAPS/TexCAPS study, little correlation was found between on-treatment LDL-C and risk of subsequent CV events, and the authors suggest that the predictive nature of LDL-C for CV risk may be especially poor when LDL-C is no longer elevated (Gotto 1999). Similarly, analyses of the WOSCOPS study suggest that, after an initial threshold of statin-induced changes in LDL-C is reached, additional differential changes in LDL-C are not predictive of differential changes in risk. For example, absolute changes between on-treatment LDL-C of 20 mg/dL, or relative changes of 10%, did not correlate with changes in coronary heart disease risk (Packard 1998). Analogous findings were observed in an exploration of the LIPID Trial, where investigators found the link between lipid levels at 12 months and subsequent CHD events to be weaker in the statin-treated group than the placebo group, and on-treatment LDL-C was not significantly associated with CHD (Simes 2002). Finally, the patient-level meta-analysis noted above also found the predictive nature of changes in statin-

treated LDL-C to be particularly weak once LDL-C was below 100 mg/dL (Beekholdt 2012). Overall, this calls into question the applicability of CV risk prediction curves, based on LDL-C changes due to initiation of LDL-lowering therapies, to further LDL-C changes in patients already treated with statin therapy, particularly for patients with LDL-C below 100 mg/dL such as in REDUCE-IT.

Also, in light of available literature and analyses discussed above, it is unlikely that the LDL-C increase observed within the placebo group is due to a placebo-mediated effect, and far more likely that the increase in LDL-C is related to underlying phenomena within this high-risk patient population. Similar increases in LDL-C have been observed across other long-term studies of statin-treated patients with comparable LDL-C requirements, particularly in studies where statin-stabilized LDL-C was selectively low (Figure 29). In addition, recent EPA literature suggests a modest LDL-C reduction with EPA therapy across studies (e.g., Ballantyne 2012; Ballantyne 2015; Ballantyne 2016; Sharp 2018; Wei 2011), which further supports the between-group differences observed within REDUCE-IT most likely being driven by a modest LDL-C-lowering effect of icosapent ethyl.

hsCRP Studies and CV Risk Predictiveness

Increased hsCRP has been correlated with increased CV risk, and elevated hsCRP is considered a possible marker of patients that may receive benefit from statin therapy (Braunwald 2012; ERFC 2010; Ridker 2016). For example, a meta-analysis conducted by the Emerging Risk Factors Collaboration using individual-level data from 160,309 people without a history of CV disease, reported an increase in CV risk with increased hsCRP levels, but importantly, most of the association between hsCRP and ischemic events was accounted for by conventional risk factors (such as cholesterol levels) and fibrinogen (ERFC 2010).

Achievement of low hsCRP levels for patients on statin therapy has been associated with decreased risk of CV events in some studies (Morrow 2006; Nissen 2005; Ridker 2005). Nonetheless, other studies found the hsCRP level in statin-treated patients to be a weak predictor of future CV events, particularly beyond other standard measures such as LDL-C (Savarese 2014; ERFC 2012; Yeboah 2012; Kinlay 2007). A full understanding of the drivers for this discordance in conclusions is not understood, but it is likely to be influenced by confounders such as patient populations, current therapies, and achieved biomarker levels.

The CANTOS study targeted reduced inflammation in isolation of LDL-C changes and results suggest a benefit to such therapy; however, this is currently the only positive trial to correlate hsCRP reductions with CV risk reduction independent of concomitant LDL-C. In contrast, the CIRT study administered methotrexate to target pathways of inflammation and did not demonstrate a CV benefit (Ridker 2019). Therefore, it is yet to be fully established how the CANTOS results relate to hsCRP changes specifically (as opposed to other pathways or markers of inflammation), and how these results fit into the larger landscape of hsCRP changes in statin-treated patients, within whom other biomarkers that correlate with disease are also affected (e.g., LDL-C). Finally, clinical and genetic studies consistently suggest that hsCRP is a marker of risk, but not a mediator of risk (and, therefore, likely not a modifiable risk factor), and that reductions in hsCRP may be insufficient to denote reductions in CV risk (Ridker 2016).

Therefore, the prediction of changes in risk per observed hsCRP change in statin-treated patients are overlapping with, and thus not additive to, the risk prediction estimated from LDL-C changes.

In light of the current state of understanding regarding hsCRP, no definitive conclusions can be drawn regarding either the distinct causality or impact of the median 0.5 mg/L change in hsCRP observed in the REDUCE-IT statin-treated placebo group, and there is no conclusive data to suggest that any impact of such a change in hsCRP would predict additive risk beyond that which would be captured in LDL-C changes.

REDUCE-IT Covariate-Adjusted Analyses

Despite biomarker measurements not being optimized in REDUCE-IT, covariate-adjusted analyses of primary and key secondary endpoints evaluating effects of LDL-C (and other biomarkers) on hazard ratios (HRs) were conducted. Slope values and 95% CIs for the slope of biomarker effects on endpoints were explored for:

- Time-varying covariate analyses based on the last available on-study biomarker value prior to an event (or the time of censoring if no endpoint event was observed), or based on change from baseline (absolute or percent).
- LDL-C (Day 120 or 1-year), or hsCRP (2-year) covariate-adjusted analyses using as the covariate on-treatment levels or change from baseline values (absolute or percent).

The adjusted HRs and 95% CIs for the treatment comparison (icosapent ethyl versus placebo) for the primary composite endpoint from these various analyses are summarized in Table 27 and Table 28. These covariate-adjusted analyses provide perspective on the estimated impact of biomarker changes on the treatment effect of CV outcomes data within REDUCE-IT. These adjusted HRs reflect the treatment effect on outcomes assuming baseline and post-treatment biomarker values were the same in both the icosapent ethyl and placebo treatment groups. Most of these covariate-adjusted analyses show a narrow range of -1 to +1% HR change, with the largest increase resulting in HR=0.788 from the analysis using Day 120 LDL-C Friedewald as the covariate, representing a 3.6 percentage point increase from HR=0.752 generated in the primary ITT analyses. Other biomarkers demonstrated similarly minimal HR impact across analyses, including TG, HDL-C, non-HDL-C, remnant lipoprotein cholesterol (RLP-C), apoB, and hsCRP, and similar results were observed across biomarkers within analyses of the key secondary endpoint.

These covariate-adjusted analyses assumed that the individual biomarker response in the placebo group was identical to that in the icosapent ethyl group, which, contrary to available data, completely nullifies any favorable effects on biomarkers from the administration of icosapent ethyl and is, therefore, biased against icosapent ethyl and beyond a worst-case scenario. Nonetheless, the HR was only minimally impacted due to these worst-case assumptions, suggesting that biomarker changes impact the overall analyses, but only by a relatively small magnitude.

If placebo were assumed to have a hypothetical negative impact on LDL-C or other biomarkers (to which we do not agree nor see evidence of this occurring), these analyses suggest the biomarker changes observed in the REDUCE-IT placebo arm could have at most translated to a small (-0.019 to +0.036) hypothetical impact on outcomes. To the contrary, based on detailed evaluation and assessment of available data, the totality of evidence leads to the conclusion that the changes in biomarker levels from baseline observed in REDUCE-IT were most likely due to regression to the mean, disease progression, and other underlying phenomena, and not due to placebo-mediated effects.

Table 27. Stratified Analysis of Time to the Primary Endpoint by Adjusting Time Varying Covariates of Post-Baseline Lipids and Biomarkers (ITT Population)

Lipid Covariate ^[1]	Treatment (Icosapent Ethyl vs Placebo)		Lipid Biomarker Covariate		
	HR (95% CI) for Treatment (Adjusting Covariate ^[2])	Significance P-value ^[3]	HR (95% CI) for One Unit Covariate Change ^[4]	Slope Value in Hazard Ratio	
				Estimated Slope ^[5]	Standard Error ^[5]
Triglycerides (mg/dL)	0.772 (0.700, 0.853)	<0.0001	1.001 (1.000, 1.001)	0.000700	0.000113
LDL-C derived (mg/dL)	0.752 (0.681, 0.830)	0.8043	1.000 (0.998, 1.002)	-0.000252	0.001015
LDL-C (Ultracentrifugation) (mg/dL)	0.759 (0.687, 0.839)	0.9766	1.000 (0.998, 1.002)	0.000029	0.000982
LDL-C (Friedewald) (mg/dL)	0.760 (0.688, 0.839)	0.0517	1.002 (1.000, 1.003)	0.001617	0.000831
LDL-C (Hopkins) (mg/dL)	0.772 (0.699, 0.852)	<0.0001	1.004 (1.002, 1.006)	0.003996	0.000810
HDL Cholesterol-CDC (mg/dL)	0.730 (0.661, 0.806)	<0.0001	0.978 (0.973, 0.983)	-0.022291	0.002518
Non-HDL Cholesterol (mg/dL)	0.784 (0.710, 0.866)	<0.0001	1.004 (1.003, 1.005)	0.003865	0.000592
Apolipoprotein B (mg/dL)	0.762 (0.689, 0.841)	0.0312	1.002 (1.000, 1.005)	0.002452	0.001138
hsCRP (mg/L)	0.758 (0.686, 0.836)	0.0043	1.007 (1.002, 1.011)	0.006584	0.002304
RLP-C (mg/dL)	0.784 (0.709, 0.866)	<0.0001	1.008 (1.006, 1.011)	0.008162	0.001213

[1] Time varying biomarker is derived as the last non-missing biomarker data collected prior to the onset of the efficacy endpoint.

[2] Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment and time varying biomarker as the covariates, and stratified by geographic region, CV risk category, and use of ezetimibe.

[3] P-value for testing significance of covariate in the Cox proportional hazard model.

[4] Hazard ratio for one unit increase of covariate from the Cox proportional hazard model.

[5] Estimated slope and its standard error for covariate from the Cox proportional hazard model.

Table 28. LDL-C Adjusted Covariate Analyses for the Treatment Comparison (Icosapent Ethyl versus Placebo) for the Primary Composite Endpoint

Covariate Type	Treatment comparison (icosapent ethyl versus placebo)			
	LDL-C adjusted hazard ratio (95% CI)			
	LDL-C Derived	LDL-C Ultra	LDL-C Friedewald	LDL-C Hopkins
Primary CSR analysis	0.752 (0.681, 0.830)			
Time-varying LDL-C covariate-adjusted analyses				
Time-varying LDL-C values	0.752 (0.681, 0.830)	0.759 (0.687, 0.839)	0.760 (0.688, 0.839)	0.772 (0.699, 0.852)
Time-varying change from baseline	0.751 (0.680, 0.829)	0.751 (0.677, 0.833)	0.753 (0.682, 0.832)	0.769 (0.696, 0.849)
Time-varying % change from baseline	0.749 (0.679, 0.827)	0.749 (0.675, 0.831)	0.749 (0.679, 0.828)	0.767 (0.694, 0.847)
1-year LDL-C covariate-adjusted analyses				
1-year LDL-C Value	0.743 (0.669, 0.826)	0.749 (0.673, 0.835)	0.761 (0.681, 0.850)	0.756 (0.680, 0.842)
1-year change from baseline	0.744 (0.669, 0.827)	0.741 (0.662, 0.830)	0.755 (0.676, 0.843)	0.754 (0.677, 0.839)
1-year % change from baseline	0.736 (0.663, 0.818)	0.733 (0.655, 0.820)	0.754 (0.675, 0.842)	0.753 (0.676, 0.838)
Day 120 LDL-C covariate-adjusted analyses				
Day 120 LDL-C Value	-	-	0.788 (0.709, 0.876)	0.781 (0.705, 0.866)
Day 120 change from baseline	-	-	0.781 (0.703, 0.869)	0.779 (0.703, 0.864)
Day 120 % change from baseline	-	-	0.778 (0.700, 0.865)	0.777 (0.701, 0.862)

Abbreviations: CI = confidence interval; CSR = clinical study report; HR = hazard ratio; LDL-C = low density lipoprotein-C; ultra = ultracentrifugation.

JELIS

In addition to the above analyses, it is worth noting that JELIS observed a 19% relative risk reduction when comparing EPA plus statin therapy to statin therapy alone, without administration of a placebo. A greater 53% relative risk reduction was observed in patients with baseline dyslipidemia. While there are limitations of the JELIS study, in hindsight following the REDUCE-IT study, the results of that large study are arguably more meaningful than previously appreciated. Salient to the current discussion, these observed reductions in CV risk could not be achieved in whole or part due to mineral oil or to any placebo, as there was no placebo administered in JELIS.

Conclusions

Per design as a CV outcomes study, REDUCE-IT hierarchical primary and secondary analyses focused on CV events, with biomarkers collected as single measures with large spans of time between measurements to support tertiary, exploratory, and *post hoc* analyses. The design of REDUCE-IT recognized that the reported clinical effects of icosapent ethyl extend beyond lipid modification and, therefore, were not expected to be defined by changes within specific biomarkers. We conducted a series of *post hoc* analyses to explore a potential mineral oil effect (or lack thereof) within REDUCE-IT. The supposition that the light mineral oil used in REDUCE-IT does not exert clinically meaningful effects on medication (including statin) efficacy or absorption, biomarkers, outcomes, or safety, agrees with conclusions from prior FDA reviews. It is also supported by multiple lines of evidence, including observed event rate agreement with REDUCE-IT design predictions, extensive literature reviews (EPA mechanisms of action, mineral oil, impact of biomarker changes on CV risk), the Amarin nonclinical and clinical studies, independent REDUCE-IT DMC review, and observed event rate and biomarker comparisons with statin-treated patients across other CV outcome studies. This supposition is also supported by *post hoc* REDUCE-IT data analyses (e.g., off drug, statin type, regression to the mean, diarrhea, lack of correlation between placebo biomarker changes and outcomes, and biomarker covariate -- adjusted analyses). Contrary to the lack of evidence for a hypothetical placebo impact on CV risk, a range of clinical and preclinical studies provide extensive data supporting cardioprotective effects of EPA ([Appendix E](#)). While based on these various sources of evidence we do not agree that placebo caused in an overestimation of the REDUCE-IT results, even if we are wrong, such potential influence cannot reasonably be estimated to account for a substantial portion of overall robust and consistent REDUCE-IT findings, including a 25% RRR in the primary endpoint that is consistent with the observed risk reduction in the JELIS study, which did not administer a mineral oil placebo. Taken together, these various analyses and comparisons are inconsistent with a placebo-mediated effect significantly overestimating the REDUCE-IT results, but rather support a conclusion that icosapent ethyl provided substantial and consistent risk reduction in statin-treated patients.

Reference List of Clinical Studies That Administered Mineral Oil

Note: References included in [Table 17](#) are in bold text. All other references did not comment regarding the efficacy or safety of mineral oil, which implies the general acceptance of mineral oil as safe within these studies.

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APPENDIX E: MECHANISM OF ACTION

The FDA has deemed icosapent ethyl to be an NCE.

The active metabolite in icosapent ethyl is EPA. A broad array of scientific literature has evaluated the mechanisms of action of EPA, and many of these mechanisms differ from other therapies, including individual or mixed omega-3 fatty acids. Multiple mechanisms of action are hypothesized to contribute to the reduction in CV events observed with EPA. Evidence suggests that EPA may impact atherosclerotic processes, resulting in reduced development, slowed progression, and increased stabilization of atherosclerotic plaque. Contributing factors to these results likely include improvement in lipid and lipoprotein profiles through reduced production and faster clearance of TG and apoB-containing particles, without raising LDL-C levels (as has been observed for other therapies, including omega-3 fatty acid mixtures), and by improving HDL function. Accordingly, while EPA is not predominantly an LDL-C lowering drug, scientific literature suggests that EPA modestly lowers LDL-C. In addition, beyond lipids, EPA may exert anti-inflammatory and antioxidant effects, as well as anti-platelet and anti-coagulant effects.

EPA improves lipid and lipoprotein profiles

Clinical studies of EPA have demonstrated TG lowering effects, with decreases ranging from 12-45% relative to placebo (Grimsgaard 1997; Bays 2011; Wei 2011; Ballantyne 2012; Jacobson 2012; Allaire 2016; Brinton 2018; Innes 2018). Compared to placebo, EPA significantly lowers several other lipid and lipoprotein atherogenic biomarkers, including non-HDL-C, apoB, total and VLDL cholesterol levels (Ballantyne 2012), total LDL particles, small dense LDL particles (Ballantyne 2015), RLP-C (Ballantyne 2016), small/dense LDL particles, total LDL particles, (Ballantyne 2015), oxidized LDL, and apoC-III (Ballantyne 2016).

The EPA-induced reduction in TG and other lipid and lipoprotein biomarkers occurs without increases in LDL-C levels (Bays 2011; Wei 2011; Sharp 2018). This is in contrast to DHA, which can significantly increase LDL-C levels compared with placebo (+7.23 mg/dL; 95% CI: 3.98-10.5) (Wei 2011; Allaire 2016; Sharp 2018). DHA is contained in other omega-3 fatty acid formulations, and the increase in LDL-C (median increase of 49% in patients taking omega-3 ethyl esters or Lovaza) that occurs with such formulations make the CV benefit of supplementation with DHA unclear (Fialkow 2016).

In one clinical study of statin-treated patients with high TG, EPA modestly decreased HDL-C (Ballantyne 2012). In other studies, EPA did not affect total HDL-C concentrations (Egert 2009; Allaire 2016), but the HDL-3 subfraction was increased while the HDL-2 subfraction was decreased (Woodman 2002). Cellular studies with EPA support qualitative changes in HDL particles that improve their functionality (Tanaka 2014) and render the particles anti-atherogenic (Tanaka 2018) through increased cholesterol efflux and the production of resolvins.

Kinetic studies show omega-3 fatty acids reduce hepatic very low-density lipoprotein triglyceride (VLDL-TG) synthesis and/or secretion, enhance TG clearance, and may alter apoB-containing particle production and clearance (Oscarsson 2017). EPA increases LDL clearance and likely decreases VLDL particle synthesis and/or secretion (Dunbar 2019). This EPA-induced increase in apoB-containing particle clearance may differ from the effects of DHA, which slowed apoB-

containing particle clearance in a preclinical study (Ishida 2013) and increased LDL-C in clinical studies (Fialkow 2016). These effects of EPA therapy may be due to increased fatty acid β -oxidation, inhibition of acyl CoA:1,2-diacylglycerol acyltransferase (DGAT), decreased lipogenesis in the liver, increased plasma lipoprotein lipase (LPL) activity, changes in particle-receptor interactions, and regulation of lipid-related genes such as peroxisome proliferator-activated receptors (PPARs), sterol-regulatory element binding proteins (SREBPs), retinoid X receptors (RXRs), or liver X receptor (LXR).

Anti-Inflammatory and Antioxidant Effects of EPA

Anti-inflammatory effects of EPA may stem in part from competitive displacement of AA in membrane phospholipids, as AA in phospholipids is metabolized into pro-inflammatory lipid mediators such as prostaglandins and thromboxanes (Innes and Calder 2018). A dose-dependent decrease in AA content of platelets and red blood cells (RBCs) is reported for clinical studies of omega-3 fatty acids containing EPA (Katan 1997; Flock 2013). When substituted in place of AA, EPA is metabolized by lipoxygenases and cyclooxygenases into 5 series leukotrienes, which have diminished inflammatory effects, as well as other mediators, such as resolvins, that modulate resolution of the inflammatory response (Serhan 2008). EPA may have other localized effects, including modified cell membrane phospholipid fatty acid composition that can alter lipid rafts, and production of lipid mediators that affect immune function, cell signaling, and gene function (Calder 2015).

Clinical trials evaluating anti-inflammatory effects of EPA have shown reductions in various biomarkers of inflammation, including C-reactive protein (CRP) (Satoh 2007; Bays 2013; Allaire 2016), LpPLA2 (Asztalos 2016; Bays 2013), and soluble intercellular adhesion molecule (ICAM) and vascular cell adhesion molecule (VCAM) in patients with metabolic syndrome and/or obesity (Yamada 2008). EPA has also been shown to increase adiponectin, an adipocytokine with anti-inflammatory and anti-atherogenic properties (Itoh 2007), and interleukin-10 (IL-10), an anti-inflammatory cytokine involved in macrophage recruitment that contributes to reducing inflammation and improving the insulin signal (Satoh-Asahara 2012). Furthermore, treatment with EPA restored the anti-inflammatory properties of HDL in dyslipidemic persons (Tanaka 2014). EPA-enriched HDL particles were also subsequently shown to be cardioprotective through increased cholesterol efflux and the production of resolvins (Tanaka 2018).

EPA did not affect inflammatory biomarkers in several studies of patients with Type 2 diabetes (Mori 2003; Azizi-Soleiman 2013; Poreba 2017), suggesting potentially differential metabolism in this patient population, although small sample sizes, low dosing, or marginal exposure may have limited the ability to observe changes. For example, in two of these studies (Azizi-Soleiman 2013; Poreba 2017), the use of a relatively low dose of EPA (1 g/day) may explain the lack of effect. Although Mori et al. evaluated effects of 4 grams/day of EPA in 59 patients, this study was of shorter duration than other studies showing positive effects (6 versus at least 10 weeks).

Notably, anti-inflammatory effects of EPA may be enhanced in combination with statin therapy (Mason 2019) and numerous preclinical studies corroborate the anti-inflammatory effects of EPA (Zhao 2004; Zeyda 2005; Matsumoto 2008; Morin 2017; Mickleborough 2009, Allam-Ndoul 2016; Hughes 1996; Honda 2015; Inoue 2017), including activation of a novel anti-inflammatory pathway (Wang 2009). Further, EPA has been shown to effectively resolve inflammation in a rat model of rheumatoid arthritis, an inflammatory condition (Morin 2015).

Regarding oxidative stress, two phase 3, double blind randomized controlled trials of 4 g/d EPA showed significant reductions in oxidized LDL in 229 (the MARINE study) and 702 (the ANCHOR study) patients with HGT (Bays 2013). In other randomized controlled clinical trials, EPA has also been shown to reduce oxidative stress as measured by urinary isoprostanes (Mori 2000; Mori 2003; Mas 2010), a marker of lipid peroxidation and oxidant stress produced by the in vivo free radical peroxidation of AA. In a randomized clinical trial comparing effects of EPA in conjunction with a statin compared to statin alone in patients with coronary artery disease and dyslipidemia, no differences were observed, although a *post hoc* analysis revealed that among persons with higher baseline levels of urinary-8 isoprostane, the combined therapy group had a significant reduction in urinary isoprostanes relative to control (Takaki 2011). In vitro studies showed that EPA inhibited LDL oxidation in a dose dependent manner in contrast to other TG-lowering drugs including fenofibrate, niacin and gemfibrozil, which had no effect (Mason 2015), and such anti-oxidant effects of EPA extended to VLDL, small dense LDL (sdLDL), and HDL (Mason 2016; Mason 2019). Further, the antioxidant activity of EPA was enhanced with concomitant treatment with atorvastatin (Mason 2016).

However, these benefits may be negatively impacted by the oxidation of EPA, given the well-characterized instability of the molecule. The chemical integrity of EPA is known to be prone to oxidation (Mason 2016). Recent research has suggested that the presence of oxidized lipids in common fish oil dietary supplements may impact the biological benefits of the omega-3 fatty acids, such as EPA. Elevated levels of oxidized lipids also play a central role in atherogenesis, may contribute to vascular injury, and may pose an increased potential for CV risk in individuals with coronary disease. Although omega-3 fatty acids, such as EPA, have the ability to interfere with lipid oxidation, that effect may be lost if the molecule's chemical integrity is altered (Mason 2017).

Oxidative stress can lead to endothelial dysfunction, and in other cellular studies EPA had beneficial effects on markers of endothelial function (Tardivel 2009). EPA has also been shown to protect against oxidative stress through induction of heme oxygenase-1 (HO-1), a stress protein that protects against oxidative stress-induced injury. Finally, EPA had cytoprotective effects in endothelial cells by reducing hydrogen peroxide-induced cell death (Hagiwara 2011).

Anti-Platelet and Anti-Coagulant Effects of EPA

EPA reduces platelet activation as well as mean platelet volume and count (Park 2002). Multiple studies have documented reduced platelet aggregation with EPA treatment (Terano 1983; Tamura 1986; Westerveld 1993; Phang 2013). In two studies, EPA decreased platelet activating factor-induced platelet aggregation, but not collagen-induced platelet aggregation (Westerveld 1993; Woodman 2003). Diminished platelet aggregation may be mediated by competitive inhibition of thromboxane generation (Kramer 1996) or displacement of AA. Anti-platelet and anti-coagulant effects of EPA may also be driven in part, by suppressing phospholipase A2 activity or reducing remnant lipoproteins, since remnants promote tissue factor and thrombin (Burke 2017). In a study in nonhuman primates, high doses of EPA, administered in an omega-3 mixture containing smaller amounts of DHA, eliminated both vascular thrombus formation and vascular lesion formation after mechanical vascular injury, while largely sparing hemostatic function and modestly reducing blood thrombotic responses (Harker 1993). These effects were attributed to selective omega-3 fatty acid-dependent alterations in cellular membrane functions.

EPA Reduces Progression, Promotes Stability and Induces Regression of Coronary Atherosclerosis

In addition to the systemic factors noted above that likely contribute to reduced endothelial insult (e.g. reduced lipid delivery/burden and reduced systemic inflammation), atherosclerotic plaque development or stabilization may be more directly impacted by EPA at a localized level.

Animal studies have documented stabilized and reduced atherosclerotic lesions following EPA treatment beyond statin therapy alone (Matsumoto 2008; Nelson 2017). Effects on atherosclerotic lesions and plaque stabilization by EPA may be due to multiple mechanisms. In vitro experiments suggest that EPA infiltrates plaque membranes, where it can disrupt lipid oxidation and signal transduction pathways associated with inflammation and endothelial cell dysfunction (Borow 2015; Mason 2019). EPA may reduce monocyte/monocyte infiltration and conversion into foam cells by reducing uptake of modified LDL (McLaren 2011) and reduce vascular smooth muscle cell proliferation (Shiina 1993; Pakala 1999). EPA has been found to preferentially incorporate into thin-cap atherosclerotic plaque (Sato 2019), and may induce changes in plaque composition, such as increased collagen content (Kawano 2002) or reduced vascular smooth muscle cell proliferation (Shiina 1993; Pakala 1999).

In patients at increased CV risk, intravascular imaging studies demonstrate significant reductions in atherosclerotic plaque formation and decreased vulnerability to plaque rupture with EPA added to statin therapy compared to statin alone (Nishio 2014; Niki 2016; Yamano 2015;), with similar results observed in studies with substantial statin background therapy (Konishi 2019). Supplementation studies of omega-3 fatty acids in both statin-treated and untreated patients awaiting carotid endarterectomy showed morphology changes, including incorporation of EPA into atherosclerotic plaque, associated with thicker fibrous caps, no inflammation (Thies 2003), and fewer foam cells (Cawood 2010). Such morphological or histological changes increase plaque stability, and EPA significantly stabilized non-obstructive neoatherosclerotic plaques in statin-treated patients (Kuroda 2019). Further, statin-treated patients with CHD randomized to EPA were shown to have significant plaque regression and lower plaque lipid volume by integrated backscatter intravascular ultrasound (IB-IVUS) compared to statin alone (CHERRY study; Watanabe 2017). These atherosclerotic plaque results are summarized by Nelson et. al. (Nelson 2017). The EVAPORATE study is an imaging study currently underway to evaluate the effects of Vascepa at 4 grams per day on atheroma volume in a North American population (Budoff 2018).

In addition to the systemic factors noted above that likely contribute to reduced endothelial insult, EPA appears to improve local arterial endothelial function by reducing early- (e.g., oxidative and inflammatory stress, foam cell formation), mid- (e.g., plaque formation and progression), and late-stage (e.g., thrombus formation and plaque rupture) atherosclerotic processes.

Figure 30. Localized Arterial Processes Potentially Affected by EPA

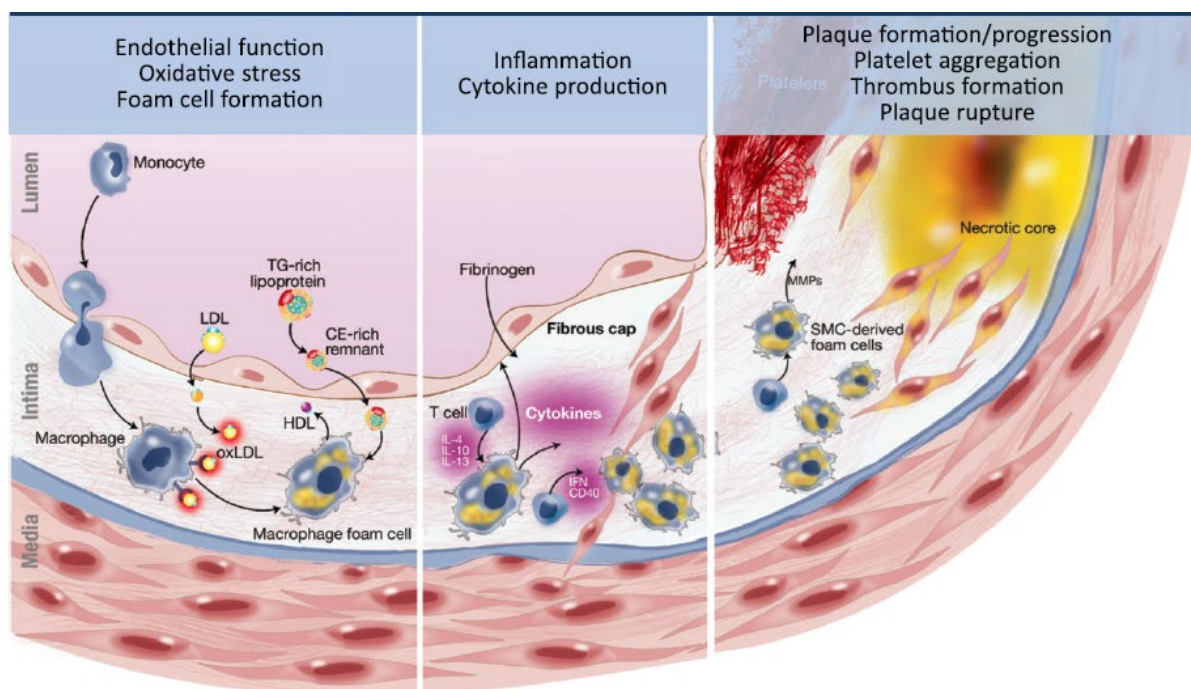


FIGURE 1 The potential effects of EPA on atherosclerosis. Atherosclerosis is a multistep process ranging from endothelial dysfunction to plaque development, progression, and rupture, leading to thrombus formation and cardiovascular events.^{2,3} EPA has been reported to have beneficial effects on multiple atherosclerosis processes including endothelial function, oxidative stress, foam-cell formation, inflammation/cytokines, plaque formation/progression, platelet aggregation, thrombus formation, and plaque rupture.² Abbreviations: CE, cholesteryl ester; EPA, eicosapentaenoic acid; HDL, high-density lipoprotein; IFN, interferon; IL, interleukin; LDL, low-density lipoprotein; MMP, matrix metalloproteinase; ox-LDL, oxidized low-density lipoprotein; SMC, smooth muscle cell; TG, triglycerides

Source: Budoff 2018. <https://creativecommons.org/licenses/by-nc-nd/4.0/>

Effects of EPA on CV Events in Japan EPA Lipid Intervention Study (JELIS)

JELIS was a prospective, randomized, open-label, blinded endpoint evaluation (PROBE design) study that enrolled 18,645 Japanese patients with statin-naïve hypercholesterolemia. Patients were randomly assigned to receive either 1.8 g/day EPA with statin (EPA group; n=9326) or statin only (controls; n=9319). JELIS enrolled 69% women and 80% primary prevention patients. The primary endpoint was a composite of the first occurrence of any major coronary event, including sudden cardiac death, fatal and non-fatal MI, and other non-fatal events including unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting. After a mean follow-up of 4.6 years, JELIS reported a 19% relative reduction in major coronary events with EPA therapy versus control (Yokoyama 2007). JELIS enrolled 80% primary prevention patients.

JELIS patients had statin-naïve baseline TG levels that were only modestly elevated (approximately 153 mg/dL; 1.7 mmol/L), which were reduced approximately 5% from baseline in the EPA plus statin group as compared to the statin-alone group. In a subgroup analysis of patients with atherogenic dyslipidemia (defined as baseline statin-naïve TG $\geq$ 150 mg/dL and HDL-C <40 mg/dL), a more substantial 53% reduction in the primary endpoint was observed (Saito 2008). Similar to the full study cohort, there was only about a 5% differential reduction in TG levels in this subgroup of patients treated with EPA plus statin as compared to the subgroup of patients treated with statin-only therapy. Therefore, while TG-reduction may have contributed to the

overall CV benefit observed in JELIS, it is likely this was a relatively small contribution to the reported 19% and 53% relative risk reductions in the full and dyslipidemic cohorts, respectively.

There were limitations to the JELIS study design, including enrolling exclusively Japanese patients, having an open-label design without a placebo (although blinded endpoint evaluation), and administering lower dose statin therapy than is currently recommended per modern non-Japanese guidelines (although in agreement with JAS guidelines at the time of study conduct). Nonetheless, while based on hypothesis-generating and/or *post hoc* analyses, the JELIS results, considered in light of REDUCE-IT results, supports the conclusion that stable, pure, isolated EPA administered at a dose sufficient to achieve high plasma EPA levels may have potential benefits in the management of patients with high CV risk despite modern doses of statin therapy. These benefits are likely at least partially driven by mechanisms beyond plasma lipid or lipoprotein modification, many of which appear to be unique from other omega-3 fatty acids or agents that lower TG levels.

Importance of Achieving Threshold EPA Levels

Achievement of threshold EPA levels may be necessary for the benefits observed in clinical studies. Icosapent ethyl therapy increases plasma EPA concentrations in a dose dependent manner and the increase in plasma EPA is correlated with the magnitude of TG reduction (Bays 2016). In addition, plasma EPA, but not DHA, has been associated with CV benefit in multiple clinical trials. For example, in the JELIS study conducted in Japan where the average fish intake is five-fold higher than other countries (Nakamura 2005) and baseline EPA concentrations are accordingly higher, persons with high versus low on-study plasma EPA concentrations (≥ 150 vs < 87 ug/ml, respectively) had a 20% reduced risk of major coronary events (Itakura 2011). In addition, erythrocyte EPA was inversely associated with total mortality in a prospective cohort study (Kleber 2016). Similarly, plasma EPA was inversely related, while plasma DHA was positively related, to total mortality in newly diagnosed patients with diabetes (Lindberg 2013).

As noted earlier, AA is the precursor to proinflammatory mediators, while EPA is the precursor to more anti-inflammatory mediators. Accordingly, EPA-to-AA ratios have also been associated with disease outcomes. In the JELIS study, patients in the highest tertile for on-treatment EPA-to-AA ratio had a significantly lower risk of cardiac death or MI than did patients in the lowest tertile (HR, 0.58; $p=0.038$; $\text{EPA/AA} \geq 1.06$ and ≤ 0.55 , respectively) (Yokoyama 2007). The EPA-to-AA ratio was also found to correlate inversely with the percent change in lipid volume in atherosclerotic plaques in the CHERRY study (Watanabe 2017); thus, greater plasma enrichment of EPA apparently led to a greater reduction in atheroma volume.

Plasma EPA-to-AA, but not the DHA-to-AA ratio, has been inversely related to MACE (Domei 2012) and acute coronary syndrome (Iwamatsu 2016). Similarly, plasma EPA-to-AA (Umemoto 2016) and plasma phospholipid EPA, but not DHA (Lindqvist 2009), was negatively associated with carotid atherosclerosis. Of note, the prostaglandins I₂ (PGI₂) and I₃ (PGI₃) to thromboxane A₂ ratio was correlated with the EPA-to-AA ratio, suggesting that effects of EPA-to-AA may be mediated in part by the actions of PGI₃ (Ohnishi 2013). Further, a threshold effect may exist, such that reduction of coronary events is observed only when the plasma EPA-to-AA ratio is greater than 0.75 (Ohnishi 2013). Thus, while based on hypothesis-generating and/or *post hoc* analyses, failure to achieve a therapeutic threshold of EPA in plasma may explain the lack of CV benefit observed in some trials administering low-dose omega-3 fatty acid mixtures.

The average dietary intake of fish in Japan is about five times higher than other countries, likely contributing to the relatively high 2.9 mol% baseline plasma EPA in JELIS, as compared to a US level of approximately 0.3 mol% (Yokoyama 2007). A comparison of EPA blood levels across relevant Amarin trials suggest that a 4 g/day dose of icosapent ethyl results in similar EPA blood levels in Western populations when compared to the 1.8g/day EPA dose in the Japanese population studied in JELIS. JELIS investigators reported that the mean plasma EPA level in the EPA-treated group increased from 97 µg/mL at baseline to 170 µg/mL on study (Itakura 2011). Similar effects were observed in patients treated with 4 g/day icosapent ethyl in the ANCHOR study (statin-treated patients with TG $\geq$ 200 and $<$ 500 mg/dL), in which mean plasma EPA increased from 28 µg/mL to 183 µg/mL, and the MARINE study (patients with TG $\geq$ 500 mg/dL), in which mean plasma EPA increased from 61 µg/mL to 327 µg/mL (Bays 2016).

Overall, randomized clinical trials and observational data, while generally based upon hypothesis-generating and/or *post hoc* analyses, support the concept that achieving effective plasma EPA concentration appears to be an important determinant of the beneficial effects of EPA. Along with EPA levels, the EPA-to-AA ratio may provide additional insight into the overall metabolic status of an individual. In both the REDUCE-IT study and the JELIS study, the formulation and encapsulation of EPA assured minimal exposure of the active ingredient to oxidation or other effects that may damage EPA and negate clinical effects.

Differences Between Long-Chain Omega-3 Fatty Acids: Chemical Structure as a Factor

Clinical and pre-clinical studies suggest that EPA has differential effects as compared to other long-chain omega-3 fatty acids. EPA is comprised of 20 carbons and five double bonds, which is different from other omega-3 fatty acid molecules, such as another common long-chain omega-3 fatty acid DHA that consists of 22 carbons and six double bonds; such differences can have substantial impact on biological function. For example, clinical studies such as the Amarin-sponsored MARINE study in patients with very high TG levels ($\geq$ 500 mg/dL) suggest no change in LDL-C levels with icosapent ethyl therapy, while substantial increases in LDL-C have been observed in studies enrolling similar patient populations and administering omega-3 fatty acid mixtures that contain DHA. Other clinical studies have also observed increases in LDL-C with DHA administration, but not with EPA. Further, other distinctions are observed between EPA and DHA in clinical and preclinical studies, such as at the levels of apoB-containing particle production or uptake, or regulation transcription or membrane function. Such differences in function are supported by preclinical studies that suggest differential cellular localization and function, including differential molecular regulation, for individual long-chain omega-3 fatty acids. The science related to CV risk reduction with omega-3 fatty acids is complex, with a lack of benefit observed in CV outcome studies that administered low-dose ($<$ 1 g/day) omega-3 fatty acid mixtures in statin-treated patients, and no outcome studies available that administered higher dose omega-3 fatty acid mixtures or DHA-only. While data may become available in the future regarding possible CV benefit of omega-3 fatty acid mixtures (e.g., from the ongoing STRENGTH study), the clinical and preclinical data strongly support that the relative clinical efficacy and safety of different omega-3 fatty acids cannot be presumed to be equivalent.

EPA Mechanism of Action Summary

Clinical studies of EPA have demonstrated a range of improvement to lipid and lipoprotein biomarkers both on a change from baseline and on a placebo-adjusted change from baseline basis. The FDA reviewed such demonstrated results in conjunction with its review of the MARINE and

ANCHOR studies of icosapent ethyl and concurred that the results of such studies were truthful and not misleading with respect to the effects of icosapent ethyl on such biomarkers. However, the FDA wanted the REDUCE-IT study to be completed, as it was designed to answer if the multifactorial effects of icosapent ethyl result in CV risk reduction. REDUCE-IT was not designed to answer how modulation of individual biomarkers correlate with risk CV reduction, but rather how the multifactorial effects of icosapent ethyl alter CV risk.

Overall, preclinical and clinical studies, including outcomes data, support EPA reducing CV events through multiple mechanisms of action, and while reductions of TG and other lipid/lipoprotein levels may contribute, they do not appear to substantially drive the observed CV risk reductions. The relative contribution of individual mechanisms to the observed CV benefit of EPA therapy is not fully known, but the totality of evidence suggests that EPA may impact multiple stages within atherosclerotic processes, resulting in reduced development, slowed progression, and increased stabilization of atherosclerotic plaque. In addition, while based on hypothesis-generating and/or *post hoc* analyses, achieving substantially increased blood concentrations of EPA appears to be necessary for an observed CV benefit in statin-treated patients, as is the importance of administering stable EPA, isolated and encapsulated to high standards to mitigate exposure to oxidation and other potentially damaging factors. Of note, data may become available regarding possible CV benefit of high-dose omega-3 fatty acid mixtures (e.g., from the ongoing STRENGTH study), but the clinical and preclinical data strongly support that the relative clinical efficacy and safety of different omega-3 fatty acids cannot be presumed to be equivalent, and therefore such results will not alter the evidence for EPA-only therapy. Finally, while mechanisms of action are of clinical and scientific interest, they do not need to be fully elucidated for clear demonstration of clinical benefit, such as observed in the REDUCE-IT study. It is not uncommon for drugs to be approved without mechanisms of action being fully elucidated as this is not a requirement for approval, which is further evidenced by various currently approved drugs for patients with diabetes (Rena 2017; Andersen 2018; Pollack 2016).

APPENDIX F: SELECT REDUCE-IT PUBLICATIONS AND RELEVANT GUIDANCE UPDATES BASED ON THE REDUCE-IT RESULTS

The following representative publications present or discuss the REDUCE-IT Results:

- Bhatt 2019(a): Bhatt DL, Steg G, Miller M, et. al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. NEJM. 2019 Apr 25;380(1):11-22.
 - https://www.nejm.org/doi/full/10.1056/NEJMoa1812792?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dpubmed
 - Chan LN. Cardiovascular Risk Reduction with Icosapent Ethyl. NEJM. 2019 Apr 25;380(17):1677.
 - Borghi C, Fogacci F, Cicero AFG. Cardiovascular Risk Reduction with Icosapent Ethyl. NEJM. 2019 Apr 25;380(17):1678.
 - Bhatt 2019(b): Bhatt DL, Steg PG, Miller M. Cardiovascular Risk Reduction with Icosapent Ethyl. Reply. NEJM. 2019 Apr 25;380(17):1678.
- Bhatt 2019(c): Bhatt DL, Steg PG, Miller M, et. al. Effects of icosapent ethyl on total ischemic events: from REDUCE-IT. J Am Coll Cardiol. 2019;380:2791-2802.
 - <http://www.onlinejacc.org/content/early/2019/03/01/j.jacc.2019.02.032>
 - Bhatt 2019(d): Bhatt DL, Steg PG, Miller M, et. al. Reduction in First and Total Ischemic Events With Icosapent Ethyl Across Baseline Triglyceride Tertiles. J Am Coll Cardiol. 2019; 74:1159-1161.

Since publication of the REDUCE-IT results, several clinical treatment guidelines and position statements have been updated.

- ADA 2019: American Diabetes Association. Diabetes Care. 2019 Jan; 42(Supplement 1): S103-S123.
 - In March 2019, the American Diabetes Association (ADA) updated its guidelines with a Level A recommendation in both secondary prevention patients and primary prevention patients with diabetes, and with elevated TG levels (135 to 499 mg/dL). It was noted that data are lacking with other omega-3 fatty acids, and results of the REDUCE-IT trial should not be extrapolated to other products
- AHA 2019: Skulas-Ray AC, Wilson PWF, Harris WS, et al. Omega-3 Fatty Acids for the Management of Hypertriglyceridemia: A Science Advisory From the American Heart Association. Circulation. 2019 Sep 17;140(12):e673-e691.
 - In August 2019, the American Heart Association (AHA) recognized the results of REDUCE-IT and recommended directing medical care away from unproven fish oil dietary supplements and to prescription drug therapy in patients with elevated TG levels.
- ESC/EAS 2019: Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The

Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) Eur. Heart J. 2019 Aug 31. pii: ehz455.

- In September 2019, the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) updated their guidelines with a Level B (Class IIa) recommendation to administer icosapent ethyl therapy in high risk primary and secondary prevention patients with elevated TG (135 to 499 mg/dL) despite statin therapy
- NLA 2019: NLA Position on the use of Icosapent Ethyl in High and Very-High-Risk Patients. National Lipid Association. Website: www.lipid.org/nla/nla-position-use-icosapent-ethyl-high-and-very-high-risk-patients September 13, 2019. Accessed October 1, 2019.
 - In September 2019, the National Lipid Association (NLA) issued a position statement recommending icosapent ethyl for atherosclerotic cardiovascular disease (ASCVD) risk reduction in the secondary prevention and high-risk primary prevention populations with elevated TG (135 to 499 mg/dL) as studied in REDUCE-IT. The NLA recommendation was issued as a Class I, Level B-R (STRONG) recommendation, its highest designation, for icosapent ethyl the publications and guideline/recommendation updates noted above, the independent drug watchdog group Institute for Clinical and Economic Review (ICER) results from a cost effectiveness analysis.

In addition to the guideline and recommendation updates noted above, in September 2019 the Institute for Clinical and Economic Review (ICER), a pharmaceutical watchdog, found icosapent ethyl to be cost effective compared to optimal medical management alone.

- ICER 2019: Institute for Clinical and Economic Review. Additive Therapies for Cardiovascular Disease: Effectiveness and Value (Evidence Report). September 12, 2019.
 - Website: (Accessed October 01, 2019): https://icer-review.org/wp-content/uploads/2019/02/ICER_CVD_Evidence_Report_09122019.pdf
- For these and other reasons, multiple patient advocacy groups and individuals are urging that icosapent ethyl be promptly approved for CV risk reduction to help address the large unmet medical need

APPENDIX G: REDUCE-IT GOVERNING COMMITTEES

The REDUCE-IT study involved a number of governing committees, presented below. These committees are comprised of experienced and esteemed members consistent with the high quality of the design and conduction of this important study.

Steering Committee (SC)

The SC included the chairperson (the Principal Investigator) and medical/scientific specialists with expertise in clinical studies, CV outcomes, and lipidology. The SC had overall responsibility for the following:

- Input into protocol development and protocol amendment development.
- Scientific and strategic direction for the study. The SC addressed and resolved all scientific issues regarding the conduct of the study. All sub-studies were approved by the SC.
- The execution of the study protocol, and the reporting and publication of the study results.
- Logistical coordination of the different study committees.

The SC met periodically as outlined in the SC Charter at least twice per year. The SC meetings were conducted as defined within the SC Charter drafted and approved by the SC. The REDUCE-IT SC members included:

- Deepak L. Bhatt, MD, MPH, FACC, FAHA, FSCAI, FESC, Chair
Professor of Medicine at Harvard Medical School, Executive Director of Interventional Cardiovascular Programs at Brigham and Women's Hospital Heart & Vascular Center, and the Global Principal Investigator and Steering Committee Chair of REDUCE-IT
- Christie M. Ballantyne, MD, Member
Professor, Baylor College of Medicine
- Eliot A. Brinton, MD, Member
Director of Atherometabolic Research, Utah Foundation for Biomedical Research
- Terry A. Jacobson, MD, Member
Director of the Office of Health Promotion and Disease Prevention, Grady Health Systems
- Michael Miller, MD, Member
Director, Center for Preventive Cardiology, University of Maryland School of Medicine
- Philippe Gabriel Steg, MD, Member
Professor, Paris Diderot University
- Jean-Claude Tardif, MD, Member
Professor, Montreal Heart Institute

Study Operations Committee

The Study Operations Committee was responsible for ensuring that study execution and management was of the highest quality, and monitored recruitment, compliance, and the adjudication process, and addressed the day-to-day issues arising from the study. This committee was composed of representatives from the Sponsor and the organization(s) conducting the study (as delegated by the Sponsor). This committee met by teleconference and/or in person on a periodic basis.

The REDUCE-IT Study Operations Committee Members included individuals from Amarin and from Syneos Health, the primary contract research organization responsible for study conduct:

- Rebecca Juliano, Amarin Pharma, Inc., SVP, Clinical Research and Development
- Ralph Doyle, Amarin Pharma, Inc., Executive Director, Clinical Development
- Lisa Jiao, Amarin Pharma, Inc., VP, Biostatistics and Data Management
- Katelyn Diffin, Amarin Pharma, Inc., Associate Director, Clinical Development
- Deirdre Albertson, Syneos Health, VP, General Medicine
- Pedro Roses, Syneos Health, Global Project Manager
- Gail Arias, Syneos Health, Director Endpoint

Clinical Endpoint Committee (CEC)

The CEC was composed of multidisciplinary medical experts (in cardiology or neurology). This committee was blinded to treatment and was responsible for adjudicating all primary, secondary, and tertiary efficacy outcome events reported by the investigators (event adjudication). The CEC operated in accordance with a charter drafted and approved by the CEC that contains details of the adjudication process and methods based on the definitions of the events.

The prespecified primary, secondary, tertiary (exploratory) endpoints, and all fatal events were all adjudicated by the CEC. The CEC did not have any affiliation with the treatment sites and was blinded to the treatment arm and patient identifiers. The Endpoint Management Team gathered all relevant medical records to generate the blinded case report forms for the CEC. When the cause of death was not apparent (e.g., found dead at home), the death was classified as CV in origin unless there was no or conflicting information. The only exception to this adjudication process was the “new onset hypertension” tertiary endpoint, which was adjudicated programmatically through reported clinical values. A more complete explanation of the endpoint adjudication process can be found in [Appendix B](#).

The REDUCE-IT CEC Members included cardiologists and one neurologist:

- C. Michael Gibson, MD, MS, FACC, Chairman
Professor of Medicine, Harvard Medical School
- Eli V. Gelfand, MD, FACC, Member
Assistant Professor of Medicine, Beth Israel Deaconess Medical Center
- Robert P. Giugliano, MD, SM, FAHA, FACC, Member
Associate Professor of Medicine, Harvard Medical School
- Duane S. Pinto, MD, MPH, FACC, FSCA, Member
Associate Professor of Medicine, Beth Israel Deaconess Medical Center
- Megan Carroll Leary, MD, Member
Lehigh Valley Health Network
- Anjan Chakrabarti, MD, MPH, Member (ECG Review)
Sentara Healthcare, Bayview Cardiovascular Associates
- Yuri Pride, MD, Member (ECG Review)
CardioVascular Group (CVG), Gwinnett Medical Center

Data Monitoring Committee (DMC)

The DMC was instituted for REDUCE-IT to ensure ongoing patient safety and to oversee and review the prespecified interim analyses. Recommendations for study continuation at the interim analyses were guided by an interim decision-making process prespecified in the interim statistical analysis plan; formal efficacy analyses were performed as well as safety evaluations at all safety data reviews. The DMC was specifically charged with monitoring the event rates in the active and placebo groups to assess any possible contribution of the placebo selection to the results. Members of the DMC did not otherwise participate in the study. The committee included two cardiologists (electrophysiologists) and one independent statistician, along with a second supporting, but non-voting independent statistician. The DMC meetings were conducted as defined within the DMC Charter drafted and approved by the DMC and the SC.

The REDUCE-IT DMC Members include two electrophysiologists and two statisticians (one voting and one non-voting):

- Brian Olshansky, MD, Chair
Professor Emeritus of Medicine, University of Iowa College of Medicine
- Mina Chung, MD, Voting Member
Professor of Medicine, Cleveland Clinic
- Al Hallstrom, PhD, Voting Member
Professor Emeritus, University of Washington
- Lesly A. Pearce, MS, Independent DMC Associated Statistician, Non-Voting Member

Two independent statisticians from the statistical contract research organization Cytel supported the analyses and DMC review of the two preplanned interim analyses at approximately 60% and 80% of total events:

- Cyrus Mehta, PhD
- Rajat Mukherjee, PhD

APPENDIX H: ADVERSE EVENT AND SERIOUS ADVERSE EVENT DEFINITIONS

Definitions of AEs and SAEs were defined and included within the FDA-agreed protocol. AEs were defined as events, either reported by the patient or observed by the investigating facility, that were neither adjudicated as a component of the primary or secondary outcome nor were they a prespecified tertiary outcome. Per study design, SAEs that were endpoint events were only recorded for the endpoint determination and not captured as SAEs. AEs were considered treatment-emergent if they were not pre-existing conditions known at baseline. Signs or symptoms not tied to a specific disease were also recorded. Following adjudication, if the event was determined to not meet the criteria for an endpoint event, the event was evaluated as an SAE.

AE severity was graded by the investigator:

- **Mild** – Usually transient in nature and generally not interfering with normal activities.
- **Moderate** – Sufficiently discomforting to interfere with normal activities.
- **Severe** – Incapacitating with inability to work or do usual activity or inability to work or perform normal daily activity.

Causality was also assessed by the investigator. AEs were categorized as either “Related, probably related, or possibly related to study drug” (causal) or “Unrelated, not related, or no relation to study drug” (not causal). Investigators had discretion to evaluate causality based on:

- The temporal sequence from study medication administration
- The event should occur after the study medication is given. The length of time from study medication exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases
- Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.
- Concomitant medication
- The other medications the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this group of medications
- Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses
- The exposure to stress might induce adverse changes in the patient and provide a logical and better explanation for the event.
- The pharmacology and pharmacokinetics of the study medication
- The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study medication should be considered.

Finally, investigators evaluated the seriousness of AEs. A SAE is defined as an AE that meets any of the following criteria:

- Results in death

- Is life-threatening- Note: The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Requires hospitalization or prolongation of existing hospitalization- Note: In general, hospitalization for treatment of a pre-existing condition(s) that did not worsen from baseline is not considered an AE(s) and should not be reported as a SAE(s).
- Results in disability/incapacity
- Is a congenital anomaly/birth defect
- An important medical event that did not result in death, was not life threatening, or did not require hospitalization but was considered a SAE based upon appropriate medical judgment because the event jeopardized the patient and required medical or surgical intervention to prevent one of the outcomes listed above.

APPENDIX I: EVENT RATE ESTIMATION AND DETERMINATION OF SAMPLE SIZE

Event Rate Estimation for the Primary Outcome of the Control Arm

The initially assumed annual event rate for the primary endpoint in the placebo group was based on published CV outcome studies with high CV risk statin-treated patients and endpoint components similar to those outlined within the REDUCE-IT study design.

The prespecified primary endpoint of REDUCE-IT was agreed to be a single composite primary endpoint based on enrollment targeting a blend of 70% of patients with established CVD (per protocol “CV Risk Category 1”) and 30% of high-risk patients with diabetes and additional risk factor(s) for CVD (per protocol “CV Risk Category 2”). Prior to commencing REDUCE-IT, to estimate the control event rate, six published trials were identified with populations and reported endpoints that closely matched the CV risk categories and endpoints planned for REDUCE-IT: Four trials for established CVD (secondary prevention, including CHARISMA (Bhatt 2006), PEACE (Braunwald 2004), IDEAL (Pedersen 2005), and PROVE-IT (Cannon 2004)), and two trials for high CV risk (primary prevention), including ACCORD (ACCORD 2010), and ADVANCE (Patel 2008). The reported event rates of the representative populations in these studies (with a discounted rate included for PROVE-IT to account for the increased event rate observed in patients with a recent acute coronary syndrome event), weighted by both their sample size and the enrollment blend, resulted in a projected annualized placebo event rate of 5.9%. Accurate event rate estimation was needed to ensure that the sample size was adequate to reach the target of approximately 1612 adjudicated primary endpoint events within a target median patient follow-up period of 4 to 5 years. See [Table 29](#) for source information.

Table 29. Sample Size Estimation for the Primary Outcome of the Control Arm in REDUCE-IT Based on Historical Event Rates

Trial (Journal Year)	Inclusion Criteria	Best-Match Endpoint: Individual Parameters of the Composite Endpoint	Best-Match Intervention(s) (n)	Statin Use: % (n/N)	Best-Match Intervention Arm(s) Event Rate (n/N): Follow-Up Duration	Estimated Annual Event Rate
Established Cardiovascular Disease (per protocol “CV Risk Category 1”) Representative Trials:						
CHARISMA (NEJM 2006)	Age ≥ 45 plus either (78.1%) documented vascular disease (coronary, cerebrovascular, symptomatic PAD) or 20.8% multiple atherothrombotic risk factors (DM, diabetic nephropathy, carotid stenosis, etc.)	<i>Principal secondary efficacy end point:</i> MI, Stroke, CV death, Hospitalization for UA, TIA, or Revascularization (coronary, cerebral, or peripheral)	Clopidogrel 75mg + aspirin (7802) and placebo + aspirin (7801)	Yes: 76.9% (11,992/15,603)	17.3% (2,696 /15,603): [28 months] 2.33 years median	8.6%
PEACE (NEJM 2004)	Age ≥ 50 and LVEF ≥40% and documented CAD (MI or CABG or >50% coronary obstruction)	<i>Primary Outcome:</i> MI, CV death, CABG or PCI	Placebo (4132)	Yes ^[1] : 70% (2892 ^[2] /4132)	22.5% (929/4132): 4.8 years median	5.5%
IDEAL (JAMA 2005)	Age ≤ 80 and Documented MI	<i>Any CHD Event:</i> CHD Death, MI, Cardiac Arrest, Stroke, Coronary Revasc., Hosp. for UA	Simvastatin 20mg (4449) and Atorvastatin 80mg (4439)	Yes: 100% (8888/8888)	22.0% (1957/8888): 4.8 years median	5.9%
PROVE IT- TIMI 22 (NEJM 2004)	Age ≥ 18 with prior MI/high-risk UA and total cholesterol ≤ 240mg/dL	<i>Primary Efficacy Outcome:</i> ACM, MI, hospitalization for UA, stroke, PCI, CABG	Pravastatin 40mg (2063); Atorvastatin 80mg (2099)	Yes: 100% (4162/4162)	24.3% (1013/4162) ^[2] : 2 years mean	7.4% ^[2]
High Risk for CVD (per protocol “CV Risk Category 2”) Representative Trials:						
ACCORD (NEJM 2010)	Age 40 to 79 with T2DM + CV Disease or Age 55-79 with atheroscl., albuminuria, left ventric. hypertrophy or 2+ CV risk factors	<i>Secondary Outcomes:</i> ACM, revascularization, or CHF hospitalization	Placebo (2753)	Yes: 60.2% (1658/2753)	4.7 years mean ^[3]	4.8% ^[3]
ADVANCE (NEJM 2008)	Age ≥ 30 with T2DM or age ≥ 55 with major macrovascular disease, microvascular disease, or 1+ risk factor for vascular disease	<i>Total Coronary Events:</i> CV death, MI, coronary revasc., hospital admission for UA and Stroke ^[4]	Normal glucose control (5569) or Intensive glu control with gliclazide 30- 120 mg (5571)	Yes: 3146/11,140 (28.2%) baseline and 4,305/11,140 (38.6%) study end	12.7% ^[4] : 5.0 years median	2.5% ^[4]

PAD: Peripheral Artery Disease; DM: Diabetes mellitus; MI: Myocardial Infarction; CV: Cardiovascular; UA: Unstable Angina; TIA: Transient Ischemic Attack; LVEF: Left Ventricular Ejection Fraction; CAD: Coronary Artery Disease; CABG: Coronary Artery Bypass Graft; PCI: Percutaneous Coronary Intervention; CHD: Coronary Heart Disease; ACM: All-Cause Mortality; T2DM: Type 2 DM

¹ Reported as “lipid-lowering drugs”

² The PROVE-IT annualized event rate was discounted, as PROVE-IT enrolled patients with recent acute coronary syndrome (ACS) events, whom are known to have a high event rates, particularly in the first year post-ACS. Only % reported was reported: (n) was estimated as % * N

³ Actual annual event rate was reported

⁴ Stroke was reported separately from the composite endpoint so was estimated at 2.5% (slightly lower than the stroke rate of 3.8% in the manuscript since there is likely overlap between the stroke rate and the composite event).

Determination of Sample Size

REDUCE-IT was designed to target a median patient follow-up period of between 4 and 5 years.

The initial sample size estimation, as presented in the original study protocol (02 August 2011), assumed an annualized placebo event rate of 5.9% and that the primary endpoint would be reduced by approximately 15% with icosapent ethyl compared with the placebo group (corresponding to an HR of 0.85).

The planned enrollment population of 7990 patients reflects a more conservative projected annual placebo event rate of 5.2%, which was decided prior to study initiation and following input from the FDA, to ensure adequate powering should the actual placebo event rate be lower than the original estimate of 5.9%. The updated sample size calculation was based on assumptions of constant hazard, asymmetric recruitment rate over time, and without factoring for dropouts. A risk reduction corresponding to an HR of 0.85 (icosapent ethyl versus placebo control) was assumed. A total of approximately 1612 events were required to detect this HR with approximately 90% power with 2-sided alpha level at 5% and with two interim analyses.

The recruitment period was assumed to be approximately 4.2 years with 20% recruitment in the first year, 40% in the second year, 20% in the third year, 19% in the fourth year and the remaining 1% in the last 0.2 years. The expected maximum study duration was estimated at 6.5 years unless the study was terminated early for efficacy or safety issues; there were no predefined mandatory stopping criteria.

Consistent with the plan stated above, an analysis and modeling of pooled, blinded primary endpoint events across the remainder of the study was performed prior to the projected enrollment of the 7990th patient. Based on this analysis, the sample size of 7990 randomized patients was within 95% confidence likely to result in the target 1612 adjudicated primary endpoint events within 2018. The results of this analysis were shared with and approved by the REDUCE-IT SC and DMC. REDUCE-IT was conducted under an FDA SPA agreement, including advance agreement regarding design elements, prespecified endpoints and testing hierarchy ([Appendix C](#)).

The actual observed annual placebo group event rate of 5.74% in REDUCE-IT compares favorably to the projected 5.9% event rate.

APPENDIX J: SUPPORTING TABLES AND FIGURES

Supplemental information are referenced within the main body of this document and are provided here.

Table 30. Summary of Primary, Key Secondary and Components of Primary Endpoint As Reported By Investigators: ITT Population

Endpoint	Icosapent Ethyl (N=4089)	Placebo (N=4090)	HR (95% CI)	P-value	Rate/1000 pt yrs	
					Icosapent Ethyl	Placebo
Primary Composite Endpoint	782 (19.1%)	1008 (24.6%)	0.740 (0.674, 0.813)	<0.0001	49.1	66.0
Key Secondary Composite Endpoint	430 (10.5%)	557 (13.6%)	0.751 (0.662, 0.851)	<0.0001	25.3	33.6
Fatal or Nonfatal MI	199 (4.9%)	308 (7.5%)	0.633 (0.530, 0.756)	<0.0001	11.6	18.3
Fatal or Nonfatal Stroke	107 (2.6%)	135 (3.3%)	0.780 (0.605, 1.006)	0.0546	6.1	7.9
CV Death including Undetermined Death*	174 (4.3%)	213 (5.2%)	0.803 (0.657, 0.981)	0.0315	9.9	12.2
Coronary Revascularization	377 (9.2%)	541 (13.2%)	0.670 (0.587, 0.764)	<0.0001	22.6	33.5
Unstable Angina	283 (6.9%)	372 (9.1%)	0.744 (0.637, 0.868)	0.0002	16.8	22.7

* CV Deaths are adjudicated by CEC.

Note: The number of subjects with event (n) is the number of subjects with the event in the ITT Population within each treatment group (N). Rate per 1000 patient years (pt-yrs) is $1000 \times n/\text{pt-yrs subjects at-risk}$.

Log-Rank test statistic and p-value are reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe

Table 31. Stratification Factors (ITT Population)

Stratification Factors	Icosapent ethyl (N=4089) n (%)	Placebo (N=4090) n (%)	Overall (N=8179) n (%)
Region			
Westernized Region ¹	2906 (71.1)	2905 (71.0)	5811 (71.0)
Eastern European Region ²	1053 (25.8)	1053 (25.7)	2106 (25.7)
Asia Pacific Region ³	130 (3.2)	132 (3.2)	262 (3.2)
CV Risk Category			
CV Risk Category 1 (Secondary Prevention)	2892 (70.7)	2893 (70.7)	5785 (70.7)
CV Risk Category 2 (High Risk Primary Prevention)	1197 (29.3)	1197 (29.3)	2394 (29.3)
Baseline Ezetimibe Use			
Patients on Ezetimibe	262 (6.4)	262 (6.4)	524 (6.4)
Patients not on Ezetimibe	3827 (93.6)	3828 (93.6)	7655 (93.6)

Abbreviations: CV = cardiovascular; ITT = Intention-to-Treat; IWRS = Interactive Web Response System.

Note: Percentages were based on the number of patients randomized to each treatment group in the ITT population (N). All stratification factors were reported from the IWRS.

1 Westernized region includes Australia, Canada, the Netherlands, New Zealand, United States, and South Africa.

2 Eastern European region includes Poland, Romania, Russian Federation, and Ukraine.

3 Asia Pacific region includes India.

Table 32. Cardiovascular Disease History and Risk Factors (ITT Population)

Category Term	Icosapent ethyl (N=4089) n (%)	Placebo (N=4090) n (%)	Overall (N=8179) n (%)
Prior Atherosclerotic Cardiovascular Disease	2816 (68.9)	2835 (69.3)	5651 (69.1)
Prior Atherosclerotic Coronary Artery Disease and Related Morbidities	2387 (58.4)	2393 (58.5)	4780 (58.4)
Ischemic dilated cardiomyopathy	137 (3.4)	109 (2.7)	246 (3.0)
Myocardial infarction	1938 (47.4)	1881 (46.0)	3819 (46.7)
Unstable angina	1017 (24.9)	1015 (24.8)	2032 (24.8)
Prior Atherosclerotic Cerebrovascular Disease and Related Morbidities	641 (15.7)	662 (16.2)	1303 (15.9)
Carotid disease	343 (8.4)	372 (9.1)	715 (8.7)
Ischemic stroke	267 (6.5)	242 (5.9)	509 (6.2)
Transient ischemic attack	194 (4.7)	181 (4.4)	375 (4.6)
Prior Atherosclerotic Peripheral Arterial Disease	387 (9.5)	388 (9.5)	775 (9.5)
Ankle brachial index <0.9 without symptoms of intermittent claudication	97 (2.4)	76 (1.9)	173 (2.1)
Peripheral arterial disease	377 (9.2)	377 (9.2)	754 (9.2)
Prior Non-Atherosclerotic Cardiovascular Disease	3649 (89.2)	3645 (89.1)	7294 (89.2)
Prior Structural Cardiac Disorders	827 (20.2)	866 (21.2)	1693 (20.7)
Congestive heart failure	703 (17.2)	743 (18.2)	1446 (17.7)
Hypertrophic cardiomyopathy	23 (0.6)	20 (0.5)	43 (0.5)
Non-ischemic dilated cardiomyopathy	35 (0.9)	29 (0.7)	64 (0.8)
Non-rheumatic valvular heart disease	150 (3.7)	163 (4.0)	313 (3.8)
Rheumatic valvular heart disease	17 (0.4)	9 (0.2)	26 (0.3)
Prior Cardiac Arrhythmias	229 (5.6)	243 (5.9)	472 (5.8)
Atrio-ventricular block above first degree	51 (1.2)	54 (1.3)	105 (1.3)
Sick sinus syndrome	30 (0.7)	32 (0.8)	62 (0.8)
Supra-ventricular tachycardia other than atrial fibrillation/atrial flutter	74 (1.8)	77 (1.9)	151 (1.8)
Sustained ventricular tachycardia	34 (0.8)	34 (0.8)	68 (0.8)
Torsades de pointes	1 (0.0)	3 (0.1)	4 (0.0)
Ventricular fibrillation	61 (1.5)	65 (1.6)	126 (1.5)
Prior Non-Cardiac/Non-Atherosclerotic Vascular Disorders	3568 (87.3)	3566 (87.2)	7134 (87.2)
Arterial embolism	12 (0.3)	9 (0.2)	21 (0.3)
Deep vein thrombosis	70 (1.7)	60 (1.5)	130 (1.6)
Hypertension	3541 (86.6)	3543 (86.6)	7084 (86.6)
Hypotension	45 (1.1)	33 (0.8)	78 (1.0)
Pulmonary embolism	31 (0.8)	42 (1.0)	73 (0.9)
Non-ischemic stroke	79 (1.9)	84 (2.1)	163 (2.0)
Hemorrhagic stroke	18 (0.4)	22 (0.5)	40 (0.5)
Stroke of unknown origin	63 (1.5)	62 (1.5)	125 (1.5)

Category Term	Icosapent ethyl (N=4089) n (%)	Placebo (N=4090) n (%)	Overall (N=8179) n (%)
Other Prior Conditions or Investigations Influencing Cardiovascular Risk	3044 (74.4)	3055 (74.7)	6099 (74.6)
Prior Metabolic Disorders	2480 (60.7)	2515 (61.5)	4995 (61.1)
Diabetes type 1	28 (0.7)	30 (0.7)	58 (0.7)
Diabetes type 2	2367 (57.9)	2363 (57.8)	4730 (57.8)
Metabolic syndrome	507 (12.4)	540 (13.2)	1047 (12.8)
Baseline Investigations	1783 (43.6)	1707 (41.7)	3490 (42.7)
Renal Disorders	470 (11.5)	429 (10.5)	899 (11.0)
Creatinine clearance >30 and <60 mL/min	309 (7.6)	286 (7.0)	595 (7.3)
Macroalbuminuria	34 (0.8)	24 (0.6)	58 (0.7)
Microalbuminuria	146 (3.6)	134 (3.3)	280 (3.4)
Proteinuria	75 (1.8)	63 (1.5)	138 (1.7)
Abnormal Lipids	1496 (36.6)	1419 (34.7)	2915 (35.6)
High HDL-C (≥60 mg/dL)	187 (4.6)	187 (4.6)	374 (4.6)
Low HDL-C (<40 mg/dL)	1327 (32.5)	1259 (30.8)	2586 (31.6)
Triglycerides >1000 mg/dL	76 (1.9)	72 (1.8)	148 (1.8)
hsCRP >3 mg/L	236 (5.8)	252 (6.2)	488 (6.0)
Other Morbidities	173 (4.2)	173 (4.2)	346 (4.2)
Pancreatitis	14 (0.3)	9 (0.2)	23 (0.3)
Retinopathy	161 (3.9)	167 (4.1)	328 (4.0)
Carotid Stenosis (%)			
n (%)	316 (7.7)	346 (8.5)	662 (8.1)
Mean (SD)	59.0 (21.04)	56.9 (22.99)	57.9 (22.09)
Median	60.0	59.0	59.5
Min, Max	0.0, 100.0	0.0, 100.0	0.0, 100.0

Abbreviations: HDL-C = high-density lipoprotein-cholesterol; hsCRP = high-sensitivity C-reactive protein; ITT = Intention-to-Treat; Max = maximum; Min = minimum; SD = standard deviation.

Note: Percentages were based on the number of patients randomized to each treatment group in the ITT population (N). This summary was based on data collected from the “Cardiovascular History” case report form. Two outliers of carotid stenosis (%) with a value over 100% were excluded from the analysis. Carotid stenosis (%) data reported in categorical format of >x% and <y% were analyzed as x% and y%, respectively, and reported as x% to y% was analyzed as an average of x% and y%.

Table 33. Time to the Primary Endpoint: Sensitivity Analyses (ITT Population)

Endpoint, n (%)	Icosapent ethyl (N=4089)	Placebo (N=4090)	Treatment Comparison ¹	
			HR (95% CI)	
			Icosapent ethyl/Placebo	P-value from Log-Rank Test
Primary Endpoint Excluding Death of Undetermined Cause	673 (16.5)	878 (21.5)	0.737 (0.667 – 0.815)	<0.0001
Primary Endpoint Censored at Study Drug Discontinuation	577 (14.1)	732 (17.9)	0.739 (0.662 – 0.824)	<0.0001
Primary Endpoint Censored at Study Drug Discontinuation + 30 Days	596 (14.6)	776 (19.0)	0.721 (0.648 – 0.802)	<0.0001
Primary Endpoint with Silent MI Censored at Last Normal ECG	705 (17.2)	901 (22.0)	0.752 (0.682 – 0.830)	<0.0001
Primary Endpoint with Silent MI Censored at Midpoint	705 (17.2)	901 (22.0)	0.752 (0.682 – 0.830)	<0.0001

Abbreviations: CI = confidence interval; CV = cardiovascular; ECG = electrocardiogram; HR = hazard ratio; ITT = Intention-to-Treat; MI = myocardial infarction.

Note: The number of patients with event (n) is the number of patients with the event in the ITT population within each treatment group (N).

¹ Log-Rank test statistic and p-value are reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

Table 34. Total Events Analyses for the Primary and Key Secondary Endpoints Including Recurrent Events on the Same Day (ITT Population)

Method	Primary Endpoint		Key Secondary Endpoint	
	HR/RR (95% CI)	P-value ¹	HR/RR (95% CI)	P-value ¹
Andersen-Gill – Intensity Model²	0.68 (0.63 – 0.74)	<0.0001	0.71 (0.63 – 0.79)	<0.0001
Andersen-Gill – Proportional Model³	0.68 (0.61 – 0.76)	<0.0001	0.71 (0.62 – 0.81)	<0.0001
Negative Binomial Model⁴	0.69 (0.61 – 0.77)	<0.0001	0.71 (0.62 – 0.82)	<0.0001
Modified Wei-Lin-Weissfeld Model⁵				
First Event	0.75 (0.68 – 0.83)	<0.0001	0.74 (0.65 – 0.83)	<0.0001
Second Event	0.68 (0.60 – 0.77)	<0.0001	0.75 (0.63 – 0.89)	0.0011
Third Event	0.70 (0.60 – 0.83)	<0.0001	0.79 (0.65 – 0.96)	0.0171
Fourth Event	0.68 (0.57 – 0.82)	<0.0001	0.81 (0.67 – 0.99)	0.0391

Abbreviations: CI = confidence interval; CV = cardiovascular; HR = hazard ratio; ITT = Intention-to-Treat; RR = rate ratio.

1 HR or RR, its 95% CI, and p-value were calculated from these analysis models with treatment and stratified by geographic region, CV risk category, and use of ezetimibe.

2 HR (95% CI) and p-value are from model-based variance-covariance estimates based on Andersen and Gill (Andersen 1982).

3 HR (95% CI) and p-value are from robust sandwich variance-covariance estimates based on Lin 2000.

4 RR (95% CI) and p-value are from a Negative binomial model (Claggett 2018, Rogers 2012, Rogers 2014).

5 HR (95% CI) and p-value of first through fourth recurrent events are from the modified Wei-Lin-Weissfeld model proposed by Li and Lagakos (Li 1997) for an analysis of recurrent events in the presence of deaths.

Analyses are based on the total adjudicated event dataset regardless if multiple endpoints occurred in a single calendar day.

Table 35. Time to Additional Tertiary Endpoint Events (ITT Population)

Endpoint Event, n (%) ²	Icosapent ethyl n/N (%)	Placebo n/N (%)	Treatment Comparison ¹	
			HR (95% CI) Icosapent ethyl/Placebo	P-value from Log-Rank Test
Newly Emergent CHF	169/4089 (4.1)	176/4090 (4.3)	0.95 (0.77 - 1.17)	0.6260
Newly Emergent CHF Requiring Hospitalization	141/4089 (3.4)	144/4090 (3.5)	0.97 (0.77 - 1.22)	0.7810
Transient Ischemic Attack	64/4089 (1.6)	48/4090 (1.2)	1.32 (0.91 - 1.92)	0.1459
Amputation for PVD	22/4089 (0.5)	21/4090 (0.5)	1.04 (0.57 - 1.89)	0.9053
Carotid Revascularization	31/4089 (0.8)	26/4090 (0.6)	1.18 (0.70 - 1.98)	0.5399
Coronary Revascularization ³	376/4089 (9.2)	544/4090 (13.3)	0.66 (0.58 - 0.76)	<0.0001
Emergent Revascularization	41/4089 (1.0)	65/4090 (1.6)	0.62 (0.42 - 0.92)	0.0158
Urgent Revascularization	181/4089 (4.4)	268/4090 (6.6)	0.66 (0.54 - 0.79)	<0.0001
Elective Revascularization	194/4089 (4.7)	278/4090 (6.8)	0.68 (0.57 - 0.82)	<0.0001
Salvage Revascularization	0/4089 (0.0)	2/4090 (0.0)	0.00 (0.00 - 0.00)	0.1563
Cardiac Arrhythmia Requiring Hospitalization of ≥24 Hours	188/4089 (4.6)	154/4090 (3.8)	1.21 (0.97 - 1.49)	0.0856
Cardiac Arrest	22/4089 (0.5)	42/4090 (1.0)	0.52 (0.31 - 0.86)	0.0105
Sudden Cardiac Death	61/4089 (1.5)	87/4090 (2.1)	0.69 (0.50 - 0.96)	0.0259
Ischemic Stroke	80/4089 (2.0)	122/4090 (3.0)	0.64 (0.49 - 0.85)	0.0020
Hemorrhagic Stroke	13/4089 (0.3)	10/4090 (0.2)	1.28 (0.56 - 2.93)	0.5507
New Onset Type 2 Diabetes ⁴	65/1695 (3.8)	63/1697 (3.7)	1.04 (0.73 - 1.47)	0.8361
New Onset Hypertension ⁵	13/4089 (0.3)	15/4090 (0.4)	0.86 (0.41 - 1.80)	0.6847
Peripheral Artery Disease	156/4089 (3.8)	159/4090 (3.9)	0.97 (0.78 - 1.21)	0.7604

Abbreviations: AE = adverse event; CHF = congestive heart failure; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; ITT = Intention-to-Treat; MedDRA = Medical Dictionary for Regulatory Activities; PVD = peripheral vascular disease.

Note: The number of patients with event (n) is the number of patients with the event in the ITT population within each treatment group (N).

- 1 Log-Rank test statistic and p-value are reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.
- 2 Based on a patient's first post-randomization occurrence of the specified endpoint event.
- 3 Coronary revascularization was defined as the composite of emergent, urgent, elective, and salvage revascularization.
- 4 Excludes patients with Type 1 or Type 2 diabetes at baseline.
- 5 As per the Clinical Endpoint Committee Charter, new onset of hypertension was determined programmatically. To identify new onset of hypertension cases, the hypertension standardized MedDRA query was used to search all AEs and negatively adjudicated endpoints. All patients who had hypertension reported on the Cardiovascular History page are excluded.

Table 36. TEAEs with an Incidence $\geq 3\%$ in Either Treatment Group, by MedDRA System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term¹	Icosapent ethyl (N=4089) n (%)	Placebo (N=4090) n (%)	Overall (N=8179) n (%)
Infections and Infestations	1822 (44.6)	1774 (43.4)	3596 (44.0)
Nasopharyngitis	314 (7.7)	300 (7.3)	614 (7.5)
Upper respiratory tract infection	312 (7.6)	320 (7.8)	632 (7.7)
Bronchitis	306 (7.5)	300 (7.3)	606 (7.4)
Pneumonia	263 (6.4)	277 (6.8)	540 (6.6)
Influenza	263 (6.4)	271 (6.6)	534 (6.5)
Urinary tract infection	253 (6.2)	261 (6.4)	514 (6.3)
Sinusitis	169 (4.1)	166 (4.1)	335 (4.1)
Musculoskeletal and Connective Tissue Disorders	1466 (35.9)	1406 (34.4)	2872 (35.1)
Back pain	335 (8.2)	309 (7.6)	644 (7.9)
Arthralgia	313 (7.7)	310 (7.6)	623 (7.6)
Osteoarthritis	241 (5.9)	218 (5.3)	459 (5.6)
Pain in extremity	235 (5.7)	241 (5.9)	476 (5.8)
Musculoskeletal pain	176 (4.3)	130 (3.2)	306 (3.7)
Myalgia	135 (3.3)	147 (3.6)	282 (3.4)
Muscle spasms	101 (2.5)	136 (3.3)	237 (2.9)
Gastrointestinal Disorders	1350 (33.0)	1437 (35.1)	2787 (34.1)
Diarrhea	367 (9.0)	453 (11.1)	820 (10.0)
Constipation	221 (5.4)	149 (3.6)	370 (4.5)
Nausea	190 (4.6)	197 (4.8)	387 (4.7)
Gastroesophageal reflux disease	124 (3.0)	118 (2.9)	242 (3.0)
General Disorders and Administration Site Conditions	1030 (25.2)	979 (23.9)	2009 (24.6)
Chest pain	273 (6.7)	290 (7.1)	563 (6.9)
Edema peripheral	267 (6.5)	203 (5.0)	470 (5.7)
Fatigue	228 (5.6)	196 (4.8)	424 (5.2)
Non-cardiac chest pain	161 (3.9)	173 (4.2)	334 (4.1)
Nervous System Disorders	1004 (24.6)	972 (23.8)	1976 (24.2)
Dizziness	235 (5.7)	246 (6.0)	481 (5.9)
Headache	171 (4.2)	180 (4.4)	351 (4.3)
Respiratory, Thoracic, and Mediastinal Disorders	989 (24.2)	946 (23.1)	1935 (23.7)
Dyspnea	254 (6.2)	240 (5.9)	494 (6.0)
Cough	241 (5.9)	241 (5.9)	482 (5.9)
Metabolism and Nutrition Disorders	953 (23.3)	877 (21.4)	1830 (22.4)
Gout	171 (4.2)	127 (3.1)	298 (3.6)
Diabetes mellitus	169 (4.1)	173 (4.2)	342 (4.2)
Type 2 diabetes mellitus	147 (3.6)	133 (3.3)	280 (3.4)

System Organ Class Preferred Term¹	Icosapent ethyl (N=4089) n (%)	Placebo (N=4090) n (%)	Overall (N=8179) n (%)
Cardiac Disorders	910 (22.3)	855 (20.9)	1765 (21.6)
Atrial fibrillation	215 (5.3)	159 (3.9)	374 (4.6)
Angina pectoris	200 (4.9)	205 (5.0)	405 (5.0)
Injury, Poisoning, and Procedural Complications	748 (18.3)	697 (17.0)	1445 (17.7)
Fall	149 (3.6)	138 (3.4)	287 (3.5)
Vascular Disorders	709 (17.3)	717 (17.5)	1426 (17.4)
Hypertension	320 (7.8)	344 (8.4)	664 (8.1)
Eye Disorders	478 (11.7)	429 (10.5)	907 (11.1)
Cataract	233 (5.7)	208 (5.1)	441 (5.4)
Psychiatric Disorders	372 (9.1)	362 (8.9)	734 (9.0)
Insomnia	124 (3.0)	111 (2.7)	235 (2.9)
Blood and Lymphatic System Disorders	321 (7.9)	372 (9.1)	693 (8.5)
Anemia	191 (4.7)	236 (5.8)	427 (5.2)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Note: A TEAE was defined as an event that first occurred or worsened in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. For each patient, multiple TEAEs of the same preferred term were counted only once within each preferred term. TEAEs are listed in descending order of icosapent ethyl frequency. Percentages were based on the number of patients randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints were not included.

1 All adverse events were coded using the MedDRA, Version 20.1.

Table 37. Study Drug-Related TEAEs with an Incidence $\geq 0.5\%$ in Either Treatment Group, by MedDRA System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term¹	Icosapent ethyl (N=4089) n (%)	Placebo (N=4090) n (%)	Overall (N=8179) n (%)
Patients With at Least 1 Study Drug-Related TEAE	514 (12.6)	499 (12.2)	1013 (12.4)
Gastrointestinal Disorders	302 (7.4)	305 (7.5)	607 (7.4)
Diarrhea	110 (2.7)	161 (3.9)	271 (3.3)
Eructation	35 (0.9)	12 (0.3)	47 (0.6)
Flatulence	34 (0.8)	34 (0.8)	68 (0.8)
Nausea	34 (0.8)	30 (0.7)	64 (0.8)
Dyspepsia	18 (0.4)	20 (0.5)	38 (0.5)
Musculoskeletal and Connective Tissue Disorders	58 (1.4)	33 (0.8)	91 (1.1)
Arthralgia	23 (0.6)	10 (0.2)	33 (0.4)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Note: A TEAE was defined as an event that first occurred or worsened in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. For each patient, multiple TEAEs of the same preferred term were counted only once within each preferred term. TEAEs are listed in descending order of icosapent ethyl frequency. Percentages were based on the number of patients randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints were not included.

Study drug-related TEAEs include those characterized as related, probably related, or possibly related by the Investigator.

¹ All adverse events were coded using the MedDRA, Version 20.1.

Table 38. Study Drug-Related TEAEs Leading to Study Drug Withdrawal with an Incidence $\geq 0.1\%$ in Either Treatment Group, by MedDRA System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term ¹	Icosapent ethyl (N=4089) n (%)	Placebo (N=4090) n (%)	Overall (N=8179) n (%)
Patients With at Least 1 Study Drug-Related TEAE Leading to Study Drug Withdrawal	139 (3.4)	164 (4.0)	303 (3.7)
Gastrointestinal Disorders	97 (2.4)	121 (3.0)	218 (2.7)
Diarrhea	41 (1.0)	66 (1.6)	107 (1.3)
Nausea	16 (0.4)	11 (0.3)	27 (0.3)
Abdominal discomfort	6 (0.1)	6 (0.1)	12 (0.1)
Flatulence	6 (0.1)	6 (0.1)	12 (0.1)
Gastroesophageal reflux disease	5 (0.1)	3 (0.1)	8 (0.1)
Abdominal pain upper	4 (0.1)	5 (0.1)	9 (0.1)
Dyspepsia	4 (0.1)	5 (0.1)	9 (0.1)
Constipation	4 (0.1)	2 (0.0)	6 (0.1)
Gastric disorder	4 (0.1)	0 (0.0)	4 (0.0)
Eructation	3 (0.1)	4 (0.1)	7 (0.1)
Vomiting	3 (0.1)	4 (0.1)	7 (0.1)
Abdominal distension	3 (0.1)	3 (0.1)	6 (0.1)
Abdominal pain	1 (0.0)	3 (0.1)	4 (0.0)
Abnormal feces	0 (0.0)	3 (0.1)	3 (0.0)
Skin and Subcutaneous Disorders	16 (0.4)	15 (0.4)	31 (0.4)
Rash	3 (0.1)	8 (0.2)	11 (0.1)
Pruritus generalized	3 (0.1)	0 (0.0)	3 (0.0)
Skin odor abnormal	3 (0.1)	0 (0.0)	3 (0.0)
Pruritus	1 (0.0)	3 (0.1)	4 (0.0)
Musculoskeletal and Connective Tissue Disorders	13 (0.3)	10 (0.2)	23 (0.3)
Arthralgia	7 (0.2)	2 (0.0)	9 (0.1)
Arthritis	3 (0.1)	0 (0.0)	3 (0.0)
Muscle spasms	0 (0.0)	3 (0.1)	3 (0.0)
Immune System Disorders	4 (0.1)	0 (0.0)	4 (0.0)
Hypersensitivity	3 (0.1)	0 (0.0)	3 (0.0)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Note: A TEAE was defined as an event that first occurred or worsened in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. For each patient, multiple TEAEs of the same preferred term were counted only once within each preferred term. TEAEs are listed in descending order of icosapent ethyl frequency. Percentages were based on the number of patients randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints were not included.

Study drug-related TEAEs include those characterized as related, probably related, or possibly related by the Investigator.

¹ All adverse events were coded using the MedDRA, Version 20.1.

APPENDIX K: BENEFIT-RISK CONSIDERATIONS ACROSS THE SECONDARY PREVENTION (ESTABLISHED CVD) AND HIGH RISK PRIMARY PREVENTION SUBGROUPS

In addition to the analyses presented in the main body of this briefing book, further analyses were conducted to explore benefit-risk considerations of icosapent ethyl across high-risk primary prevention patients (CV risk category 2) and secondary prevention patients with established CVD (CV risk category 1).

Per study design, subgroup analyses were not powered to detect statistically significant results within each individual subgroup, particularly when a subgroup represents a lower proportion of enrolled patients (e.g., less than 50%), and/or when a subgroup has low event rates, which can result in wide 95% confidence intervals (CI) and nonsignificant findings for a particular subgroup. Such exploratory subgroup analyses can be informative for hypothesis-generating efforts, but should not be overly relied upon to substantiate individual subgroup efficacy conclusions. Nonetheless, the analyses of the primary (Figure 9) and key secondary (Figure 10) endpoints across the high-risk primary prevention subgroup and the secondary prevention subgroup with established CVD both demonstrated hazard ratios suggestive of benefit, with an exploratory finding of a possible differential benefit in the primary endpoint (HR [95% CIs] = 0.73 [0.65 to 0.81] for secondary prevention as compared to 0.88 [0.70 to 1.10] for primary prevention; interaction $p=0.14$ which is above the pre-specified 0.15 significance level; Figure 9). There was no significant interaction for benefit observed in the key secondary endpoint between the high-risk primary prevention subgroup and the established CVD secondary prevention subgroup (HR [95% CIs] = 0.72 [0.63 to 0.82] for secondary prevention as compared to 0.81 [0.62 to 1.06] for primary prevention; interaction $p = 0.41$; Figure 10). The established CVD secondary prevention cohort represented approximately 71% of enrolled patients with a high observed event rate, which supported these subgroup analyses reaching independent statistical significance for both the primary and key secondary endpoints. In contrast, the high-risk primary prevention cohort represented approximately 29% of enrolled patients with a lower observed event rate, and therefore it is not surprising that these subgroup analyses did not quite achieve statistical significance. Nonetheless, the hazard ratios suggest benefit with icosapent ethyl treatment in both subgroups and the interaction p -values suggest little to no substantial difference in benefit in high-risk primary versus secondary prevention patients.

Baseline characteristics across the high-risk primary prevention and established CVD secondary prevention subgroups by treatment group are presented in Table 39. The p -values represent the comparison between the totals for the secondary prevention cohort versus the high-risk primary prevention cohort. Patients in the high-risk primary prevention as compared to the secondary prevention subgroup have slightly higher representation from Westernized countries, lower ezetimibe use, increased use of low-intensity statins and less frequent use of high-intensity statins, and a higher representation of women.

**Table 39. Demographic and Baseline Characteristics by Treatment and CV Risk Category Subgroup: Established CVD
Secondary and High-risk Primary Prevention Subgroups**

Parameter Statistic	Secondary Prevention Subgroup			Primary Prevention Subgroup			P-value ¹
	Icosapent Ethyl (N=2892)	Placebo (N=2893)	Overall (N=5785)	Icosapent Ethyl (N=1197)	Placebo (N=1197)	Overall (N=2394)	
Region							<0.0001
Westernized Region ²	1991 (68.8%)	1990 (68.8%)	3981 (68.8%)	915 (76.4%)	915 (76.4%)	1830 (76.4%)	
Eastern European Region ³	833 (28.8%)	834 (28.8%)	1667 (28.8%)	220 (18.4%)	219 (18.3%)	439 (18.3%)	
Asia Pacific Region ⁴	68 (2.4%)	69 (2.4%)	137 (2.4%)	62 (5.2%)	63 (5.3%)	125 (5.2%)	
Baseline Ezetimibe Use							<0.0001
Patients on Ezetimibe	216 (7.5%)	215 (7.4%)	431 (7.5%)	46 (3.8%)	47 (3.9%)	93 (3.9%)	
Patients not on Ezetimibe	2676 (92.5%)	2678 (92.6%)	5354 (92.5%)	1151 (96.2%)	1150 (96.1%)	2301 (96.1%)	
Statin Intensity							<0.0001
Low	113 (3.9%)	126 (4.4%)	239 (4.1%)	141 (11.8%)	141 (11.8%)	282 (11.8%)	
Moderate	1737 (60.1%)	1753 (60.6%)	3490 (60.3%)	796 (66.5%)	822 (68.7%)	1618 (67.6%)	
High	1038 (35.9%)	999 (34.5%)	2037 (35.2%)	252 (21.1%)	227 (19.0%)	479 (20.0%)	
Data Missing	4 (0.1%)	15 (0.5%)	19 (0.3%)	8 (0.7%)	7 (0.6%)	15 (0.6%)	
Age (years) at Randomization⁵							0.0147
n	2892	2893	5785	1197	1197	2394	
Mean (SD)	63.2 (8.69)	63.3 (8.69)	63.2 (8.69)	63.7 (7.52)	63.8 (7.75)	63.7 (7.64)	
Median	63.5	64.0	64.0	64.0	64.0	64.0	
Min, Max	45.0, 88.0	44.0, 91.0	44.0, 91.0	50.0, 92.0	50.0, 86.0	50.0, 92.0	
Sex, n (%)							<0.0001
Male	2269 (78.5%)	2267 (78.4%)	4536 (78.4%)	658 (55.0%)	628 (52.5%)	1286 (53.7%)	
Female	623 (21.5%)	626 (21.6%)	1249 (21.6%)	539 (45.0%)	569 (47.5%)	1108 (46.3%)	
Race, n (%)							<0.0001
White							
Black Or African American	2677 (92.6%)	2675 (92.5%)	5352 (92.5%)	1014 (84.7%)	1013 (84.6%)	2027 (84.7%)	
Asian	26 (0.9%)	47 (1.6%)	73 (1.3%)	43 (3.6%)	42 (3.5%)	85 (3.6%)	
American Indian Or Alaska Native	128 (4.4%)	116 (4.0%)	244 (4.2%)	97 (8.1%)	105 (8.8%)	202 (8.4%)	
Native Hawaiian Or Other Pacific Islander	10 (0.3%)	8 (0.3%)	18 (0.3%)	8 (0.7%)	3 (0.3%)	11 (0.5%)	
Other	6 (0.2%)	2 (0.1%)	8 (0.1%)	1 (0.1%)	1 (0.1%)	2 (0.1%)	
Multiple	23 (0.8%)	15 (0.5%)	38 (0.7%)	7 (0.6%)	20 (1.7%)	27 (1.1%)	
Missing	22 (0.8%)	29 (1.0%)	51 (0.9%)	27 (2.3%)	13 (1.1%)	40 (1.7%)	

Parameter Statistic	Secondary Prevention Subgroup			Primary Prevention Subgroup			P-value ¹
	Icosapent Ethyl (N=2892)	Placebo (N=2893)	Overall (N=5785)	Icosapent Ethyl (N=1197)	Placebo (N=1197)	Overall (N=2394)	
BMI (kg/m²)							<0.0001
n	2889	2881	5770	1189	1190	2379	
Mean (SD)	30.9 (5.01)	31.0 (4.98)	31.0 (5.00)	33.2 (5.97)	33.2 (6.22)	33.2 (6.09)	
Median	30.2	30.3	30.3	32.4	32.4	32.4	
Min, Max	18.3, 59.9	16.4, 55.7	16.4, 59.9	20.0, 65.0	19.7, 64.0	19.7, 65.0	
Duration of Diabetes, (years)							<0.0001
n	1199	1187	2386	1189	1188	2377	
Mean (SD)	8.86 (7.782)	8.23 (7.442)	8.55 (7.619)	9.59 (7.499)	9.29 (7.371)	9.44 (7.435)	
Median	6.86	6.22	6.57	7.76	7.75	7.76	
Min, Max	0.03, 69.50	0.03, 62.38	0.03, 69.50	0.11, 48.18	0.07, 46.10	0.07, 48.18	
Current Smoker, n (%)	487 (16.8%)	469 (16.2%)	956 (16.5%)	141 (11.8%)	144 (12.0%)	285 (11.9%)	<0.0001
Hypertension, n (%)	2837 (98.1%)	2819 (97.4%)	5656 (97.8%)	1150 (96.1%)	1141 (95.3%)	2291 (95.7%)	<0.0001

Abbreviations: BMI = body mass index; CRF = case report form; eGFR = estimated glomerular filtration rate; ITT = Intent-to-Treat; Max = maximum; Min = minimum; SD = standard deviation.

Note: Percentages were based on the number of patients randomized to each treatment group in the ITT population (N) except as noted below.

1 Balance between treatment group p-values were reported from a chi-square test for categorical variables and a t-test for continuous variables. Missing categories were excluded from any comparisons.

2 Westernized region includes Australia, Canada, the Netherlands, New Zealand, United States, and South Africa.

3 Eastern European region includes Poland, Romania, Russian Federation, and Ukraine.

4 Asia Pacific region includes India.

5 Age (years) was at randomization.

A summary of baseline medication classes of special interest are summarized by CV risk category in [Table 40](#). The high proportion of patients taking antidiabetic, antihypertensive, and antithrombotic medications in both CV risk categories is indicative of appropriate treatment of this at-risk patient population. Differences in medication use across CV risk categories reflect the enrollment criteria. For example, as expected there is substantial use of antidiabetic medications in the high-risk primary prevention patients, who were required to have diabetes at baseline, as compared to about a third of the secondary prevention subgroup. In contrast, antithrombotic use was more prevalent in the secondary prevention subgroup as compared to the high-risk primary prevention subgroup. Antihypertensive use was high across both subgroups.

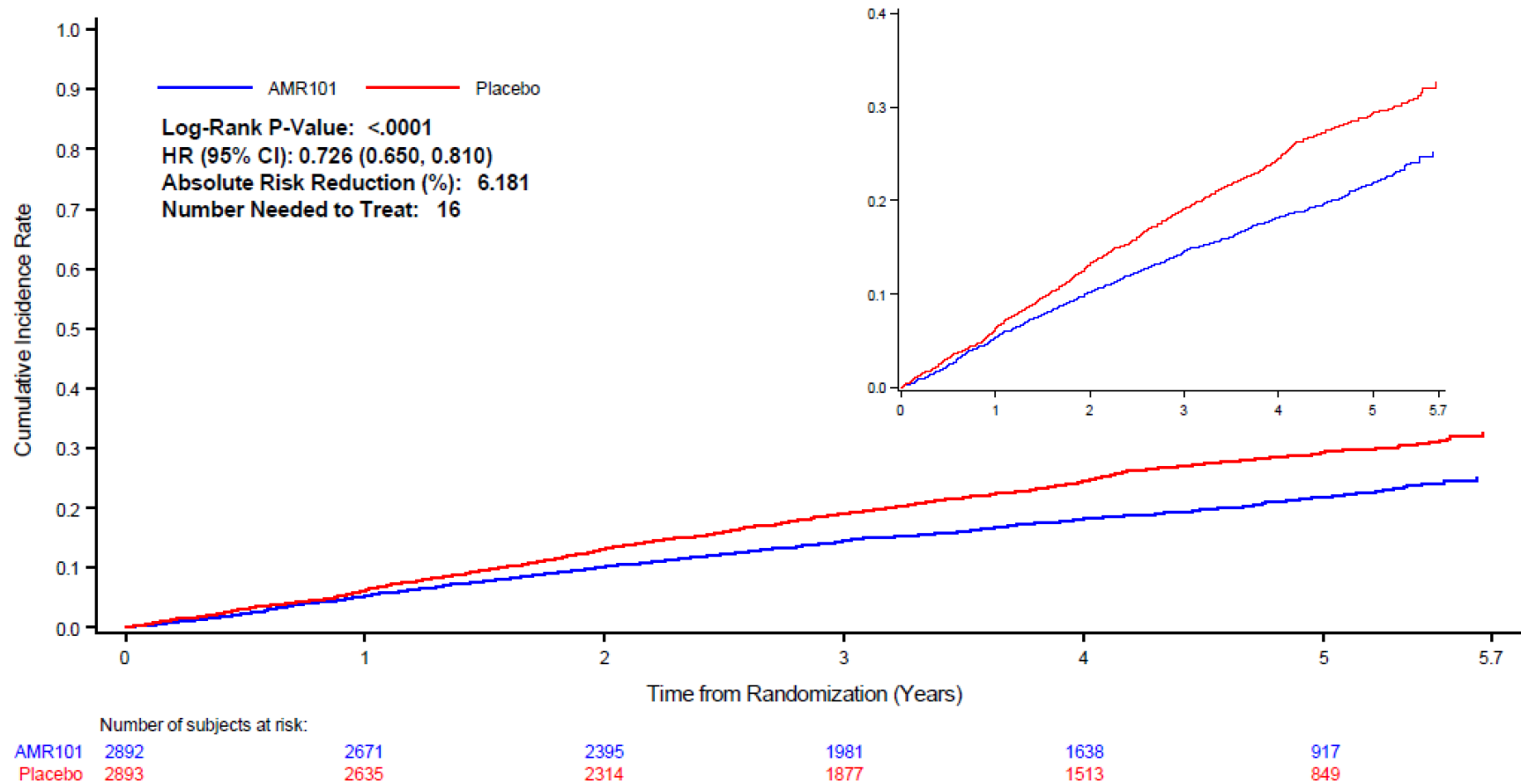
Table 40. Baseline Medication Summary by CV Risk Category (ITT Population)

Medication Taken at Baseline, n (%)	Secondary Prevention (N=5785)	Primary Prevention (N=2394)	Overall (N=8179)
Antihypertensive	5573 (96.34)	2217 (92.61)	7790 (95.24)
Antithrombotic	5491 (94.92)	1503 (62.78)	6994 (85.51)
Antidiabetic	2049 (35.42)	2337 (97.62)	4386 (53.63)
ACE Inhibitors or ARBs	4440 (76.75)	1900 (79.37)	6340 (77.52)
ACE Inhibitors	3059 (52.88)	1184 (49.46)	4243 (51.88)
ARBs	1440 (24.89)	764 (31.91)	2204 (26.95)
Beta Blockers	4630 (80.03)	1152 (48.12)	5782 (70.69)

Abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blockers; CV = cardiovascular; ITT = Intention-to-Treat.
Note: Percentages were based on the number of patients randomized to each treatment group in the ITT population (N).

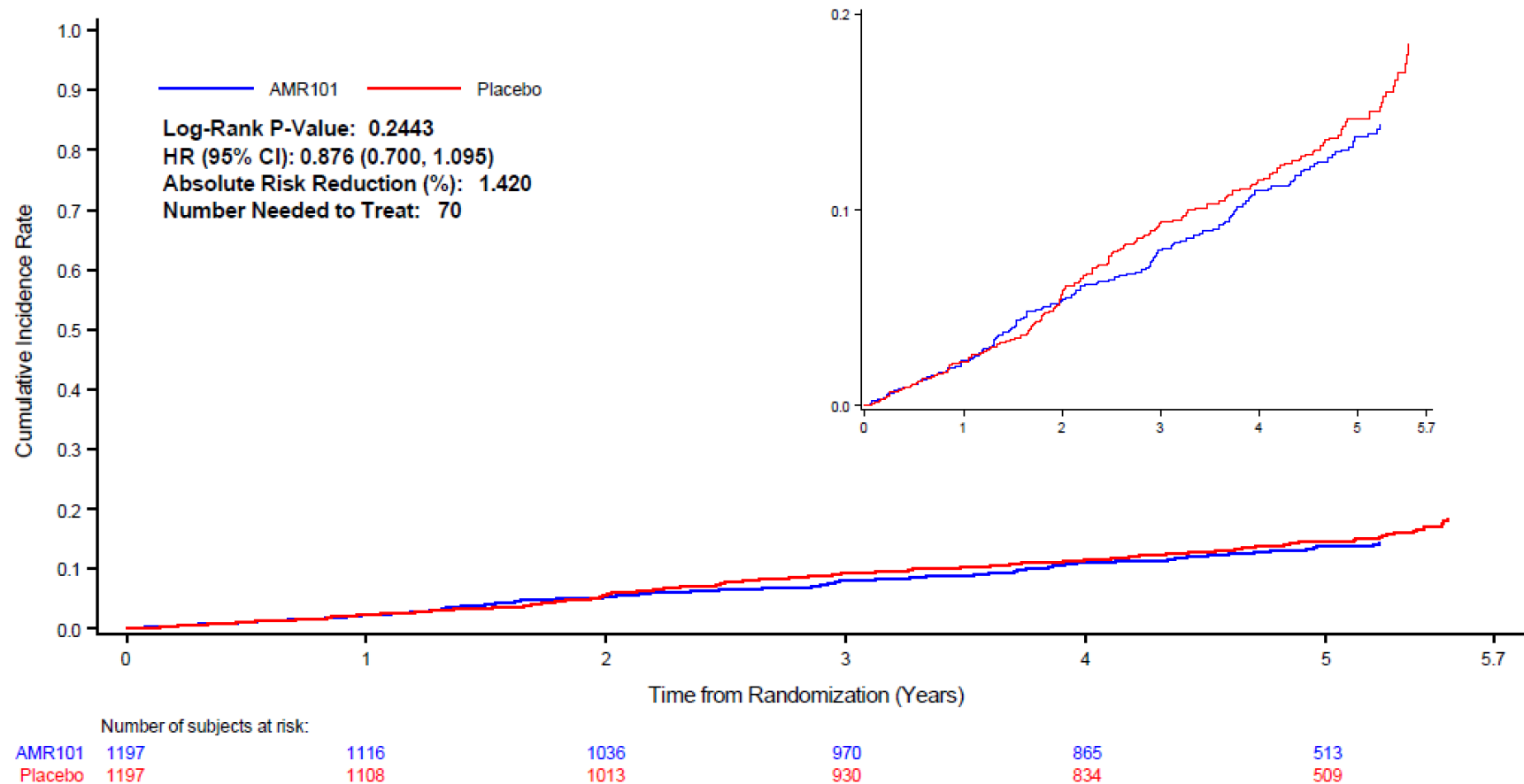
The Kaplan-Meier curves for the primary endpoint within the secondary prevention ([Figure 31](#)) and high-risk primary prevention ([Figure 32](#)) subgroups are provided below. Also below are the Kaplan-Meier curves for the key secondary endpoint within the secondary prevention ([Figure 33](#)) and high-risk primary prevention ([Figure 34](#)) subgroups. The primary endpoint curves begin to separate at approximately one year in the secondary prevention subgroup ([Figure 31](#)), while they begin to separate after about two years in the high-risk primary prevention subgroup ([Figure 32](#)). The key secondary endpoint curves begin to separate at around 1.5 years in the secondary prevention subgroup ([Figure 33](#)), as compared to separation after approximately two years in the high-risk primary prevention subgroup ([Figure 34](#)). Also plotted below are total (first and subsequent) event curves for the secondary ([Figure 35](#)) and high-risk primary prevention ([Figure 36](#)) subgroups. Together, these analyses suggest that both the secondary prevention and high-risk primary prevention subgroups likely experience benefit with icosapent ethyl therapy, but as one might expect, benefit seems to become apparent earlier in the secondary prevention subgroup.

Figure 31. Kaplan-Meier Curve for Time to Primary Composite Endpoint: Established CVD Secondary Prevention Subgroup



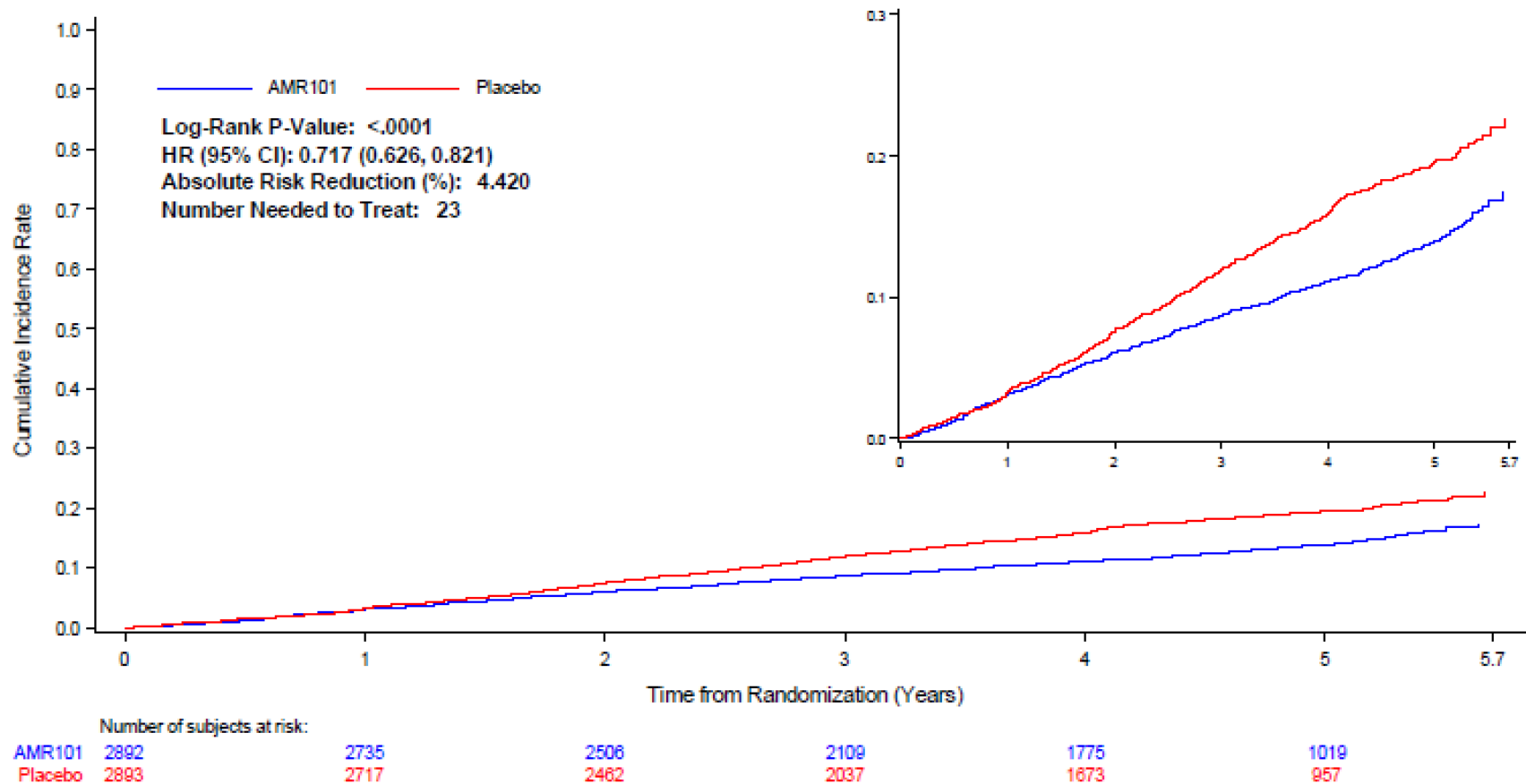
Note: Curves were visually truncated at 5.7 years due to a limited number of events occurring beyond that time point; all patient data were included in the analyses.
AMR101 = icosapent ethyl.

Figure 32. Kaplan-Meier Curve for Time to Primary Composite Endpoint: High-risk Primary Prevention Subgroup



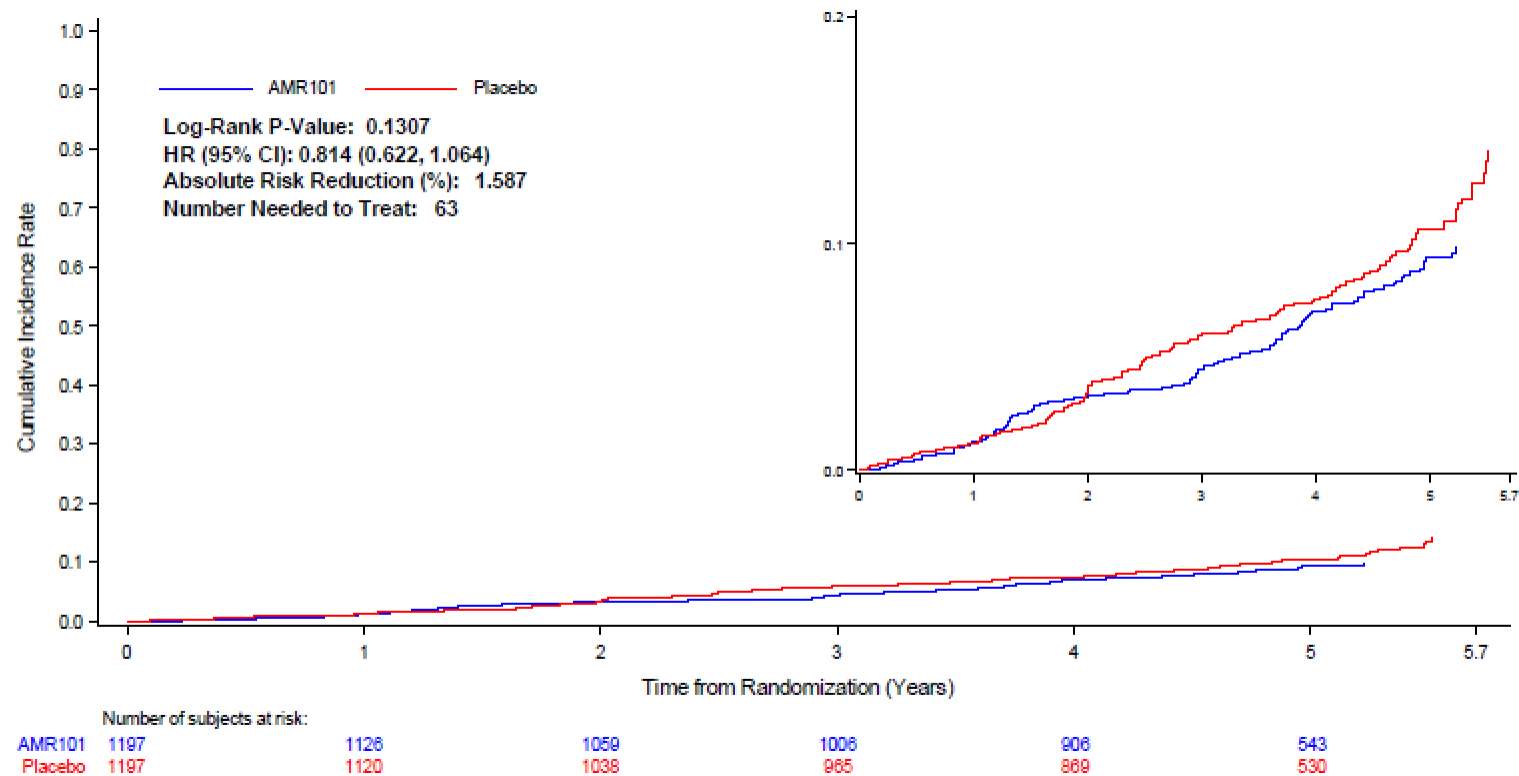
Note: Curves were visually truncated at 5.7 years due to a limited number of events occurring beyond that time point; all patient data were included in the analyses.
AMR101 = icosapent ethyl.

Figure 33. Kaplan-Meier Curve for Time to Key Secondary Composite Endpoint: Established CVD Secondary Prevention Subgroup



Note: Curves were visually truncated at 5.7 years due to a limited number of events occurring beyond that time point; all patient data were included in the analyses.
AMR101 = icosapent ethyl.

Figure 34. Kaplan-Meier Curve for Time to Key Secondary Composite Endpoint: High-risk Primary Prevention Subgroup



Note: Curves were visually truncated at 5.7 years due to a limited number of events occurring beyond that time point; all patient data were included in the analyses.
AMR101 = icosapent ethyl.

Figure 35. Total Event Curves for All Occurrences (First and Subsequent) of the Primary Endpoint (ITT)

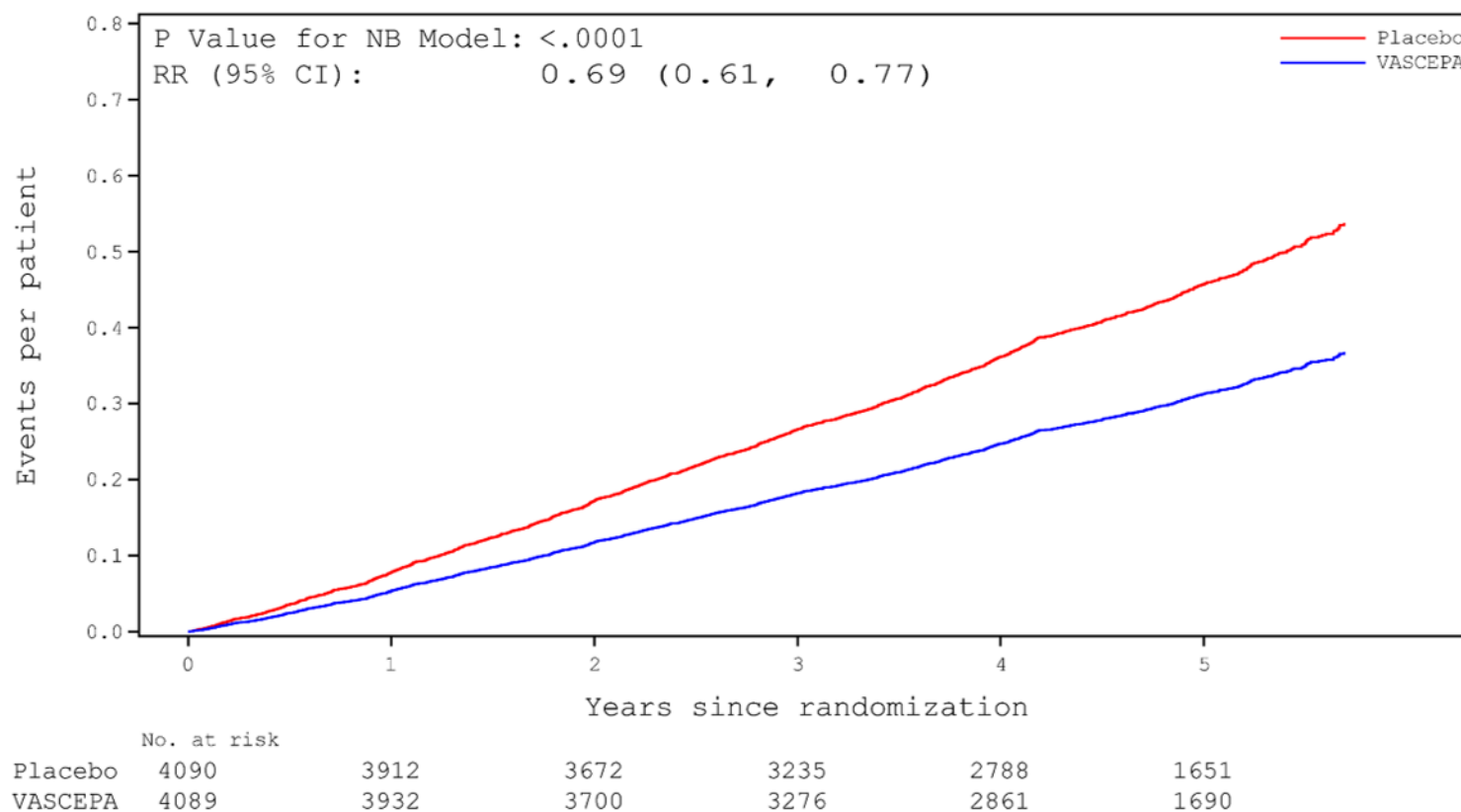


Figure 36. Total Event Curves for All Occurrences (First and Subsequent) of the Primary Endpoint by CV Risk Category: Secondary Prevention

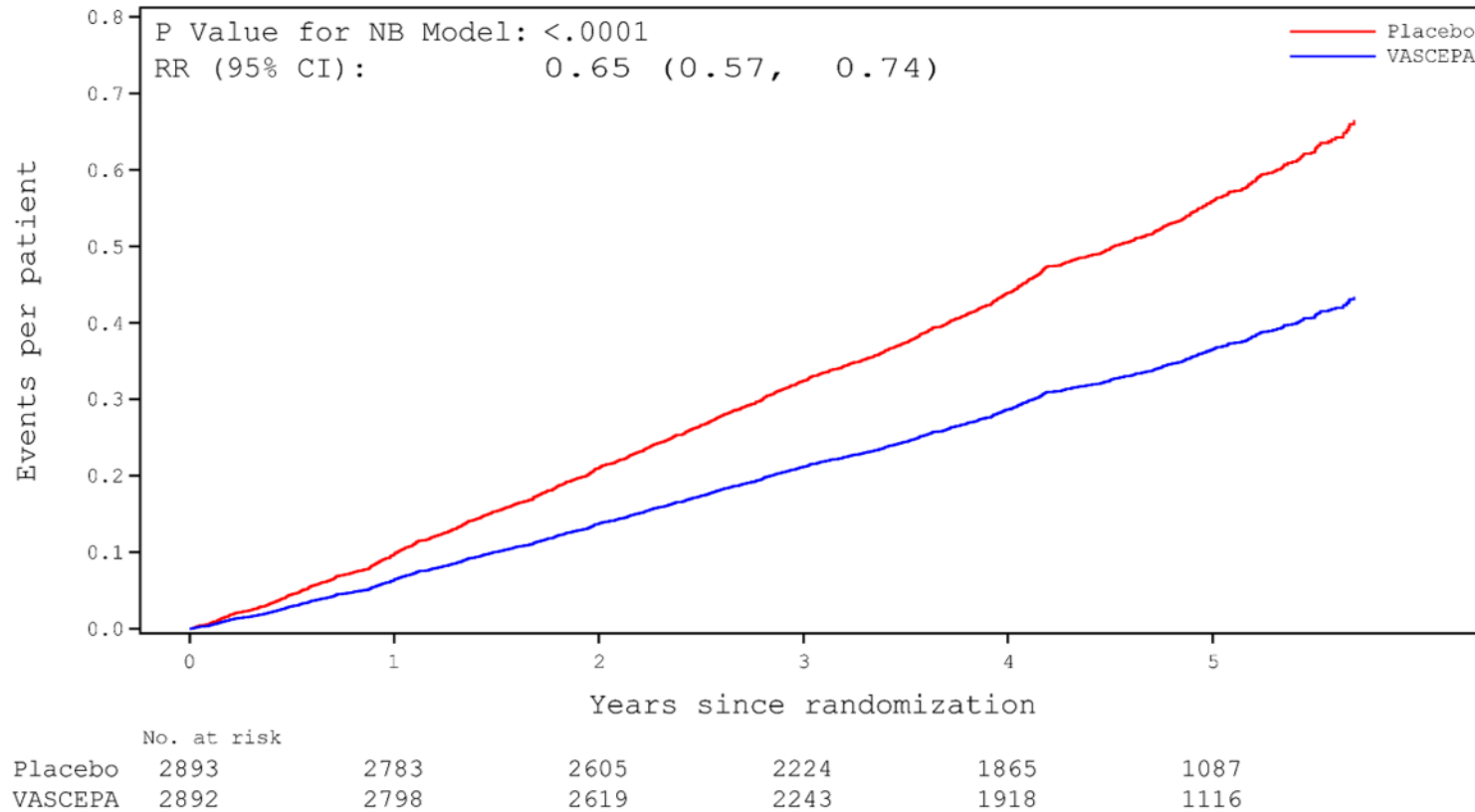
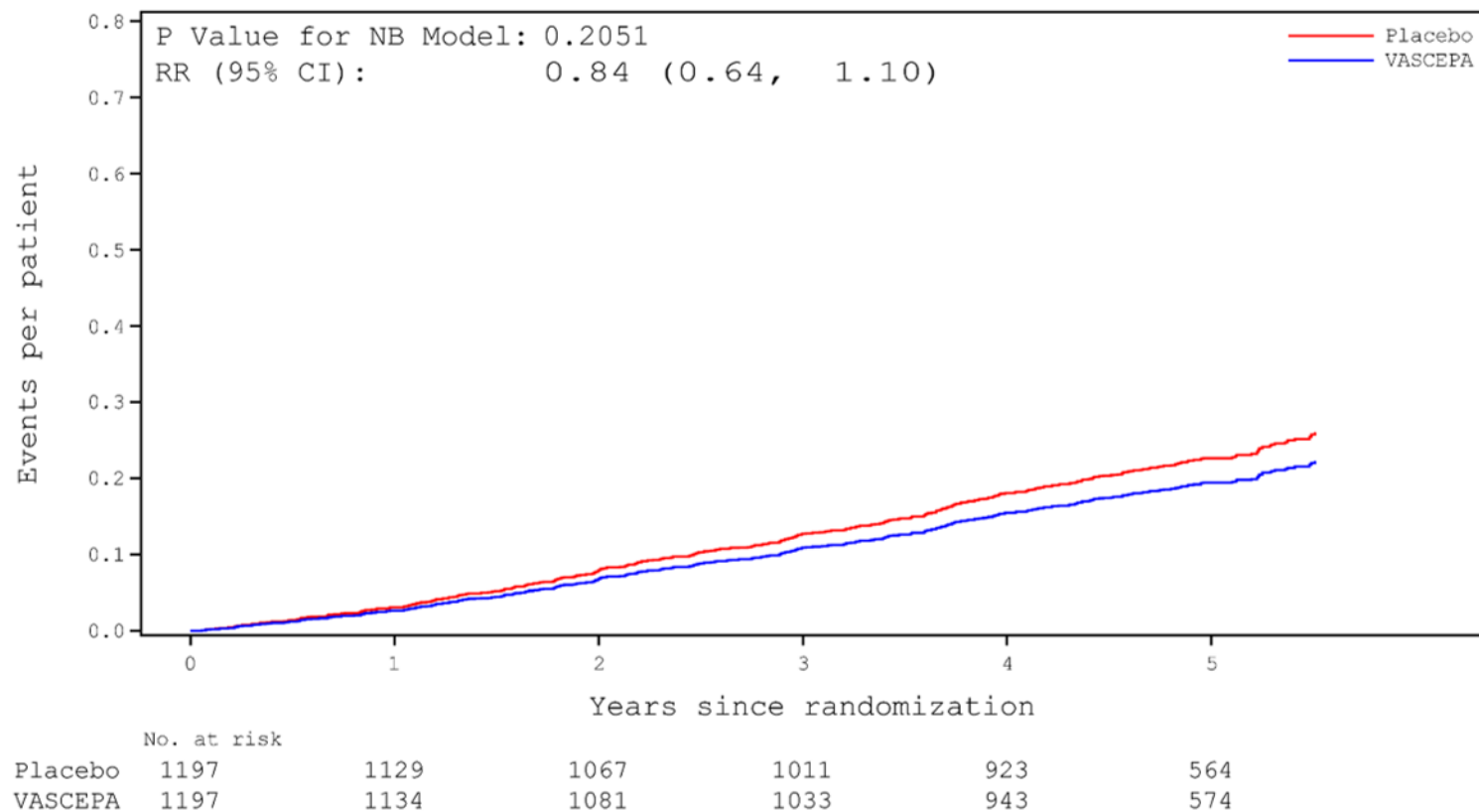


Figure 37. Total Event Curves for All Occurrences (First and Subsequent) of the Primary Endpoint by CV Risk Category: High-Risk Primary Prevention



The safety population consists of 8179 patients with a median follow up of 4.9 years, accounting for 35,014 patient years of experience. An overview of TEAEs is presented by CV risk category and treatment group for the secondary prevention ([Table 41](#)) and high-risk primary prevention ([Table 42](#)) subgroups. Similar to the overall study results, no significant differences were observed in the proportions of patients who experienced the categories of TEAEs listed in [Table 41](#) and [Table 42](#), and results were similar across the secondary prevention and the high-risk primary prevention subgroups.

Table 41. TEAEs by CV Risk Category: Secondary Prevention Subgroup (Safety Population)

	Icosapent Ethyl (N=2892)	Placebo (N=2893)	Overall (N=5785)	p-value³
Subjects with at Least One TEAE , n(%)	2360 (81.6)	2350 (81.2)	4710 (81.4)	0.74
Severe TEAE	555 (19.2)	564 (19.5)	1119 (19.3)	0.79
Drug-Related TEAE ¹	360 (12.4)	346 (12.0)	706 (12.2)	0.57
Serious TEAE	876 (30.3)	912 (31.5)	1788 (30.9)	0.32
Drug-Related Serious TEAE ¹	5 (0.2)	3 (0.1)	8 (0.1)	0.51
TEAE Leading to Withdrawal of Study Drug ²	236 (8.2)	226 (7.8)	462 (8.0)	0.63
Drug-Related TEAE Leading to Withdrawal of Study Drug ^{1,2}	97 (3.4)	111 (3.8)	208 (3.6)	0.36
Serious TEAE Leading to Withdrawal of Study Drug ²	67 (2.3)	62 (2.1)	129 (2.2)	0.66
Serious TEAE Leading to Death	74 (2.6)	76 (2.6)	150 (2.6)	0.93
Drug-Related Serious TEAE Leading to Withdrawal of Study Drug ^{1,2}	1 (0.0)	3 (0.1)	4 (0.1)	0.62

Note: A treatment-emergent adverse event (TEAE) is defined as an event that first occurs or worsens in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study.

Percentages are based on the number of subjects randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints are not included.

1 All adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 20.1).

2 Withdrawal of study drug excludes subjects who were off drug in study (ODIS) for 30 days or more, and restarted study drug.

3 Compares Icosapent Ethyl vs Placebo.

Table 42. TEAEs by CV Risk Category: High-risk Primary Prevention Subgroup (Safety Population)

	Icosapent Ethyl (N=1197)	Placebo (N=1197)	Overall (N=2394)	Fisher's Exact p- value³
Subjects with at Least One TEAE , n(%)	983 (82.1)	976 (81.5)	1959 (81.8)	0.75
Severe TEAE	250 (20.9)	252 (21.1)	502 (21.0)	0.96
Drug-Related TEAE ¹	154 (12.9)	153 (12.8)	307 (12.8)	1.00
Serious TEAE	376 (31.4)	342 (28.6)	718 (30.0)	0.14
Drug-Related Serious TEAE ¹	3 (0.3)	2 (0.2)	5 (0.2)	1.00
TEAE Leading to Withdrawal of Study Drug ²	85 (7.1)	109 (9.1)	194 (8.1)	0.08
Drug-Related TEAE Leading to Withdrawal of Study Drug ^{1,2}	42 (3.5)	53 (4.4)	95 (4.0)	0.30
Serious TEAE Leading to Withdrawal of Study Drug ²	21 (1.8)	26 (2.2)	47 (2.0)	0.56
Serious TEAE Leading to Death	20 (1.7)	26 (2.2)	46 (1.9)	0.46
Drug-Related Serious TEAE Leading to Withdrawal of Study Drug ^{1,2}	1 (0.1)	1 (0.1)	2 (0.1)	1.00

Note: A treatment-emergent adverse event (TEAE) is defined as an event that first occurs or worsens in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study.

Percentages are based on the number of subjects randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints are not included.

1 All adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 20.1).

2 Withdrawal of study drug excludes subjects who were off drug in study (ODIS) for 30 days or more, and restarted study drug.

3 Compares Icosapent Ethyl vs Placebo.

The most frequently reported TEAEs, defined as occurring in >5% of patients in either treatment group and statistically significantly different across treatment groups, are presented in Table 6 for the full safety population, and by CV risk category in Table 43 (secondary prevention) and Table 44 (high-risk primary prevention). Overall trends across the secondary and high-risk-primary prevention subgroups are consistent with the full safety population findings.

Table 43. Most Frequent TEAEs: ≥5% in Either Treatment Group and Significantly Different (Full Cohort); Reported by CV Risk: Secondary Prevention Subgroup (Safety Population)

Preferred Term ¹ , n (%)	Icosapent Ethyl (N=2892)	Placebo (N=2893)	p-value ²
Hypertension	235 (8.1%)	229 (7.9%)	0.77
Diarrhoea	228 (7.9%)	299 (10.3%)	0.001
Back pain	219 (7.6%)	196 (6.8%)	0.24
Chest pain	211 (7.3%)	242 (8.4%)	0.14
Nasopharyngitis	205 (7.1%)	210 (7.3%)	0.84
Dyspnoea	201 (7.0%)	190 (6.6%)	0.57
Influenza	200 (6.9%)	211 (7.3%)	0.61
Pneumonia	196 (6.8%)	203 (7.0%)	0.76
Arthralgia	190 (6.6%)	190 (6.6%)	1.00
Oedema peripheral	181 (6.3%)	124 (4.3%)	0.0008
Bronchitis	178 (6.2%)	189 (6.5%)	0.59
Upper respiratory tract infection	171 (5.9%)	191 (6.6%)	0.30
Fatigue	171 (5.9%)	154 (5.3%)	0.33
Angina pectoris	168 (5.8%)	186 (6.4%)	0.35
Dizziness	160 (5.5%)	176 (6.1%)	0.40
Cough	160 (5.5%)	160 (5.5%)	1.00
Cataract	156 (5.4%)	146 (5.0%)	0.56
Pain in extremity	155 (5.4%)	160 (5.5%)	0.82
Atrial fibrillation	155 (5.4%)	123 (4.3%)	0.05
Osteoarthritis	153 (5.3%)	132 (4.6%)	0.20
Constipation	149 (5.2%)	103 (3.6%)	0.003
Anaemia	114 (3.9%)	156 (5.4%)	0.01

Note: A treatment-emergent adverse event (TEAE) is defined as an event that first occurs or worsens in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. For each subject, multiple TEAEs of the same Preferred Term will be counted only once within each Preferred Term.

TEAEs are listed in descending order of Icosapent Ethyl frequency. Percentages are based on the number of subjects randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints are not included.

¹ All adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 20.1).

² Fishers Exact test.

Table 44. Most Frequent TEAEs: $\geq 5\%$ in Either Treatment Group and Significantly Different (Full Cohort); Reported by CV Risk: High-risk Primary Prevention Subgroup (Safety Population)

Preferred Term ¹ , n (%)	Icosapent Ethyl (N=2892)	Placebo (N=2893)	p-value ²
Upper respiratory tract infection	141 (11.8%)	129 (10.8%)	0.48
Diarrhoea	139 (11.6%)	154 (12.9%)	0.38
Bronchitis	128 (10.7%)	111 (9.3%)	0.28
Arthralgia	123 (10.3%)	120 (10.0%)	0.89
Back pain	116 (9.7%)	113 (9.4%)	0.89
Urinary tract infection	110 (9.2%)	117 (9.8%)	0.68
Nasopharyngitis	109 (9.1%)	90 (7.5%)	0.18
Osteoarthritis	88 (7.4%)	86 (7.2%)	0.94
Oedema peripheral	86 (7.2%)	79 (6.6%)	0.63
Hypertension	85 (7.1%)	115 (9.6%)	0.03
Cough	81 (6.8%)	81 (6.8%)	1.00
Pain in extremity	80 (6.7%)	81 (6.8%)	1.00
Anaemia	77 (6.4%)	80 (6.7%)	0.87
Cataract	77 (6.4%)	62 (5.2%)	0.22
Dizziness	75 (6.3%)	70 (5.8%)	0.73
Constipation	72 (6.0%)	46 (3.8%)	0.02
Sinusitis	69 (5.8%)	65 (5.4%)	0.79
Pneumonia	67 (5.6%)	74 (6.2%)	0.60
Influenza	63 (5.3%)	60 (5.0%)	0.85
Fall	63 (5.3%)	54 (4.5%)	0.45
Type 2 diabetes mellitus	62 (5.2%)	57 (4.8%)	0.71
Chest pain	62 (5.2%)	48 (4.0%)	0.20
Musculoskeletal pain	61 (5.1%)	46 (3.8%)	0.17
Atrial fibrillation	60 (5.0%)	36 (3.0%)	0.02
Nausea	57 (4.8%)	65 (5.4%)	0.52
Diabetes mellitus	53 (4.4%)	60 (5.0%)	0.56
Headache	52 (4.3%)	61 (5.1%)	0.44

Note: A treatment-emergent adverse event (TEAE) is defined as an event that first occurs or worsens in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. For each subject, multiple TEAEs of the same Preferred Term will be counted only once within each Preferred Term.

TEAEs are listed in descending order of Icosapent Ethyl frequency. Percentages are based on the number of subjects randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints are not included.

¹ All adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 20.1).

² Fishers Exact test.

We also examined the risk of bleeding events (non-serious and serious), including adjudicated hemorrhagic stroke events, by CV risk stratum and by treatment arm; trends were similar across CV risk strata ([Table 45](#)).

Table 45. Number (%) of Subjects with Bleeding TEAEs (Serious and Non-Serious, Including Hemorrhagic Stroke) by CV Risk Category

CV Risk Category 1 (Secondary Prevention)	Icosapent Ethyl (N=2892)	Placebo (N=2893)	P-value ²
Bleeding Related Disorders¹	347 (12.0%)	292 (10.1%)	0.0211
Gastrointestinal Bleeding	89 (3.1%)	82 (2.8%)	0.5880
CNS Bleeding	17 (0.6%)	9 (0.3%)	0.1212
Hemorrhagic Stroke	13 (0.4%)	8 (0.3%)	0.2854
Other Bleeding	255 (8.8%)	220 (7.6%)	0.0939
Serious Bleeding Related Disorders¹	92 (3.2%)	69 (2.4%)	0.0665
Gastrointestinal Bleeding	43 (1.5%)	35 (1.2%)	0.3649
CNS Bleeding	12 (0.4%)	7 (0.2%)	0.2623
Hemorrhagic Stroke	13 (0.4%)	8 (0.3%)	0.2854
Other Bleeding	29 (1.0%)	21 (0.7%)	0.2603
CV Risk Category 2 (Primary Prevention)	(N=1197)	(N=1197)	
Bleeding Related Disorders¹	147 (12.3%)	120 (10.0%)	0.0912
Gastrointestinal Bleeding	38 (3.2%)	34 (2.8%)	0.7199
CNS Bleeding	3 (0.3%)	3 (0.3%)	>0.99
Hemorrhagic Stroke	0	2 (0.2%)	0.4998
Other Bleeding	121 (10.1%)	92 (7.7%)	0.0442
Serious Bleeding Related Disorders¹	31 (2.6%)	26 (2.2%)	0.5922
Gastrointestinal Bleeding	19 (1.6%)	12 (1.0%)	0.2779
CNS Bleeding	2 (0.2%)	3 (0.3%)	>0.99
Hemorrhagic Stroke	0	2 (0.2%)	0.4998
Other Bleeding	12 (1.0%)	9 (0.8%)	0.6622

¹ Bleeding-related disorders are identified by the SMQs of "Gastrointestinal haemorrhage," "Central Nervous System haemorrhages and cerebrovascular conditions," and "Haemorrhage terms (excl laboratory terms)."

² Fishers Exact test.

Use of antithrombotic medications during bleeding events was evaluated and there was no specific antithrombotic or class of antithrombotic therapy that had a significant interaction between treatment arms for bleeding TEAEs including hemorrhagic stroke in the secondary (Table 46) or high-risk primary prevention (Table 47) subgroups, or in bleeding SAEs including hemorrhagic stroke in the secondary (Table 48) or high-risk primary prevention (Table 49) subgroups.

Table 46. Anti-thrombotic Use in Patients with Bleeding TEAEs (Serious and Non-Serious) Including Hemorrhagic Stroke by CV Risk Category: Secondary Prevention

Category Medication	Icosapent Ethyl (N=2892)	Placebo (N=2893)	P-value
Subjects with at least one bleeding event	347/2892 (12.0)	292/2893 (10.1)	0.0211
Subjects on Anti-Platelet OR Anti-Coagulant at or before bleeding event	341/ 347 (98.3)	289/ 292 (99.0)	0.5194
Single Anti-Platelet: Aspirin Only	127/ 347 (36.6)	103/ 292 (35.3)	0.7413
>1 Anti-Platelet: Aspirin AND (Clopidogrel OR Prasugrel OR Ticagrelor)	110/ 347 (31.7)	110/ 292 (37.7)	0.1324
Anti-Coagulant: Warfarin OR Rivaroxaban OR Apixaban	11/ 347 (3.2)	12/ 292 (4.1)	0.5317
Both Anticoagulants Plus Any Anti-platelet listed above	61/ 347 (17.6)	39/ 292 (13.4)	0.1561
Subjects not on Anti-Platelet OR Anti-Coagulant at or before bleeding event	6/ 347 (1.7)	3/ 292 (1.0)	0.5194

Note: Categories are mutually exclusive.

P-values are based on Fishers Exact test.

Table 47. Anti-thrombotic Use in Patients with Bleeding TEAEs (Serious and Non-Serious) Including Hemorrhagic Stroke by CV Risk Category: High-risk Primary Prevention

Category Medication	Icosapent Ethyl (N=2892)	Placebo (N=2893)	P-value
Subjects with at least one bleeding event	147/1197 (12.3)	120/1197 (10.0)	0.0912
Subjects on Anti-Platelet OR Anti-Coagulant at or before bleeding event	123/ 147 (83.7)	94/ 120 (78.3)	0.2744
Single Anti-Platelet: Aspirin Only	69/ 147 (46.9)	52/ 120 (43.3)	0.6214
>1 Anti-Platelet: Aspirin AND (Clopidogrel OR Prasugrel OR Ticagrelor)	21/ 147 (14.3)	10/ 120 (8.3)	0.1784
Anti-Coagulant: Warfarin OR Rivaroxaban OR Apixaban	8/ 147 (5.4)	7/ 120 (5.8)	1.0000
Both Anticoagulants Plus Any Anti-platelet listed above	16/ 147 (10.9)	14/ 120 (11.7)	0.8481
Subjects not on Anti-Platelet OR Anti-Coagulant at or before bleeding event	24/ 147 (16.3)	26/ 120 (21.7)	0.2744

Note: Categories are mutually exclusive.

P-values are based on Fishers Exact test.

Table 48. Anti-thrombotic Use in Patients with Bleeding SAEs Including Hemorrhagic Stroke by CV Risk Category: Secondary Prevention

Category Medication	Icosapent Ethyl (N=2892)	Placebo (N=2893)	P-value
Subjects with at least one bleeding event	92/2892 (3.2)	69/2893 (2.4)	0.0665
Subjects on Anti-Platelet OR Anti-Coagulant at or before bleeding event	90/ 92 (97.8)	69/ 69 (100.0)	0.5071
Single Anti-Platelet: Aspirin Only	31/ 92 (33.7)	13/ 69 (18.8)	0.0489
>1 Anti-Platelet: Aspirin AND (Clopidogrel OR Prasugrel OR Ticagrelor)	26/ 92 (28.3)	27/ 69 (39.1)	0.1760
Anti-Coagulant: Warfarin OR Rivaroxaban OR Apixaban	3/ 92 (3.3)	6/ 69 (8.7)	0.1736
Both Anticoagulants Plus Any Anti-platelet listed above	21/ 92 (22.8)	14/ 69 (20.3)	0.8472
Subjects not on Anti-Platelet OR Anti-Coagulant at or before bleeding event	2/ 92 (2.2)	0/ 69 (0.0)	0.5071

Note: Categories are mutually exclusive.

P-values are based on Fishers Exact test.

Table 49. Anti-thrombotic Use in Patients with Bleeding SAEs Including Hemorrhagic Stroke by CV Risk Category: High-risk Primary Prevention

Category Medication	Icosapent Ethyl (N=2892)	Placebo (N=2893)	P-value
Subjects with at least one bleeding event	31/1197 (2.6)	26/1197 (2.2)	0.5922
Subjects on Anti-Platelet OR Anti-Coagulant at or before bleeding event	29/ 31 (93.5)	24/ 26 (92.3)	1.0000
Single Anti-Platelet: Aspirin Only	7/ 31 (22.6)	12/ 26 (46.2)	0.0907
>1 Anti-Platelet: Aspirin AND (Clopidogrel OR Prasugrel OR Ticagrelor)	5/ 31 (16.1)	1/ 26 (3.8)	0.2046
Anti-Coagulant: Warfarin OR Rivaroxaban OR Apixaban	3/ 31 (9.7)	3/ 26 (11.5)	1.0000
Both Anticoagulants Plus Any Anti-platelet listed above	9/ 31 (29.0)	5/ 26 (19.2)	0.5392
Subjects not on Anti-Platelet OR Anti-Coagulant at or before bleeding event	2/ 31 (6.5)	2/ 26 (7.7)	1.0000

Note: Categories are mutually exclusive.

P-values are based on Fishers Exact test.

Although not prespecified as TEAEs of special interest, atrial fibrillation and atrial flutter were also explored *post hoc* as potential safety signals. Atrial fibrillation and/or flutter requiring hospitalization for at least 24 hours was a prespecified adjudicated endpoint event (an efficacy endpoint). Occurrences of atrial fibrillation and/or flutter that were not positively adjudicated were counted as TEAEs or SAEs, per seriousness criteria. Summaries of TEAEs and SAEs of atrial fibrillation/flutter are presented below for the secondary prevention (Table 50) and high-risk primary prevention (Table 51) subgroups, along with positively adjudicated endpoints of atrial fibrillation/flutter requiring hospitalization of ≥ 24 hours (endpoint events adjudicated by the CEC), as a comprehensive compilation of all documented post-randomization occurrences of these atrial arrhythmias.

The incidences of atrial fibrillation/flutter TEAEs reported in the AE dataset within the clinical database (i.e., not positively adjudicated as endpoints) were statistically significantly higher in the icosapent ethyl group than in the placebo group within the high-risk primary prevention subgroup

($p=0.0035$; Table 51), but not in the secondary prevention subgroup ($p=0.1832$; Table 50), while the incidences of atrial fibrillation/flutter SAEs reported in the safety/clinical dataset (i.e., meeting seriousness criteria, but not positively adjudicated as endpoints) were similar between the icosapent ethyl and placebo groups for both the secondary and high-risk primary prevention subgroups. The incidences of positively adjudicated atrial fibrillation/flutter endpoints requiring hospitalization of ≥ 24 hours were also statistically significantly higher in the icosapent ethyl group than in the placebo group in both the secondary ($p=0.0498$; Table 50) and high-risk primary ($p=0.0189$; Table 51) prevention subgroups.

Table 50. Atrial Fibrillation and Atrial Flutter AEs and Endpoints by CV Risk Category: Secondary Prevention Subgroup

Summary of Atrial Fibrillation/Flutter, n (%)	Icosapent ethyl (N=2892)	Placebo (N=2893)	p-Value
Treatment Emergent Atrial Fibrillation/Flutter¹	169 (5.8)	146 (5.0)	0.1832
Serious Treatment Emergent Atrial Fibrillation/Flutter ²	14 (0.5)	17 (0.6)	0.7194
Positively Adjudicated Atrial Fibrillation/Flutter Requiring ≥ 24 Hours Hospitalization³	89 (3.1)	64 (2.2)	0.0498

Note: Percentages are based on the number of subjects in the ITT Population within each treatment group (N).

All AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 20.1).

1 Includes Atrial Fibrillation/Flutter treatment emergent adverse events and excludes positively adjudicated events. P-value was based on Fishers Exact test.

2 Includes Atrial Fibrillation/Flutter treatment emergent adverse events meeting seriousness criteria. P-value is based on Fishers Exact test.

3 Includes positively adjudicated Atrial Fibrillation/Flutter requiring ≥ 24 hours of hospitalization clinical events by the Clinical Endpoint Committee (CEC). P-value is based on stratified log-rank test.

Table 51. Atrial Fibrillation and Atrial Flutter AEs and Endpoints by CV Risk Category: High-risk Primary Prevention Subgroup

Summary of Atrial Fibrillation/Flutter, n (%)	Icosapent ethyl (N=1197)	Placebo (N=1197)	p-Value
Treatment Emergent Atrial Fibrillation/Flutter¹	67 (5.6)	37 (3.1)	0.0035
Serious Treatment Emergent Atrial Fibrillation/Flutter ²	8 (0.7)	3 (0.3)	0.2255
Positively Adjudicated Atrial Fibrillation/Flutter Requiring ≥ 24 Hours Hospitalization³	38 (3.2)	20 (1.7)	0.0189

Note: Percentages are based on the number of subjects in the ITT Population within each treatment group (N).

All AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 20.1).

1 Includes Atrial Fibrillation/Flutter treatment emergent adverse events and excludes positively adjudicated events. P-value was based on Fishers Exact test.

2 Includes Atrial Fibrillation/Flutter treatment emergent adverse events meeting seriousness criteria. P-value is based on Fishers Exact test.

3 Includes positively adjudicated Atrial Fibrillation/Flutter requiring ≥ 24 hours of hospitalization clinical events by the Clinical Endpoint Committee (CEC). P-value is based on stratified log-rank test.

To explore a somewhat extreme scenario of the relative impacts of atrial fibrillation or atrial flutter and bleeding on patient outcomes, *post hoc* analyses were conducted with positively adjudicated atrial fibrillation/flutter and bleeding SAEs added to the composites of the primary and key secondary endpoints. Similar to the primary+risk and key secondary+risk analyses presented in Table 15 for the full patient cohort, we looked at these endpoints in established CVD secondary prevention (Table 52) and the high-risk primary prevention (Table 53) subgroups. As shown in Table 52, despite inclusion of atrial fibrillation/flutter endpoints and/or bleeding SAEs in the primary and key secondary endpoints, the primary plus risk and key secondary plus risk endpoints

are still substantially reduced for the established CVD secondary prevention cohort. For example, for the most extreme analyses of including both atrial fibrillation or atrial flutter endpoints and bleeding SAEs in the primary and key secondary endpoint composites, the primary+risk (HR of 0.797; $p<0.0001$) and key secondary+risk (HR of 0.821; $p=0.0015$) endpoints remain significantly reduced. Not surprisingly, since the high-risk primary prevention subgroup did not reach significance in the primary or the key secondary endpoint, the plus risk analyses are also not significant, and the hazard ratios of 0.88 for the primary endpoint and 0.81 for the key secondary endpoint are muted. Nonetheless, despite these rather extreme analyses, the hazard ratios remain consistently below unity. More specific to atrial fibrillation/flutter, atrial arrhythmias can contribute to CHF, but there were no changes in newly emergent CHF, Stroke, MI, cardiac arrest, and sudden cardiac death can also be serious sequelae associated with atrial fibrillation/flutter, so we also explored the composite endpoint of positively adjudicated atrial fibrillation/flutter, stroke, MI, cardiac arrest, and sudden cardiac death, which in the established CVD secondary prevention subgroup suggests overall CV benefit despite inclusion of atrial fibrillation or atrial flutter (HR of 0.757; $p<0.0001$), and remains below unity in the high-risk primary prevention subgroup (HR of 0.923; $p=0.5471$). While positively adjudicated atrial fibrillation/flutter and bleeding SAEs are of clinical import, they are typically not as concerning as the other clinical events represented within these analyses, and therefore, these *post hoc* analyses are heavily biased against the icosapent ethyl with the equal statistical consideration of these events and the components of the primary and key secondary endpoints. Despite this bias, these analyses continue to support the conclusion of substantial benefit with icosapent ethyl therapy in the full study cohort and in the established CVD secondary prevention cohort, with benefit still appearing to outweigh risk in the high-risk primary prevention subgroup.

Table 52. Summary of *Post Hoc* Analyses of the Primary+ Risk and Key Secondary+ Risk Composite Endpoints: Established CVD Secondary Prevention Subgroup

Endpoint	Icosapent Ethyl (N=2892)	Placebo (N=2893)	HR (95% CI)	P-value	Rate/1000 pt yrs	
					Icosapent Ethyl	Placebo
Primary + AFib/Aflutter	612 (21.2%)	767 (26.5%)	0.768 (0.691, 0.855)	<0.0001	55.7	72.3
Key Secondary + Afib/Aflutter	423 (14.6%)	525 (18.1%)	0.787 (0.693, 0.895)	0.0002	36.8	46.6
Primary + Serious Bleeding	609 (21.1%)	768 (26.5%)	0.760 (0.684, 0.846)	<0.0001	55.3	72.4
Key Secondary + Serious Bleeding	416 (14.4%)	528 (18.3%)	0.765 (0.673, 0.870)	<0.0001	36.0	46.9
Primary + Afib/Aflutter + Serious Bleeding	658 (22.8%)	796 (27.5%)	0.797 (0.719, 0.884)	<0.0001	60.4	75.6
Key Secondary + Afib/Aflutter + Serious Bleeding	473 (16.4%)	563 (19.5%)	0.821 (0.727, 0.928)	0.0015	41.5	50.4
Afib/Aflutter + MI + Stroke + Cardiac Arrest + Sudden Cardiac Death	381 (13.2%)	492 (17.0%)	0.757 (0.663, 0.866)	<0.0001	33.1	43.7

Notes: All components presented on the table except serious bleeding are adjudicated by CEC

Number of subjects with event (n) is the number of subjects with the event in the ITT Population within each treatment group (N). Rate per 1000 patient years (pt-yrs) is $1000 \times n/\text{pt-yrs}$ subjects at-risk. Log-Rank test statistic and p-value are reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe. Log-Rank test statistic and p-value are reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

Table 53. Summary of *Post Hoc* Analyses of the Primary+ Risk and Key Secondary+ Risk Composite Endpoints: High-risk Primary Prevention Subgroup

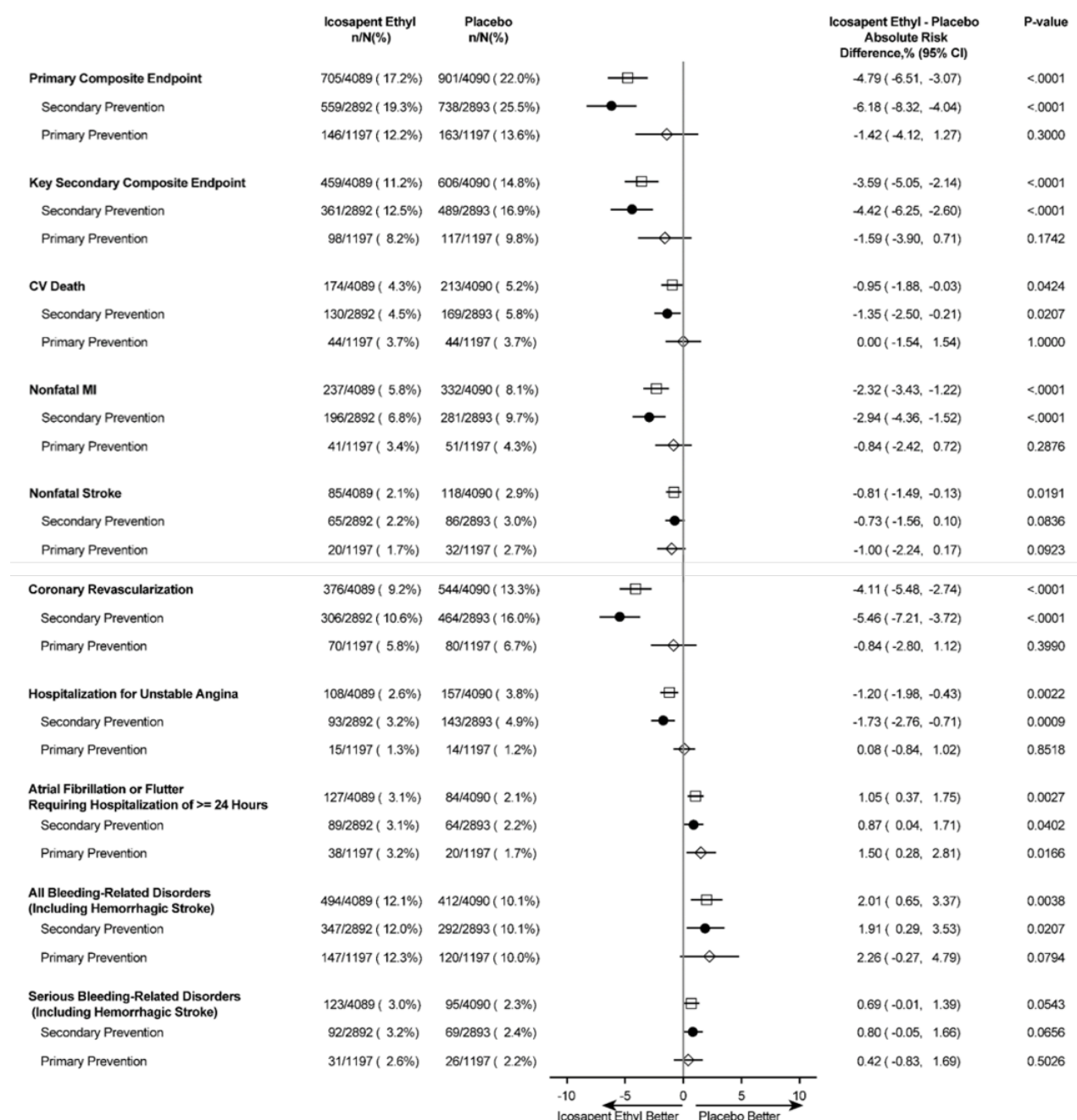
Endpoint	Icosapent Ethyl (N=1197)	Placebo (N=1197)	HR (95% CI)	P-value	Rate/1000 pt yrs	
					Icosapent Ethyl	Placebo
Primary + AFib/Aflutter	173 (14.5%)	179 (15.0%)	0.953 (0.773, 1.175)	0.6514	34.3	35.9
Key Secondary + Afib/Aflutter	129 (10.8%)	135 (11.3%)	0.937 (0.736, 1.192)	0.5946	24.9	26.5
Primary + Serious Bleeding	166 (13.9%)	182 (15.2%)	0.891 (0.722, 1.100)	0.2822	32.7	36.7
Key Secondary + Serious Bleeding	123 (10.3%)	136 (11.4%)	0.880 (0.690, 1.123)	0.3049	23.6	26.8
Primary + Afib/Aflutter + Serious Bleeding	192 (16.0%)	196 (16.4%)	0.966 (0.791, 1.179)	0.7318	38.4	39.7
Key Secondary + Afib/Aflutter + Serious Bleeding	152 (12.7%)	152 (12.7%)	0.983 (0.785, 1.230)	0.8779	29.6	30.1
Afib/Aflutter + MI + Stroke + Cardiac Arrest + Sudden Cardiac Death	110 (9.2%)	117 (9.8%)	0.923 (0.712, 1.198)	0.5471	21.2	23.0

Notes: All components presented on the table except serious bleeding are adjudicated by CEC

Number of subjects with event (n) is the number of subjects with the event in the ITT Population within each treatment group (N). Rate per 1000 patient years (pt-yrs) is $1000 \times n/\text{pt-yrs}$ subjects at-risk. Log-Rank test statistic and p-value are reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

We also looked at the individual components of the primary and key secondary endpoints across CV risk category subgroups, along with safety events noted within the full study cohort ([Figure 38](#)). Consistent with other analyses presented earlier, numerically greater absolute risk reductions were observed in the secondary prevention subgroup as compared with the high-risk primary prevention subgroup, but there is a generally consistent suggestion of benefit within the primary prevention group, particularly for the primary and key secondary endpoints, and for the individual endpoints of nonfatal MI, nonfatal stroke, and coronary revascularization. Of note, absolute risk differences are more substantial for the primary and key secondary endpoints, and for the individual components of these endpoints, as compared to the absolute risk differences observed for atrial arrhythmias and bleeding events, again supporting an overall positive benefit-risk conclusion for both the secondary prevention and the high-risk primary prevention subgroups.

Figure 38. Forest Plot for Key Endpoints by CV Risk Category (ITT Population)



CVA = Cerebrovascular Accident; BP = Blood pressure

Patients with missing baseline subgroup data are not included in the corresponding baseline subgroup classifications and therefore not included in the denominator (N) of the corresponding subgroup analyses.

Overall, REDUCE-IT high-risk primary prevention patients contributed fewer first events to each endpoint compared to secondary prevention patients (Figure 9 and Figure 10). This is reflective of

the study design requiring enrollment of fewer high-risk primary prevention patients (30% of targeted enrollment) than secondary prevention patients, and is consistent with overall lower event rate in the primary versus secondary prevention subgroup. For example, the primary prevention placebo patients contributed 163 first primary endpoint events, while the secondary prevention placebo patients contributed 738 first primary endpoint events (Figure 9). Despite contributing 22% of all first events, the primary prevention cohort hazard ratios and interaction p-values (primary versus secondary prevention) are consistent with the overall demonstration of benefit in REDUCE-IT. For example, the primary prevention hazard ratios are all below unity for the primary and key secondary endpoints, as well as for each individual component, except hospitalization for unstable angina where events were particularly low in the primary prevention cohort (Figure 38). Additionally, the interaction p-values support the conclusion of benefit across the secondary and high-risk primary prevention cohorts, with most interaction p-values being above the pre-specified 0.15 significance level (Figure 9 and Figure 10). Finally, the primary endpoint Kaplan-Meier curves begin to visually separate at about two years for the high-risk primary prevention cohort, while the secondary prevention curves begin to visually separate by one year. The lower event rates and potentially delayed onset of benefit in primary versus secondary prevention patients, along with substantially fewer enrolled patients, suggest that benefit is present that would have reached statistical significance in the primary prevention cohort alone had the study been designed to demonstrate efficacy in the individual subgroups by, for example, the enrollment of more primary prevention patients who were followed for a longer period of time. The findings are also consistent with what was observed with EPA in the JELIS trial, where there were also consistent benefits in secondary and primary prevention subgroups. Finally, benefit-risk considerations suggest that the benefits of icosapent ethyl outweigh the risks for both the secondary and high-risk primary prevention subgroups.

APPENDIX L: BLEEDING: FURTHER *POST HOC* ANALYSES

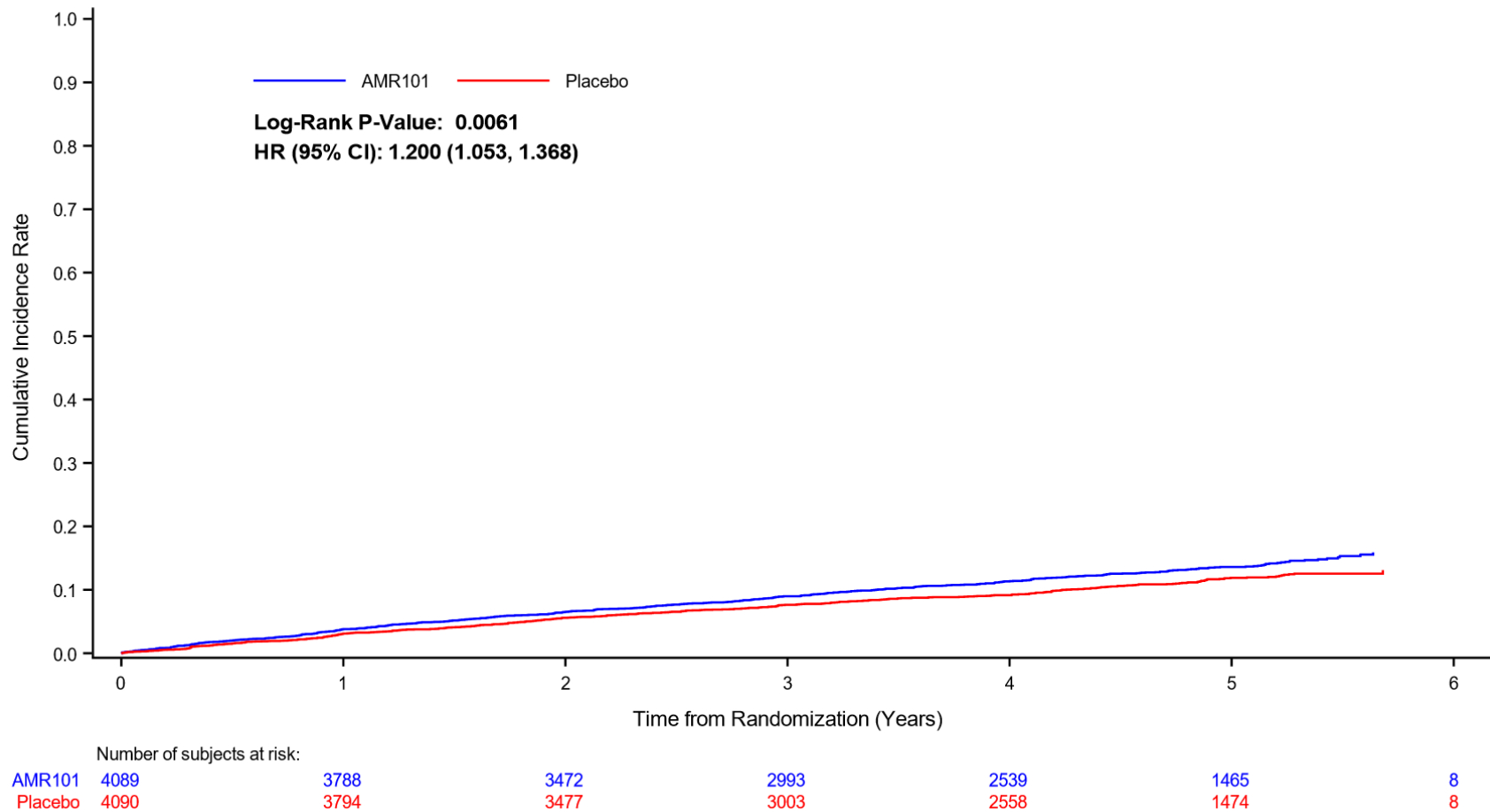
In addition to the analyses presented in the main body of this briefing book, other analyses were conducted to further explore the apparent increase in bleeding events in the icosapent ethyl group.

The analyses of bleeding-related adverse events in REDUCE-IT did not include (positively adjudicated) hemorrhagic stroke endpoint events. This was consistent with the REDUCE-IT SAP which excluded endpoint events (efficacy endpoints) from safety analyses. However, for a comprehensive assessment of all bleeding events, the following analyses combine all reported bleeding-related events (non-serious and serious AEs) and hemorrhagic stroke endpoint events (e.g., [Figure 39](#) and [Figure 41](#); [Table 9](#) and [Table 10](#)). Analyses of a subset of those events ([Figure 40](#) and [Figure 42](#); [Table 56](#)) represent the most consequential bleeding events, i.e., all serious bleeding-related adverse events combined with hemorrhagic stroke endpoint events.

Kaplan-Meier (K-M) curves for time to first bleeding TEAE (serious and non-serious) including positively adjudicated hemorrhagic stroke events ([Figure 39](#)) and first bleeding SAE including hemorrhagic stroke ([Figure 40](#)) are provided below. Consistent with the summary statistics for bleeding TEAEs ([Table 9](#)) and SAEs ([Table 10](#)), Kaplan-Meier curves for serious and non-serious bleeds including hemorrhagic stroke begin to visually separate around one year, while bleeding SAE rates including hemorrhagic strokes are lower and the Kaplan-Meier curves do not visually separate.

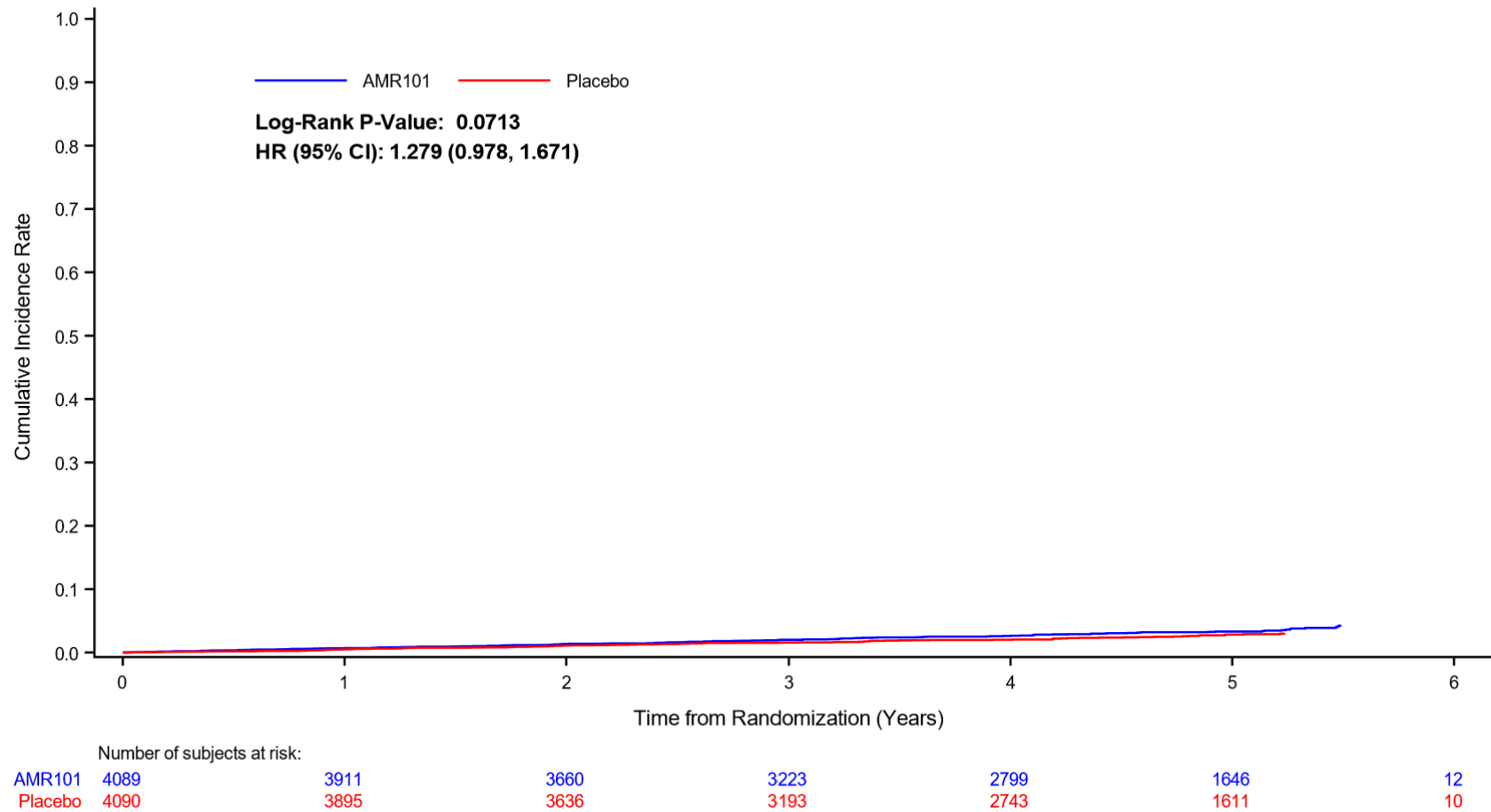
There were no significant differences in bleeding TEAEs or SAEs (both including positively adjudicated endpoints of hemorrhagic stroke) leading to study drug withdrawal across treatment groups. Kaplan-Meier curves for time to permanent study drug discontinuation due to bleeding events (serious and non-serious; [Figure 41](#)) or due to serious bleeding events ([Figure 42](#)), each including hemorrhagic stroke events, are presented below by treatment arm. For permanent study drug discontinuation due to bleeding events (serious and nonserious), including hemorrhagic stroke events, incidence rates were very low, 11/4089 (0.27%) and 10/4090 (0.24%) for icosapent ethyl and placebo, respectively. For permanent study drug discontinuation due to serious bleeding events, including hemorrhagic stroke events were also very low, with incidence rates of 9/4089 (0.22%) and 8/4090 (0.20%) for icosapent ethyl and placebo groups, respectively. Bleeding SAEs that required (or prolonged) hospitalization were low overall, and marginally higher with icosapent ethyl, but not statistically significantly different from placebo (2.6% with icosapent ethyl and 2.1% with placebo; $p=0.11$; [Table 54](#)).

Figure 39. Kaplan-Meier Curve for Time to First Bleeding Event (Serious and Non-serious) Including Hemorrhagic Stroke



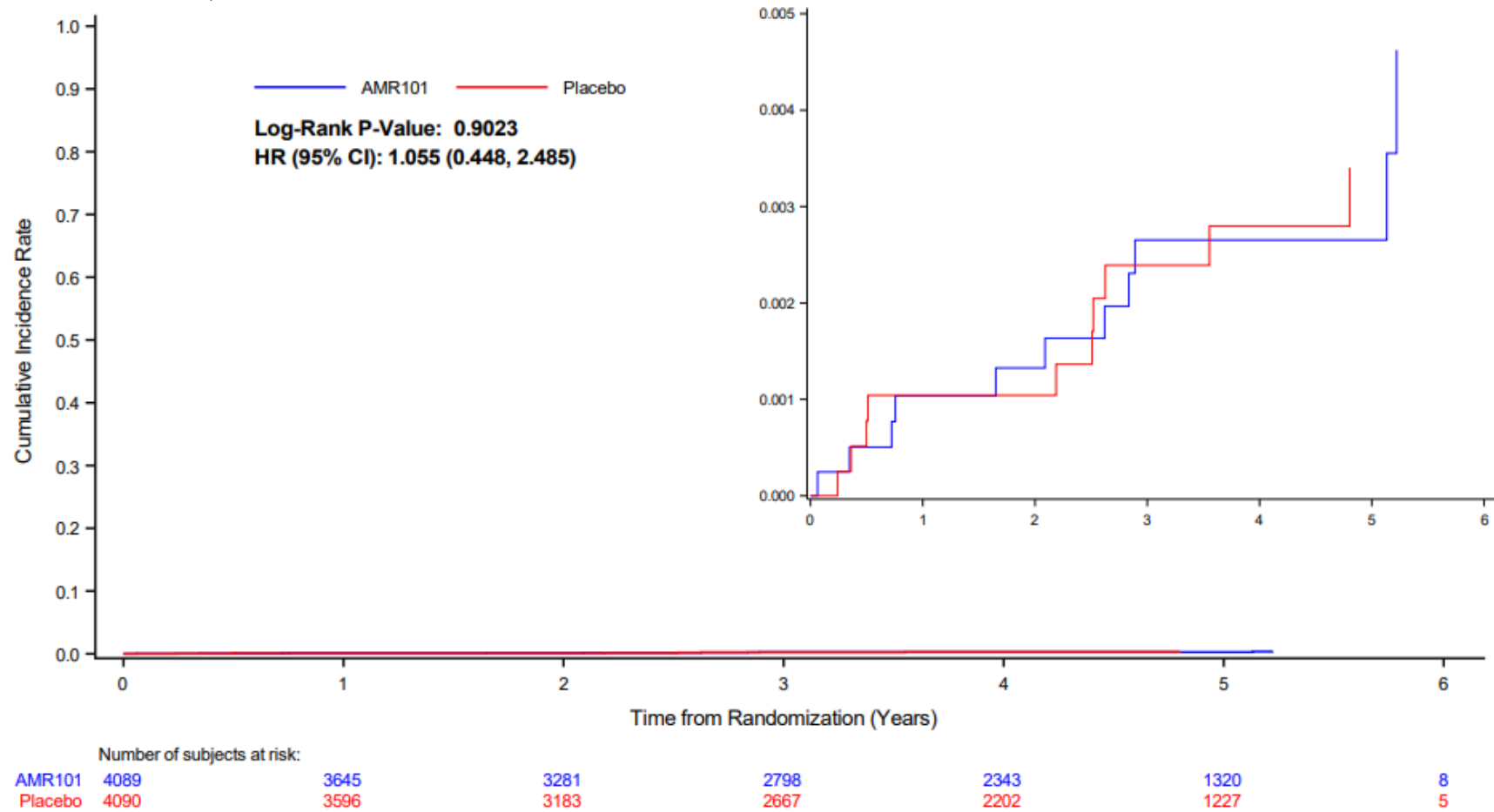
AMR101 = icosapent ethyl.

Figure 40. Kaplan-Meier Curve for Time to First Serious Bleeding Event Including Hemorrhagic Stroke



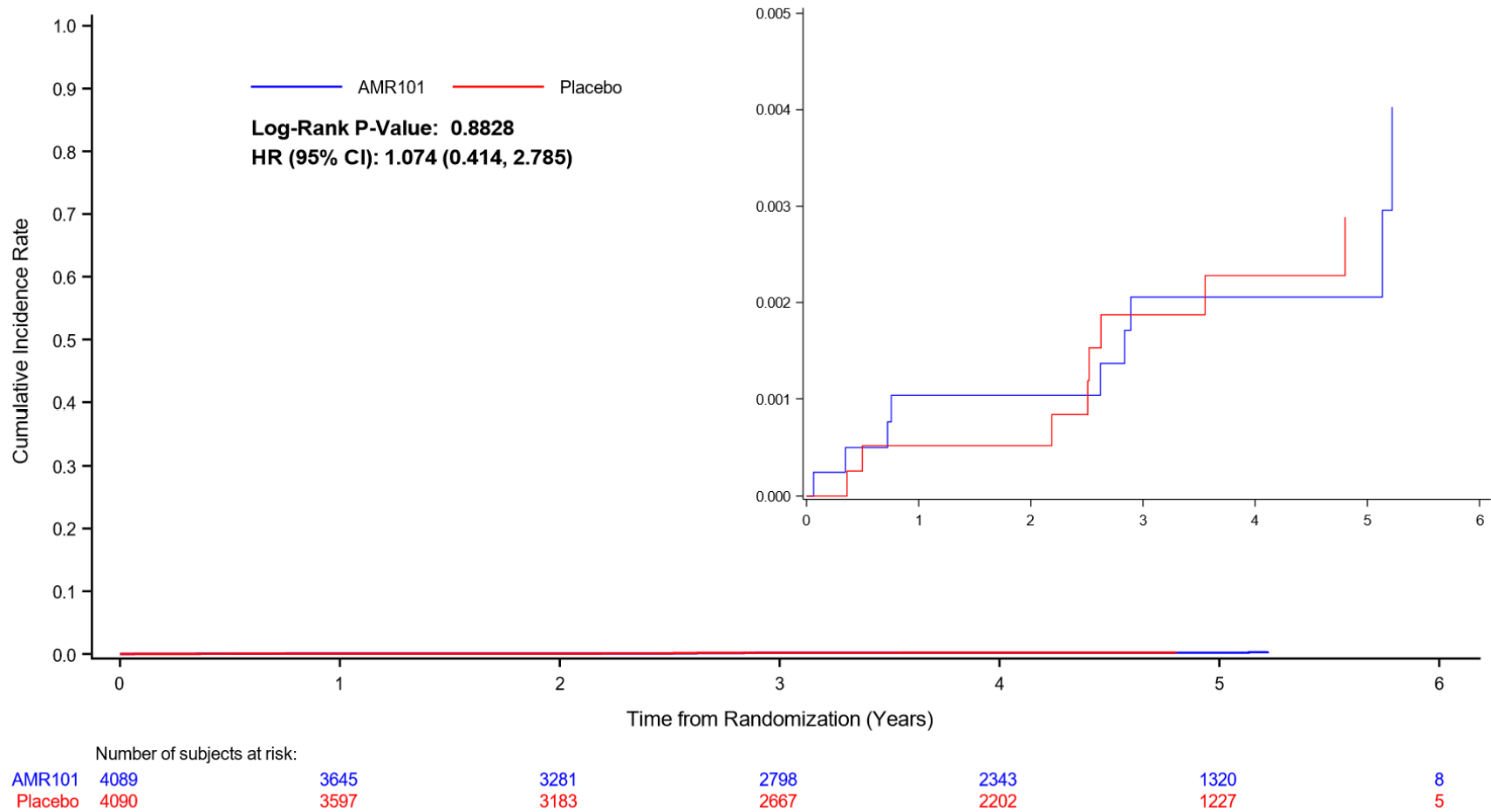
AMR101 = icosapent ethyl.

Figure 41. Kaplan-Meier Curve for Time to Permanent Study Drug Discontinuation Due to Bleeding (Including Hemorrhagic Stroke)



AMR101 = icosapent ethyl.

Figure 42. Kaplan-Meier Curve for Time to Permanent Study Drug Discontinuation Due to Serious Bleeding (Including Hemorrhagic Stroke)



AMR101 = icosapent ethyl.

Table 54. Bleeding SAEs Leading to (or Prolonging) Hospitalization by Preferred Term

AE of Interest Preferred Term	Icosapent Ethyl (N=4089)	Placebo (N=4090)	p-value^[1]
Serious Bleeding Disorders That Requires or Prolongs Hospitalization	106 (2.6%)	84 (2.1%)	0.11
Gastrointestinal Haemorrhage	25 (0.6%)	19 (0.5%)	0.37
Rectal Haemorrhage	10 (0.2%)	6 (0.1%)	0.33
Subdural Haematoma	9 (0.2%)	5 (0.1%)	0.30
Haematuria	8 (0.2%)	4 (0.1%)	0.27
Epistaxis	5 (0.1%)	4 (0.1%)	0.75
Lower Gastrointestinal Haemorrhage	5 (0.1%)	4 (0.1%)	0.75
Post Procedural Haemorrhage	5 (0.1%)	3 (0.1%)	0.51
Haemorrhagic Anaemia	4 (0.1%)	1 (0.0%)	0.22
Diverticulum Intestinal Haemorrhagic	3 (0.1%)	3 (0.1%)	>0.99
Gastric Ulcer Haemorrhage	3 (0.1%)	1 (0.0%)	0.37
Haematemesis	3 (0.1%)	0 (0.0%)	0.12
Haemorrhoidal Haemorrhage	3 (0.1%)	1 (0.0%)	0.37
Melaena	3 (0.1%)	4 (0.1%)	>0.99
Upper Gastrointestinal Haemorrhage	3 (0.1%)	3 (0.1%)	>0.99
Cystitis Haemorrhagic	2 (0.0%)	0 (0.0%)	0.25
Duodenal Ulcer Haemorrhage	2 (0.0%)	0 (0.0%)	0.25
Subarachnoid Haemorrhage	2 (0.0%)	1 (0.0%)	0.62
Subdural Haemorrhage	2 (0.0%)	1 (0.0%)	0.62
Traumatic Haematoma	2 (0.0%)	1 (0.0%)	0.62
Ecchymosis	1 (0.0%)	0 (0.0%)	0.50
Extravasation Blood	1 (0.0%)	0 (0.0%)	0.50
Gastric Haemorrhage	1 (0.0%)	3 (0.1%)	0.62
Gastrointestinal Angiodysplasia Haemorrhagic	1 (0.0%)	0 (0.0%)	0.50
Genital Haemorrhage	1 (0.0%)	0 (0.0%)	0.50
Haematochezia	1 (0.0%)	2 (0.0%)	>0.99
Haematoma	1 (0.0%)	1 (0.0%)	>0.99
Haemoptysis	1 (0.0%)	0 (0.0%)	0.50
Haemorrhagic Transformation Stroke	1 (0.0%)	0 (0.0%)	0.50
Haemothorax	1 (0.0%)	1 (0.0%)	>0.99
Intra-Abdominal Haemorrhage	1 (0.0%)	0 (0.0%)	0.50
Large Intestinal Haemorrhage	1 (0.0%)	1 (0.0%)	>0.99
Mallory-Weiss Syndrome	1 (0.0%)	0 (0.0%)	0.50
Menorrhagia	1 (0.0%)	0 (0.0%)	0.50
Pancreatitis Haemorrhagic	1 (0.0%)	0 (0.0%)	0.50
Peptic Ulcer Haemorrhage	1 (0.0%)	0 (0.0%)	0.50
Post Procedural Haematoma	1 (0.0%)	1 (0.0%)	>0.99
Retroperitoneal Haemorrhage	1 (0.0%)	0 (0.0%)	0.50
Shock Haemorrhagic	1 (0.0%)	0 (0.0%)	0.50
Ulcer Haemorrhage	1 (0.0%)	0 (0.0%)	0.50
Urinary Bladder Haemorrhage	1 (0.0%)	1 (0.0%)	>0.99
Aortic Aneurysm Rupture	0 (0.0%)	1 (0.0%)	>0.99
Brain Contusion	0 (0.0%)	2 (0.0%)	0.50
Catheter Site Haemorrhage	0 (0.0%)	1 (0.0%)	>0.99
Cerebral Haemorrhage	0 (0.0%)	2 (0.0%)	0.50
Diverticulitis Intestinal Haemorrhagic	0 (0.0%)	1 (0.0%)	>0.99
Duodenitis Haemorrhagic	0 (0.0%)	1 (0.0%)	>0.99

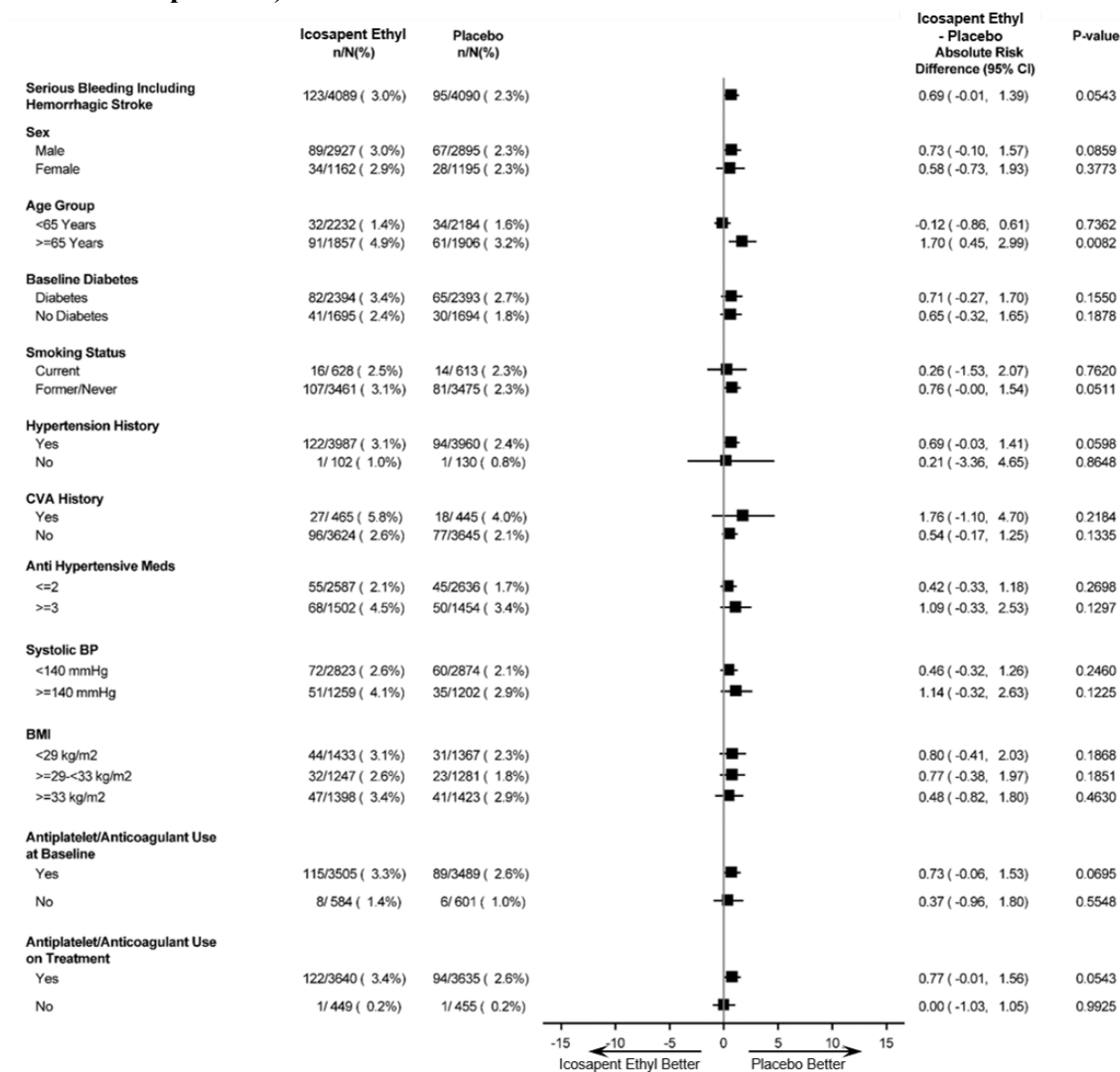
AE of Interest Preferred Term	Icosapent Ethyl (N=4089)	Placebo (N=4090)	p-value^[1]
Haemarthrosis	0 (0.0%)	1 (0.0%)	>0.99
Haemorrhage Intracranial	0 (0.0%)	1 (0.0%)	>0.99
Immune Thrombocytopenic Purpura	0 (0.0%)	1 (0.0%)	>0.99
Mouth Haemorrhage	0 (0.0%)	1 (0.0%)	>0.99
Oesophageal Haemorrhage	0 (0.0%)	1 (0.0%)	>0.99
Pericardial Haemorrhage	0 (0.0%)	1 (0.0%)	>0.99
Post Procedural Haematuria	0 (0.0%)	1 (0.0%)	>0.99
Renal Haemorrhage	0 (0.0%)	1 (0.0%)	>0.99
Retinal Haemorrhage	0 (0.0%)	1 (0.0%)	>0.99
Retroperitoneal Haematoma	0 (0.0%)	1 (0.0%)	>0.99
Traumatic Intracranial Haemorrhage	0 (0.0%)	1 (0.0%)	>0.99

Note: Percentages are based on the number of randomized subjects within each treatment group (N).

[1] p-value from Fishers Exact test

Figure 43 presents serious TEAEs plus positively adjudicated hemorrhagic stroke events across subgroups. No differences were observed across subgroups of gender, tobacco use, hypertension, diabetes, any CVA history, number of hypertension medications, systolic blood pressure, BMI, or antiplatelet/anticoagulant use (at baseline or on study). Age above or below 65 years is the one subgroup with a suggestion of difference in bleeding events. Patients ≥ 65 years old may be more likely to experience a serious bleeding event, including hemorrhagic stroke (interaction $p=0.0671$), whereas the younger subgroup was no more likely to have an event on icosapent ethyl. The small number of patients with hemorrhagic stroke complicates the ability to draw conclusions regarding whether specific baseline characteristics place patients on icosapent ethyl at increased risk for serious bleeds including hemorrhagic stroke. Examining hemorrhagic stroke hazard ratios between icosapent ethyl and placebo in these subgroups revealed no significant differences across subgroups.

Figure 43. Forest Plot for Bleeding SAEs Plus Hemorrhagic Stroke by Subgroups (ITT Population)



CVA = Cerebrovascular Accident; BP = Blood pressure

Patients with missing baseline subgroup data are not included in the corresponding baseline subgroup classifications and therefore not included in the denominator (N) of the corresponding subgroup analyses.

Use of antithrombotic medications during bleeding events was evaluated and there was no specific antithrombotic or class of antithrombotic therapy that had a significant interaction between treatment arms for bleeding TEAEs including hemorrhagic stroke (Table 55) or bleeding SAEs including hemorrhagic stroke (Table 56).

Table 55. Anti-thrombotic Medication Use in Patients with Bleeding TEAEs (Serious and Non-Serious) Including Hemorrhagic Stroke (Safety Population)

Category Medication	Icosapent Ethyl (N=2892)	Placebo (N=2893)	P-value
Subjects with at least one bleeding event	494/4089 (12.1)	412/4090 (10.1)	0.0039
Subjects on Anti-Platelet OR Anti-Coagulant at or before bleeding event	464/ 494 (93.9)	383/ 412 (93.0)	0.5901
Single Anti-Platelet: Aspirin Only	196/ 494 (39.7)	155/ 412 (37.6)	0.5383
>1 Anti-Platelet: Aspirin AND (Clopidogrel OR Prasugrel OR Ticagrelor)	131/ 494 (26.5)	120/ 412 (29.1)	0.4124
Anti-Coagulant: Warfarin OR Rivaroxaban OR Apixaban	19/ 494 (3.8)	19/ 412 (4.6)	0.6193
Both Anticoagulants Plus Any Anti-platelet listed above	77/ 494 (15.6)	53/ 412 (12.9)	0.2548
Subjects not on Anti-Platelet OR Anti-Coagulant at or before bleeding event	30/ 494 (6.1)	29/ 412 (7.0)	0.5901

Note: Categories are mutually exclusive.

P-values are based on Fishers Exact test.

Table 56. Anti-thrombotic Medication Use in Patients with Bleeding SAEs Including Hemorrhagic Stroke (Safety Population)

Category Medication	Icosapent Ethyl (N=2892)	Placebo (N=2893)	P-value
Subjects with at least one bleeding event	123/4089 (3.0)	95/4090 (2.3)	0.0549
Subjects on Anti-Platelet OR Anti-Coagulant at or before bleeding event	119/ 123 (96.7)	93/ 95 (97.9)	0.6988
Single Anti-Platelet: Aspirin Only	38/ 123 (30.9)	25/ 95 (26.3)	0.5470
>1 Anti-Platelet: Aspirin AND (Clopidogrel OR Prasugrel OR Ticagrelor)	31/ 123 (25.2)	28/ 95 (29.5)	0.5395
Anti-Coagulant: Warfarin OR Rivaroxaban OR Apixaban	6/ 123 (4.9)	9/ 95 (9.5)	0.2802
Both Anticoagulants Plus Any Anti-platelet listed above	30/ 123 (24.4)	19/ 95 (20.0)	0.5138
Subjects not on Anti-Platelet OR Anti-Coagulant at or before bleeding event	4/ 123 (3.3)	2/ 95 (2.1)	0.6988

Note: Categories are mutually exclusive.

P-values are based on Fishers Exact test.

We considered whether bleeding altered the study findings with the primary or key secondary endpoint, or within the contributing components. The outcome results for patients with on-study bleeding TEAEs (Table 57), SAEs (Table 58), or SAEs plus positively adjudicated hemorrhagic stroke endpoints (Table 59) are provided below. A limitation to this analysis is that the REDUCE-IT study was not powered for such analyses, which were undertaken *post hoc* to explore a potential signal that may have emerged across the trial, and even then, on a fairly small subgroup. Thus, confidence intervals are wide and there may be insufficient power to test for interactions. For bleeding TEAEs (serious and nonserious; Table 57), hospitalization for unstable angina is the only endpoint with a significant interaction p-value (defined as interaction $p < 0.15$; interaction $p = 0.1021$), where unstable angina event counts for patients with bleeding events were low with a suggestion of no difference across treatment groups, while total event counts were higher in patients without bleeding TEAEs and benefit was observed with icosapent ethyl as compared to

placebo. For bleeding SAEs excluding hemorrhagic stroke ([Table 58](#)) nonfatal stroke (i.e. ischemic or hemorrhagic stroke) is the only endpoint with a significant interaction p-value (interaction $p=0.0086$). As a caveat, nonfatal stroke event counts for patients with bleeding SAEs were low (14 total events across treatment arms). Nevertheless, more strokes occurred in the icosapent ethyl arm than the placebo arm. In contrast, total nonfatal stroke counts were higher in patients without bleeding events, and benefit was observed with icosapent ethyl as compared to placebo. Similar results were observed when grouping patients with positively adjudicated hemorrhagic stroke endpoints and patients with bleeding SAEs ([Table 59](#)); again, the event counts were low (25 total events across treatment arms, interaction $p=0.0067$).

Table 57. Summary of Primary and Key Secondary Composite Endpoints and Each Component by Patients With or Without On-Study Bleeding TEAEs Excluding Hemorrhagic Stroke (Serious and Nonserious; ITT Population)

Endpoint	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Icosapent Ethyl vs. Placebo		Interaction P-value
			HR (95% CI)	P-value	
Primary Composite Endpoint	705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68, 0.83)	<0.0001	0.9531
Any Bleeding-Yes	128/ 482 (26.6%)	138/ 404 (34.2%)	0.75 (0.59, 0.96)	0.0208	
Any Bleeding-No	577/3607 (16.0%)	763/3686 (20.7%)	0.74 (0.67, 0.83)	<0.0001	
Key Secondary Composite Endpoint	459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65, 0.83)	<0.0001	0.9913
Any Bleeding-Yes	82/ 482 (17.0%)	92/ 404 (22.8%)	0.74 (0.55, 1.00)	0.0480	
Any Bleeding-No	377/3607 (10.5%)	514/3686 (13.9%)	0.73 (0.64, 0.83)	<0.0001	
CV Death	174/4089 (4.3%)	213/4090 (5.2%)	0.80 (0.66, 0.98)	0.0315	0.1925
Any Bleeding-Yes	22/ 482 (4.6%)	31/ 404 (7.7%)	0.56 (0.32, 0.97)	0.0373	
Any Bleeding-No	152/3607 (4.2%)	182/3686 (4.9%)	0.84 (0.68, 1.05)	0.1176	
Nonfatal MI	237/4089 (5.8%)	332/4090 (8.1%)	0.70 (0.59, 0.82)	<0.0001	0.6014
Any Bleeding-Yes	49/ 482 (10.2%)	54/ 404 (13.4%)	0.76 (0.52, 1.12)	0.1640	
Any Bleeding-No	188/3607 (5.2%)	278/3686 (7.5%)	0.68 (0.56, 0.81)	<0.0001	
Nonfatal Ischemic or Hemorrhagic Stroke*	85/4089 (2.1%)	118/4090 (2.9%)	0.71 (0.54, 0.94)	0.0149	0.3378
Any Bleeding-Yes	20/ 482 (4.1%)	18/ 404 (4.5%)	0.97 (0.51, 1.84)	0.9300	
Any Bleeding-No	65/3607 (1.8%)	100/3686 (2.7%)	0.66 (0.48, 0.90)	0.0076	
Coronary Revascularization	376/4089 (9.2%)	544/4090 (13.3%)	0.66 (0.58, 0.76)	<0.0001	0.5840
Any Bleeding-Yes	82/ 482 (17.0%)	94/ 404 (23.3%)	0.69 (0.52, 0.94)	0.0158	
Any Bleeding-No	294/3607 (8.2%)	450/3686 (12.2%)	0.64 (0.56, 0.75)	<0.0001	
Hospitalization for Unstable Angina	108/4089 (2.6%)	157/4090 (3.8%)	0.68 (0.53, 0.87)	0.0018	0.1021
Any Bleeding-Yes	27/ 482 (5.6%)	22/ 404 (5.4%)	0.99 (0.56, 1.75)	0.9753	
Any Bleeding-No	81/3607 (2.2%)	135/3686 (3.7%)	0.61 (0.46, 0.80)	0.0003	

Note: The number of subjects with event (n) is the number of subjects with the event in the ITT Population within each treatment group (N).

Log-Rank p-value is reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

*Endpoints that incorporate nonfatal stroke include hemorrhagic stroke (n=23 pooling both groups) in addition to ischemic stroke. Since hemorrhagic stroke is also a bleeding event, endpoints including nonfatal stroke are susceptible to autocorrelation, especially the isolated nonfatal stroke endpoint. Accordingly, autocorrelation may bias results toward overestimating the influence of hemorrhagic stroke.

Table 58. Summary of Primary and Key Secondary Composite Endpoints and Each Component by Patients With or Without On-Study Bleeding SAEs Excluding Hemorrhagic Stroke (ITT Population)

Endpoint	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Icosapent Ethyl vs. Placebo		Interaction P-value
			HR (95% CI)	P-value	
Primary Composite Endpoint	705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68, 0.83)	<0.0001	0.6395
Serious Bleeding-Yes	41/ 111 (36.9%)	36/ 85 (42.4%)	0.85 (0.54, 1.34)	0.4827	
Serious Bleeding-No	664/3978 (16.7%)	865/4005 (21.6%)	0.74 (0.67, 0.82)	<0.0001	
Key Secondary Composite Endpoint	459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65, 0.83)	<0.0001	0.4854
Serious Bleeding-Yes	31/ 111 (27.9%)	27/ 85 (31.8%)	0.86 (0.51, 1.45)	0.5836	
Serious Bleeding-No	428/3978 (10.8%)	579/4005 (14.5%)	0.72 (0.64, 0.82)	<0.0001	
CV Death	174/4089 (4.3%)	213/4090 (5.2%)	0.80 (0.66, 0.98)	0.0315	0.6374
Serious Bleeding-Yes	7/ 111 (6.3%)	8/ 85 (9.4%)	0.68 (0.25, 1.87)	0.4513	
Serious Bleeding-No	167/3978 (4.2%)	205/4005 (5.1%)	0.81 (0.66, 0.99)	0.0394	
Nonfatal MI	237/4089 (5.8%)	332/4090 (8.1%)	0.70 (0.59, 0.82)	<0.0001	0.8073
Serious Bleeding-Yes	17/ 111 (15.3%)	20/ 85 (23.5%)	0.59 (0.31, 1.14)	0.1124	
Serious Bleeding-No	220/3978 (5.5%)	312/4005 (7.8%)	0.69 (0.58, 0.82)	<0.0001	
Nonfatal Ischemic or Hemorrhagic Stroke*	85/4089 (2.1%)	118/4090 (2.9%)	0.71 (0.54, 0.94)	0.0149	0.0086
Serious Bleeding-Yes	12/ 111 (10.8%)	2/ 85 (2.4%)	5.20 (1.15, 23.55)	0.0175	
Serious Bleeding-No	73/3978 (1.8%)	116/4005 (2.9%)	0.62 (0.46, 0.83)	0.0014	
Coronary Revascularization	376/4089 (9.2%)	544/4090 (13.3%)	0.66 (0.58, 0.76)	<0.0001	0.7696
Serious Bleeding-Yes	23/ 111 (20.7%)	23/ 85 (27.1%)	0.71 (0.40, 1.28)	0.2548	
Serious Bleeding-No	353/3978 (8.9%)	521/4005 (13.0%)	0.66 (0.57, 0.75)	<0.0001	
Hospitalization for Unstable Angina	108/4089 (2.6%)	157/4090 (3.8%)	0.68 (0.53, 0.87)	0.0018	0.2209
Serious Bleeding-Yes	6/ 111 (5.4%)	3/ 85 (3.5%)	1.56 (0.39, 6.25)	0.5252	
Serious Bleeding-No	102/3978 (2.6%)	154/4005 (3.8%)	0.66 (0.51, 0.84)	0.0010	

Note: The number of subjects with event (n) is the number of subjects with the event in the ITT Population within each treatment group (N). Log-Rank p-value is reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

*Endpoints that incorporate nonfatal stroke include hemorrhagic stroke (n=23 pooling both groups) in addition to ischemic stroke. Since hemorrhagic stroke is also a bleeding event, endpoints including nonfatal stroke are susceptible to autocorrelation, especially the isolated nonfatal stroke endpoint. Accordingly, autocorrelation may bias results toward overestimating the influence of hemorrhagic stroke.

Table 59. Summary of Primary and Key Secondary Composite Endpoints and Each Component by Patients With or Without On-Study Bleeding SAEs Including Hemorrhagic Stroke (ITT Population)

Endpoint	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Icosapent Ethyl vs. Placebo		Interaction P-value
			HR (95% CI)	P-value	
Primary Composite Endpoint	705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68, 0.83)	<0.0001	0.3698
Serious Bleeding-Yes	53/ 123 (43.1%)	46/ 95 (48.4%)	0.89 (0.60, 1.33)	0.5672	
Serious Bleeding-No	652/3966 (16.4%)	855/3995 (21.4%)	0.74 (0.67, 0.82)	<0.0001	
Key Secondary Composite Endpoint	459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65, 0.83)	<0.0001	0.2613
Serious Bleeding-Yes	43/ 123 (35.0%)	37/ 95 (38.9%)	0.91 (0.58, 1.42)	0.6827	
Serious Bleeding-No	416/3966 (10.5%)	569/3995 (14.2%)	0.71 (0.63, 0.81)	<0.0001	
CV Death	174/4089 (4.3%)	213/4090 (5.2%)	0.80 (0.66, 0.98)	0.0315	0.7423
Serious Bleeding-Yes	14/ 123 (11.4%)	15/ 95 (15.8%)	0.73 (0.35, 1.53)	0.4096	
Serious Bleeding-No	160/3966 (4.0%)	198/3995 (5.0%)	0.80 (0.65, 0.99)	0.0364	
Nonfatal MI	237/4089 (5.8%)	332/4090 (8.1%)	0.70 (0.59, 0.82)	<0.0001	0.7417
Serious Bleeding-Yes	17/ 123 (13.8%)	21/ 95 (22.1%)	0.58 (0.31, 1.11)	0.0944	
Serious Bleeding-No	220/3966 (5.5%)	311/3995 (7.8%)	0.70 (0.59, 0.83)	<0.0001	
Nonfatal Ischemic or Hemorrhagic Stroke*	85/4089 (2.1%)	118/4090 (2.9%)	0.71 (0.54, 0.94)	0.0149	0.0067
Serious Bleeding-Yes	18/ 123 (14.6%)	7/ 95 (7.4%)	2.26 (0.93, 5.47)	0.0642	
Serious Bleeding-No	67/3966 (1.7%)	111/3995 (2.8%)	0.60 (0.44, 0.81)	0.0007	
Coronary Revascularization	376/4089 (9.2%)	544/4090 (13.3%)	0.66 (0.58, 0.76)	<0.0001	0.8025
Serious Bleeding-Yes	24/ 123 (19.5%)	25/ 95 (26.3%)	0.69 (0.39, 1.22)	0.1980	
Serious Bleeding-No	352/3966 (8.9%)	519/3995 (13.0%)	0.66 (0.57, 0.75)	<0.0001	
Hospitalization for Unstable Angina	108/4089 (2.6%)	157/4090 (3.8%)	0.68 (0.53, 0.87)	0.0018	0.3608
Serious Bleeding-Yes	6/ 123 (4.9%)	4/ 95 (4.2%)	1.18 (0.33, 4.20)	0.7954	
Serious Bleeding-No	102/3966 (2.6%)	153/3995 (3.8%)	0.66 (0.52, 0.85)	0.0012	

Note: The number of subjects with event (n) is the number of subjects with the event in the ITT Population within each treatment group (N).

Log-Rank p-value is reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

*Endpoints that incorporate nonfatal stroke include hemorrhagic stroke (n=23 pooling both groups) in addition to ischemic stroke. Since hemorrhagic stroke is also a bleeding event, endpoints including nonfatal stroke are susceptible to autocorrelation, especially the isolated nonfatal stroke endpoint. Accordingly, autocorrelation may bias results toward overestimating the influence of hemorrhagic stroke.

In summary, the overall incidence of bleeding events (non-serious, serious and positively adjudicated hemorrhagic stroke) was higher with icosapent ethyl than placebo (494/4089 [12.1%] vs. 412/4090 [10.1%], respectively $p=0.0039$). A 2% increase in bleeding implies treating 50 patients matching REDUCE-IT entry criteria with icosapent ethyl for five years might result in one more bleeding event, chiefly non-serious events. On balance, this risk would seem reasonable compared to lowered risk for MACE in quantitative terms, more so if bleeding events are more manageable clinically than MACE events. Broadly, this is a safety finding common to the class of omega-3 fatty acid products. From a clinical perspective, most of the bleeding events observed with icosapent ethyl in REDUCE-IT were not serious and can be readily managed by clinicians. Patients age 65 and over treated with icosapent ethyl may be at increased risk for serious bleeding events, including hemorrhagic stroke; they should be counseled accordingly and advised to consult with their health care professional if signs or symptoms of increased bleeding become apparent as modification of therapy may be warranted. Patients receiving warfarin or aspirin concomitantly with icosapent ethyl may also be at marginally increased risk for bleeding and should be advised to consult with their health care professional if signs or symptoms of increased bleeding become apparent.

APPENDIX M: ATRIAL FIBRILLATION/FLUTTER: FURTHER *POST HOC* ANALYSES

In addition to the analyses presented in the main body of this briefing book, other analyses were conducted to explore the observed increase in atrial fibrillation and/or flutter in the icosapent ethyl group relative to placebo

The analyses of atrial arrhythmia-related AEs in REDUCE-IT did not include (positively adjudicated) atrial fibrillation and/or flutter endpoint events. This was consistent with the REDUCE-IT SAP which excluded endpoint events (efficacy endpoints) from safety analyses. However, for a comprehensive assessment of all atrial fibrillation and/or flutter events, select analyses below combine all reported atrial fibrillation and/or flutter -related events (non-serious and serious AEs) and atrial fibrillation and/or flutter endpoint events. Analyses of a subset of those events represent the most consequential atrial arrhythmia events, i.e., all serious atrial fibrillation and/or flutter -related AEs combined with atrial fibrillation and/or flutter endpoint events.

As noted earlier, cardiac arrhythmias requiring hospitalization (or prolongation of hospitalization) ≥ 24 hours (including atrial fibrillation and/or flutter) were efficacy endpoint events if positively adjudicated by the CEC; if not positively adjudicated, they were captured within the safety analyses as AEs or SAEs.

As presented in [Table 35](#) and [Table 60](#) below, the tertiary endpoint of cardiac arrhythmia requiring hospitalization ≥ 24 hours was numerically higher in the icosapent ethyl group compared to the placebo group (4.6% versus 3.8%, respectively; HR [95% CI] of 1.21 [0.97 to 1.49]; $p=0.0856$). In clinical terms, a difference in slightly $<1\%$ would translate to a need to treat >100 patients for 6 years to encounter one additional case. An increase in positively adjudicated endpoints of atrial fibrillation and/or flutter was observed in the icosapent ethyl group (3.1%) as compared to 2.1% in the placebo group (HR [95% CI] of 1.50 [1.14 to 1.98; $p=0.0037$; [Table 11](#) and [Table 60](#) below). Other positively adjudicated arrhythmias were not significantly different between treatment groups when evaluated as individual endpoints ([Table 60](#)). Time to event analyses for cardiac arrhythmias ([Figure 44](#)), and for atrial fibrillation and/or flutter ([Figure 45](#)), requiring hospitalization ≥ 24 hours are also provided below. Consistent with the summary statistics for arrhythmias in [Table 60](#) below, the cardiac arrhythmia curves show low event rates with little to no separation; the atrial fibrillation and/or flutter curves also show low event rates with visual separation beginning around two years.

Considering atrial fibrillation and/or flutter specifically, rates differed the most across groups for regular TEAEs (5.8% on icosapent ethyl and 4.5% on placebo, $p=0.0079$) and positively-adjudicated atrial fibrillation and/or flutter requiring ≥ 24 hours of hospitalization (3.1% on icosapent ethyl and 2.1% on placebo, $p=0.0037$, [Table 11](#)). Serious TEAEs varied little by group (0.5% in both groups, $p=0.76$). The suggestion of enhanced risk for atrial fibrillation and/or flutter motivated several other *post hoc* analyses presented below.

Table 60. Time to the Tertiary Endpoint of Cardiac Arrhythmia Requiring Hospitalization of ≥ 24 Hours and Contributing Arrhythmia Types (ITT Population)

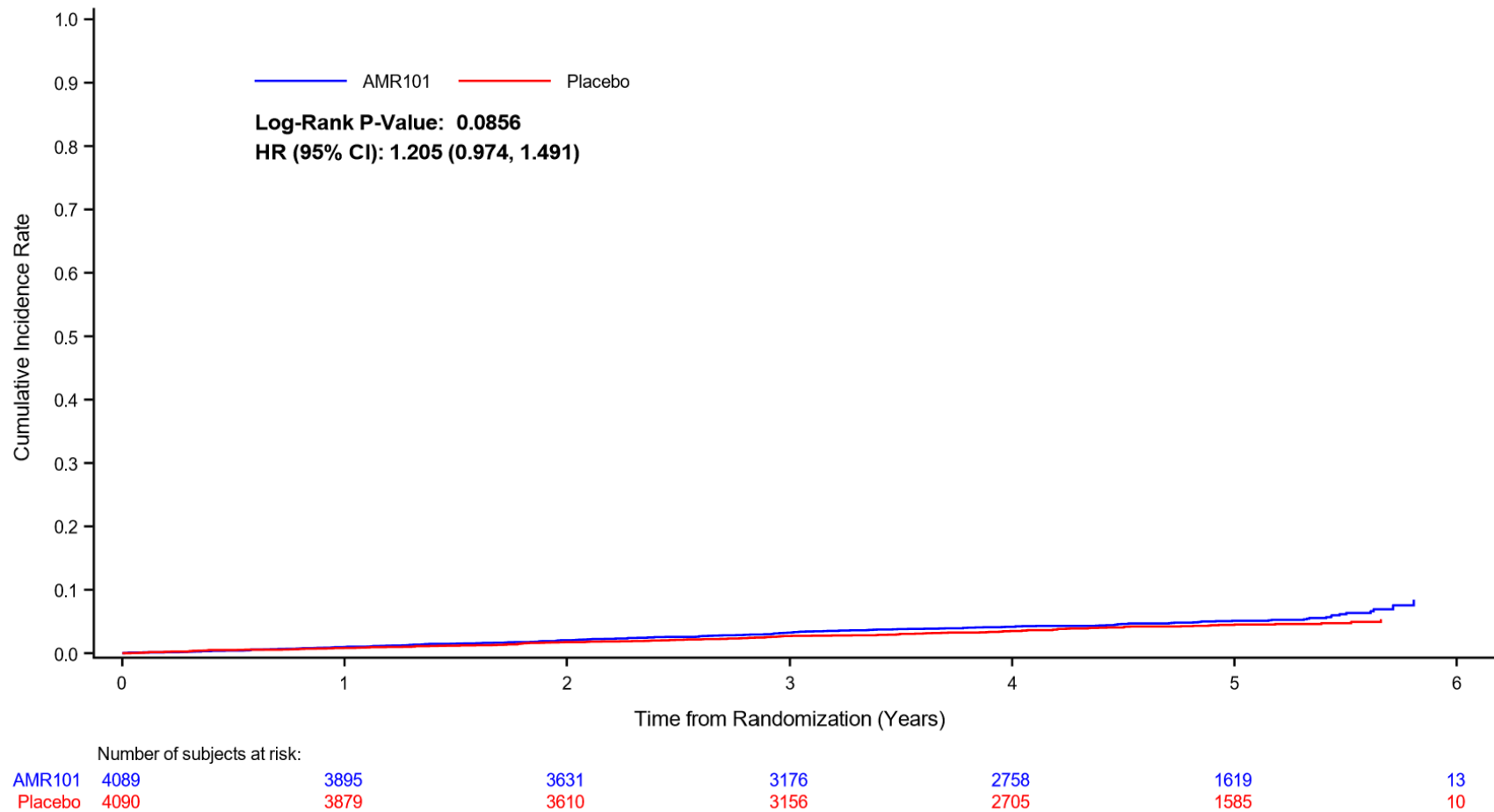
Endpoint Event, n (%) ²	Icosapent Ethyl (N=4089)	Placebo (N=4090)	Treatment Comparison ¹	
			P-value from Log-Rank Test	HR (95% CI) Icosapent Ethyl /Placebo
Cardiac Arrhythmia Requiring Hospitalization of ≥ 24 Hours	188 (4.6)	154 (3.8)	0.0856	1.21 (0.97 – 1.49)
Atrial Fibrillation or Flutter Requiring Hospitalization of ≥ 24 Hours	127 (3.1)	84 (2.1)	0.0037	1.50 (1.14 – 1.98)
Bradycardia/Heart Block Requiring Hospitalization of ≥ 24 Hours	28 (0.7)	40 (1.0)	0.1248	0.69 (0.42 – 1.11)
Ventricular Tachycardia or Ventricular Fibrillation Requiring Hospitalization of ≥ 24 Hours	35 (0.9)	37 (0.9)	0.7564	0.93 (0.59 – 1.48)
Other Tachycardia Requiring Hospitalization of ≥ 24 Hours	7 (0.2)	7 (0.2)	0.9819	0.99 (0.35 – 2.82)

Abbreviations: CI = confidence interval; CV = cardiovascular; HR = hazard ratio; ITT = Intention-to-Treat.

Note: The number of patients with event (n) is the number of patients with the event in the ITT population within each treatment group (N).

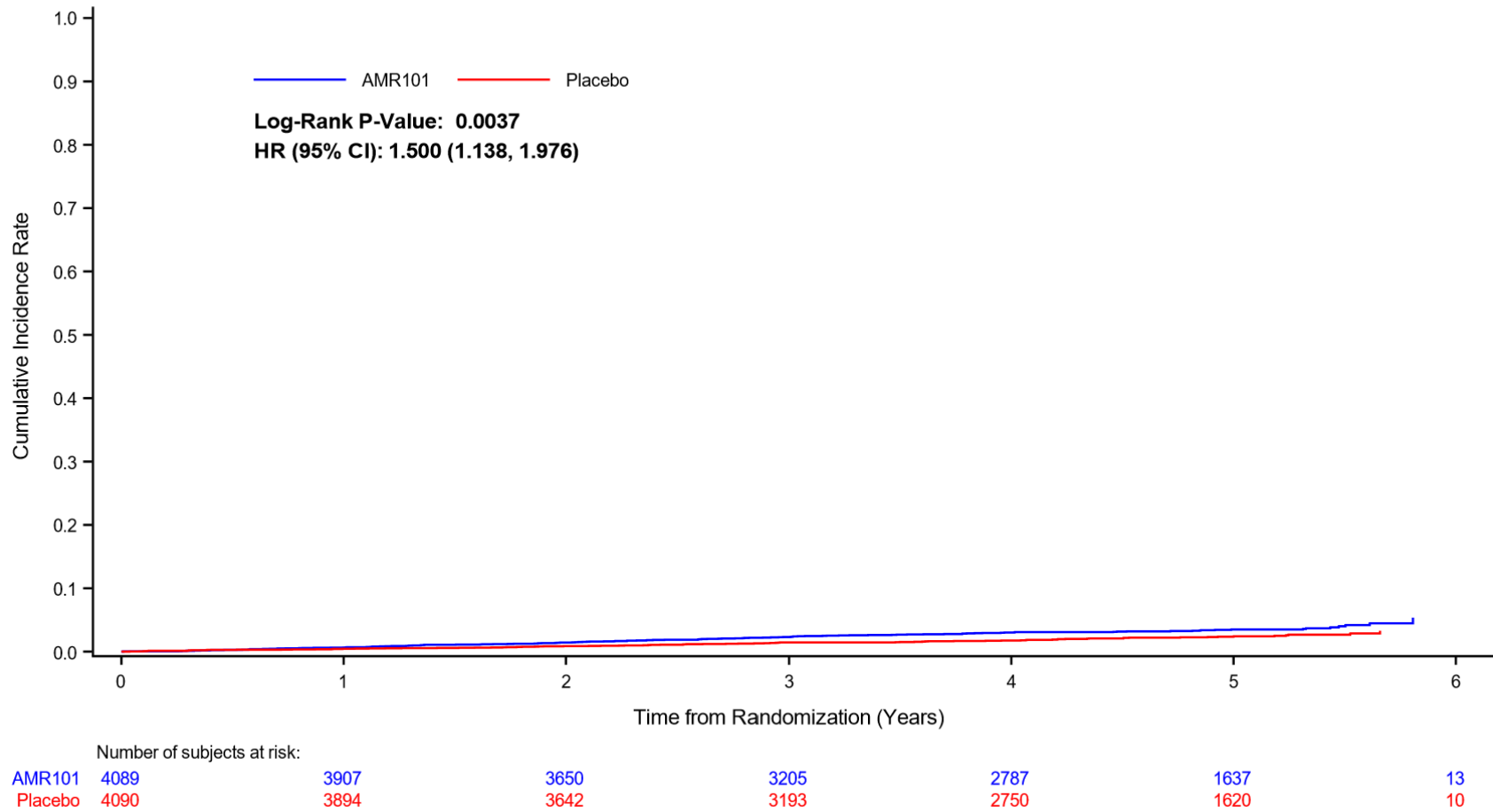
- 1 Log-Rank test statistic and p-value are reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.
- 2 Based on a patient's first post-randomization occurrence of the endpoint event.

Figure 44. Kaplan-Meier Curve for Time to Endpoint of Cardiac Arrhythmia Requiring Hospitalization of ≥ 24 Hours by Treatment Arm



AMR101 = icosapent ethyl.

Figure 45. Kaplan-Meier Curve for Time to Endpoint of Atrial Fibrillation and/or Flutter Requiring Hospitalization of ≥ 24 Hours by Treatment Arm



AMR101 = icosapent ethyl.

The incidence of positively adjudicated atrial fibrillation and/or flutter endpoints by year is presented in Table 61, along with the risk difference across treatment groups. Incidence in the first 6 months was 0.3% in both treatment groups and, as expected, the cumulative incidence increased with time on study, but the risk difference across treatment groups remained at approximately 2% or less across all time points. Clinically, the 2% risk difference implies that in treating 50 patients matching REDUCE-IT entry criteria for five years with icosapent ethyl, might result in one additional atrial fibrillation and/or flutter event, which could either be new-onset or a recurrence in a patient with established/managed atrial fibrillation and/or flutter. In practice, this would likely be considered reasonable given the lowered risk of MACE.

Table 61. Time to First Onset of Positively Adjudicated Endpoint Atrial Fibrillation and/or Atrial Flutter by 6 Month Intervals (ITT Population)

Time (Days)	Cumulative Incidence Rate ^[1] , % (SE)		Icosapent Ethyl- Placebo Risk Diff., % (95% CI)
	Icosapent Ethyl (N=4089)	Placebo (N=4090)	
At 0.5 years (Day 180)	0.3 (0.08)	0.3 (0.08)	-0.00 (-0.23, 0.23)
At 1 year (Day 360)	0.6 (0.12)	0.4 (0.10)	0.20 (-0.12, 0.51)
At 1.5 years (Day 540)	1.1 (0.16)	0.6 (0.12)	0.51 (0.11, 0.91)
At 2 years (Day 720)	1.4 (0.19)	0.8 (0.15)	0.59 (0.12, 1.06)
At 2.5 years (Day 900)	1.9 (0.22)	1.1 (0.17)	0.78 (0.24, 1.32)
At 3 years (Day 1080)	2.3 (0.24)	1.4 (0.20)	0.83 (0.22, 1.44)
At 3.5 years (Day 1260)	2.6 (0.26)	1.4 (0.20)	1.17 (0.52, 1.81)
At 4 years (Day 1440)	2.9 (0.28)	1.7 (0.22)	1.23 (0.53, 1.93)
At 4.5 years (Day 1620)	3.1 (0.29)	2.1 (0.25)	1.00 (0.25, 1.74)
At 5 years (Day 1800)	3.4 (0.31)	2.4 (0.27)	1.08 (0.27, 1.89)
At 5.5 years (Day 1980)	3.7 (0.35)	2.7 (0.31)	1.00 (0.09, 1.92)
At 6 years (Day 2160)	5.4 (1.03)	3.3 (0.56)	2.07 (-0.23, 4.37)

Note: SE = Standard Error

[1] Cumulative incidence rate was estimated based on a Kaplan-Meier analysis.

The third most frequently reported baseline cardiac history finding (by preferred term) was atrial fibrillation (8.7% [713/8179]), with only coronary artery disease (12.8% [1045/8179]) and angina pectoris (11.6% [947/8179]) being more common; history of atrial flutter at baseline was present in 0.6% of patients (51/8179). Table 62 shows a higher rate of positively adjudicated atrial fibrillation and/or flutter endpoints with icosapent ethyl in both patients with and without a baseline history of atrial fibrillation and/or flutter; the hazard ratios for on-study atrial arrhythmias suggest numerically, but not statistically significantly, higher rates in patients with a history of atrial fibrillation and/or flutter (interaction $p = 0.2074$). Clinically, the absolute difference in risk appears greater for those who entered the trial with a history of atrial fibrillation and/or flutter, suggesting patients with atrial fibrillation and/or flutter may warrant more careful consideration when embarking upon icosapent ethyl therapy. On the other hand, those entering the trial with no history of atrial fibrillation and/or flutter appear to have a narrow risk difference. As a caveat, the interaction was not statistically significant for this *post hoc* analysis and the study was not powered for such analyses.

Table 62. Time to First Onset of Positively Adjudicated Endpoint Atrial Fibrillation and/or Atrial Flutter by Subjects with/without Atrial Fibrillation/Atrial Flutter at Baseline (ITT Population)

				<u>Treatment Comparison</u>		
				Hazard Ratio (Icosapent Ethyl/Placebo)		P-value ²
Icosapent Ethyl (N=4089)		Placebo (N=4090)				
Event (%)	Rate/ 1000 pt-yr	Event (%)	Rate/ 1000 pt-yr	Log-rank p-value ¹	HR (95% CI) ¹	
Atrial Fibrillation or Flutter Requiring Hospitalization of ≥24 hours by Baseline Atrial Fibrillation/Atrial Flutter						
Atrial Fibrillation/Atrial Flutter history/AE (prerandomization) - Yes						
46/368 (12.5%)	31.20	24/383 (6.3%)	15.99	0.0066	1.960 (1.195, 3.215)	0.2074
Atrial Fibrillation/Atrial Flutter history/AE (prerandomization) - No						
81/3721 (2.2%)	5.11	60/3707 (1.6%)	3.81	0.0913	1.332 (0.954, 1.860)	

Abbreviations: AE = adverse event; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; ITT = Intention-to-Treat; pt-yr = patient-year

¹Log-Rank test statistic and p-value for each subgroup are reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI for each subgroup are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

²P-value for treatment by the subgroup interaction is reported from a Cox proportional hazard model with treatment, subgroup, and treatment by subgroup interaction as the covariates, and stratified by geographic region, CV risk category, and use of ezetimibe.

In practice, atrial fibrillation and/or flutter patients are often treated with anti-coagulants, perhaps in addition to anti-platelets such as aspirin for MACE prevention. In theory, this could render atrial fibrillation and/or flutter patients more prone to bleeding events. Accordingly, we also explored bleeding events in patients with (Table 63) and without (Table 64) atrial fibrillation and/or flutter either by medical history or while in study. Bleeding events and differences across treatment groups were proportionally higher in patients with atrial fibrillation and/or flutter as compared to those without, but general trends in bleeding were consistent across patients with or without atrial fibrillation and/or flutter.

Table 63. Bleeding TEAEs(Including Hemorrhagic Stroke in Patients with Baseline or Post-Baseline Atrial Fibrillation and/or Flutter

	Icosapent Ethyl (N=449)	Placebo (N=443)	p-value ²
Bleeding related disorders ¹	113 (25.2%)	77 (17.4%)	0.0054
Gastrointestinal bleeding	25 (5.6%)	31 (7.0%)	0.4095
Central nervous system bleeding	5 (1.1%)	5 (1.1%)	1.0000
Hemorrhagic stroke	3 (0.7%)	1 (0.2%)	0.6242
Other bleeding	91 (20.3%)	49 (11.1%)	0.0002

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities.

¹Bleeding-related disorders are identified by the standardized MedDRA queries of "Gastrointestinal haemorrhage," "Central Nervous System haemorrhages and cerebrovascular conditions," and "Haemorrhage terms (excl laboratory terms)."

²Fishers Exact test.

Baseline: Atrial Fibrillation/Atrial Flutter history/AE (prerandomization)

Post-Baseline: Atrial Fibrillation or Flutter Requiring Hospitalization of ≥24 hours

Table 64. Bleeding TEAEs Including Hemorrhagic Stroke in Patients without Baseline or Post-Baseline Atrial Fibrillation and/or Flutter

	Icosapent Ethyl (N=449)	Placebo (N=443)	p-value ²
Bleeding related disorders ¹	381 (10.5%)	335 (9.2%)	0.0702
Gastrointestinal bleeding	102 (2.8%)	85 (2.3%)	0.2086
Central nervous system bleeding	15 (0.4%)	7 (0.2%)	0.0924
Hemorrhagic stroke	10 (0.3%)	9 (0.2%)	0.8234
Other bleeding	285 (7.8%)	263 (7.2%)	0.3286

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities.

¹Bleeding-related disorders are identified by the standardized MedDRA queries of “Gastrointestinal haemorrhage,” “Central Nervous System haemorrhages and cerebrovascular conditions,” and “Haemorrhage terms (excl laboratory terms).”

²Fishers Exact test.

Baseline: Atrial Fibrillation/Atrial Flutter history/AE (prerandomization)

Post-Baseline: Atrial Fibrillation or Flutter Requiring Hospitalization of ≥ 24 hours

To explore factors that might influence the occurrence of atrial fibrillation and/or flutter, we conducted multivariate Cox regression analyses; factors included age, sex, race, CV risk stratum, baseline biomarker levels (TG, LDL-C, hsCRP), concomitant therapies (ezetimibe use, statin intensity), and geographic region. These Cox regression analyses were run for two sets of atrial fibrillation and/or flutter events separately; positively adjudicated endpoints of atrial fibrillation/atrial flutter requiring ≥ 24 hours hospitalization, and TEAEs (excluding positively adjudicated endpoints). Table 65 (positively adjudicated endpoints) and Table 66 (TEAEs, excluding positively adjudicated endpoints) present covariates that remained significant baseline characteristics after a stepwise selection process using the multivariate Cox proportional hazards model (with p-values of 0.05 to enter the model and 0.10 to remain in the model). The analysis of the adjudicated endpoint of atrial fibrillation/atrial flutter requiring hospitalization ≥ 24 hours presented in Table 60 with a HR of 1.50 (95% CI of 1.14 to 1.98) is only marginally different from the range of hazard ratios for covariates identified as significant in both stratified and un-stratified multivariate Cox regression analyses with an estimated HR range of 1.503 – 1.526 (Table 65). Similar limited impact was observed in TEAE analyses (Table 66). The heterogeneity of hazard ratio estimates from the Cox model analyses presented below demonstrate minimal effect from covariate adjustments and suggest limited clinical impact of the individual covariates.

Table 65. Multivariate Cox Regression on Positively Adjudicated Endpoint Atrial Fibrillation and/or Flutter to Identify Significant Baseline Covariates by Stepwise Selection (ITT Population)

		Stepwise Selected Covariate	
		Significance P-value ²	HR (95% CI) (Icosapent Ethyl/ Placebo)
Covariates ¹			
Stratified by geographic region, CV risk category, and use of ezetimibe	Age (yr) at Baseline (<65, ≥ 65)	<0.0001	1.516 (1.151, 1.997)
	hsCRP at Baseline by 2*std deviation (≤ 1.27 , >1.27)	0.0011	1.505 (1.143, 1.983)
	Overall (with all selected covariates)		1.520 (1.154, 2.003)
Non-Stratified	Age (yr) at Baseline (<65, ≥ 65)	<0.0001	1.518 (1.152, 1.999)
	Race (White, Non-White)	0.0404	1.503 (1.141, 1.980)
	hsCRP at Baseline by 2*std deviation (≤ 1.27 , >1.27)	0.0013	1.507 (1.144, 1.985)
	US vs. Non-US	0.0084	1.505 (1.143, 1.983)
	Overall (with all selected covariates)		1.526 (1.158, 2.010)

Abbreviations: CI = confidence interval; CV = cardiovascular; hsCRP = high-sensitivity C-reactive protein; HR = hazard ratio; ITT = Intention-to-Treat; std = standard; US = United States; yr = year.

Baseline variables considered: Age, Sex, Race, Cardiovascular risk stratum, Triglycerides (150, 150-200, ≥ 200), Triglycerides by median (≤ 216 , >216), LDL-C (≤ 70 , > 70), LDL-C by mean (<76.21 , ≥ 76.21), hs-CRP by 2*std deviation (≤ 1.27 , >1.27), Ezetimibe use, Location (Westernized, Eastern Europe, Asia Pacific), Western region vs. other regions, US vs. Non-US, Baseline statin intensity.

¹Covariates are from a Cox proportional hazard model with treatment as factor and the identified significant baseline variable as covariate.

²P-value for significance of the covariate is from the final model per a stepwise selection process using the Cox proportional hazard model with p-value of 0.05 and 0.1 for a covariate to enter and stay in the model, respectively.

Table 66. Multivariate Cox Regression on Atrial Fibrillation and/or Atrial Flutter TEAEs (Excluding Positively Adjudicated Endpoints) to Identify Significant Baseline Covariates by Stepwise Selection (ITT Population)

		Stepwise Selected Covariate	
		Significance P-value ²	HR (95% CI) (Icosapent Ethyl/ Placebo)
Covariates ¹			
Stratified by geographic region, CV risk category, and use of ezetimibe	Age (yr) at Baseline (<65 , ≥ 65)	<0.0001	1.295 (1.068, 1.571)
	Sex	0.0231	1.281 (1.056, 1.553)
	Race (White, Non-White)	0.0073	1.284 (1.058, 1.557)
	Overall (with all selected covariates)		1.292 (1.065, 1.567)
Non-Stratified	Age (yr) at Baseline (<65 , ≥ 65)	<0.0001	1.296 (1.069, 1.573)
	Sex	0.0051	1.281 (1.056, 1.554)
	Race (White, Non-White)	0.0002	1.285 (1.059, 1.558)
	CV Risk Stratum	0.0466	1.283 (1.058, 1.556)
	Region (Western, Other)	<0.0001	1.284 (1.059, 1.558)
	Overall (with all selected covariates)		1.293 (1.066, 1.569)

Abbreviations: CI = confidence interval; CV = cardiovascular; HR = hazard ratio; ITT = Intention-to-Treat; TEAE = treatment emergent adverse event; yr = year.

Baseline variables considered: Age, Sex, Race, Cardiovascular risk stratum, Triglycerides (150, 150-200, ≥ 200), Triglycerides by median (≤ 216 , >216), LDL-C (≤ 70 , > 70), LDL-C by mean (<76.21 , ≥ 76.21), hs-CRP by 2*std deviation (≤ 1.27 , >1.27), Ezetimibe use, Location (Westernized, Eastern Europe, Asia Pacific), Western region vs. other regions, US vs. Non-US, Baseline statin intensity.

¹Covariates are from a Cox proportional hazard model with treatment as factor and the identified significant baseline variable as covariate.

²P-value for significance of the covariate is from the final model per a stepwise selection process using the Cox proportional hazard model with p-value of 0.05 and 0.1 for a covariate to enter and stay in the model, respectively.

Finally, we conducted analyses of the primary and key secondary composite endpoints, and each component of these endpoints, with consideration of whether patients had a history of atrial fibrillation and/or flutter (Table 67), or if patients had atrial fibrillation and/or flutter at any time while on study (Table 68). As a caveat, the study was not powered to support such *post hoc* analyses, especially for the comparatively small subgroup with atrial arrhythmias; as such, confidence intervals are expected to be wide and tests for interaction may lack sensitivity. For patients with a history of atrial fibrillation and/or flutter at baseline (Table 67), coronary revascularization was the only endpoint event with a significant interaction p-value (defined as interaction $p < 0.15$; interaction $p = 0.1210$), where event counts were relatively low (78 total) and little difference was observed across the treatment arms, while total event counts were higher in patients without a history of atrial fibrillation and/or flutter and benefit was observed with icosapent ethyl compared to placebo. For patients with atrial fibrillation and/or flutter while in study, nonfatal MI (interaction $p = 0.1481$), coronary revascularization (interaction $p = 0.1496$), and unstable angina (interaction $p = 0.0831$) were events with a significant interaction p-value. Event rates were low for patients with atrial fibrillation and/or flutter while on study, with a total of 86 MIs, 112 revascularizations, and 27 unstable anginas, and hazard ratios suggest potential benefit with icosapent ethyl. Overall, these analyses of patients with a history or on-study occurrence of atrial fibrillation and/or flutter suggest general benefit with icosapent ethyl across the primary and key secondary endpoints, and generally across the individual components of these endpoints.

Table 67. Summary of Primary and Key Secondary Composite Endpoints and Each Component by Patients With or Without a History of Atrial Fibrillation and/or Atrial Flutter (ITT Population)

Endpoint	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Icosapent Ethyl vs. Placebo		Interaction P-value
			HR (95% CI)	P-value	
Primary Composite Endpoint	705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68, 0.83)	<0.0001	0.3720
Atrial Fibrillation/Flutter-Yes	87/ 368 (23.6%)	98/ 383 (25.6%)	0.87 (0.65, 1.17)	0.3627	
Atrial Fibrillation/Flutter-No	618/3721 (16.6%)	803/3707 (21.7%)	0.74 (0.67, 0.82)	<0.0001	
Key Secondary Composite Endpoint	459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65, 0.83)	<0.0001	0.5496
Atrial Fibrillation/Flutter-Yes	64/ 368 (17.4%)	75/ 383 (19.6%)	0.81 (0.58, 1.14)	0.2260	
Atrial Fibrillation/Flutter-No	395/3721 (10.6%)	531/3707 (14.3%)	0.72 (0.64, 0.82)	<0.0001	
CV Death	174/4089 (4.3%)	213/4090 (5.2%)	0.80 (0.66, 0.98)	0.0315	0.9880
Atrial Fibrillation/Flutter-Yes	30/ 368 (8.2%)	36/ 383 (9.4%)	0.81 (0.50, 1.31)	0.3829	
Atrial Fibrillation/Flutter-No	144/3721 (3.9%)	177/3707 (4.8%)	0.80 (0.64, 1.00)	0.0479	
Nonfatal MI	237/4089 (5.8%)	332/4090 (8.1%)	0.70 (0.59, 0.82)	<0.0001	0.2465
Atrial Fibrillation/Flutter-Yes	25/ 368 (6.8%)	25/ 383 (6.5%)	0.95 (0.55, 1.66)	0.8692	
Atrial Fibrillation/Flutter-No	212/3721 (5.7%)	307/3707 (8.3%)	0.68 (0.57, 0.81)	<0.0001	
Nonfatal Stroke	85/4089 (2.1%)	118/4090 (2.9%)	0.71 (0.54, 0.94)	0.0149	0.5757
Atrial Fibrillation/Flutter-Yes	15/ 368 (4.1%)	24/ 383 (6.3%)	0.60 (0.31, 1.14)	0.1155	
Atrial Fibrillation/Flutter-No	70/3721 (1.9%)	94/3707 (2.5%)	0.73 (0.54, 1.00)	0.0486	
Coronary Revascularization	376/4089 (9.2%)	544/4090 (13.3%)	0.66 (0.58, 0.76)	<0.0001	0.1210
Atrial Fibrillation/Flutter-Yes	38/ 368 (10.3%)	40/ 383 (10.4%)	0.95 (0.61, 1.48)	0.8097	
Atrial Fibrillation/Flutter-No	338/3721 (9.1%)	504/3707 (13.6%)	0.64 (0.56, 0.74)	<0.0001	
Hospitalization for Unstable Angina	108/4089 (2.6%)	157/4090 (3.8%)	0.68 (0.53, 0.87)	0.0018	0.4185
Atrial Fibrillation/Flutter-Yes	9/ 368 (2.4%)	9/ 383 (2.3%)	1.04 (0.41, 2.64)	0.9261	
Atrial Fibrillation/Flutter-No	99/3721 (2.7%)	148/3707 (4.0%)	0.66 (0.51, 0.85)	0.0013	

Note: The number of subjects with event (n) is the number of subjects with the event in the ITT Population within each treatment group (N).

Log-Rank p-value is reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

Table 68. Summary of Primary and Key Secondary Composite Endpoints and Each Component by Patients With or Without On-Study Atrial Fibrillation and/or Atrial Flutter (ITT Population)

Endpoint	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Icosapent Ethyl vs. Placebo		Interaction P-value
			HR (95% CI)	P-value	
Primary Composite Endpoint	705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68, 0.83)	<0.0001	0.3589
Atrial Fibrillation/Flutter-Yes	102/ 321 (31.8%)	94/ 251 (37.5%)	0.85 (0.64, 1.12)	0.2425	
Atrial Fibrillation/Flutter-No	603/3768 (16.0%)	807/3839 (21.0%)	0.73 (0.66, 0.81)	<0.0001	
Key Secondary Composite Endpoint	459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65, 0.83)	<0.0001	0.3391
Atrial Fibrillation/Flutter-Yes	75/ 321 (23.4%)	70/ 251 (27.9%)	0.84 (0.61, 1.16)	0.2951	
Atrial Fibrillation/Flutter-No	384/3768 (10.2%)	536/3839 (14.0%)	0.71 (0.62, 0.81)	<0.0001	
CV Death	174/4089 (4.3%)	213/4090 (5.2%)	0.80 (0.66, 0.98)	0.0315	0.3752
Atrial Fibrillation/Flutter-Yes	22/ 321 (6.9%)	27/ 251 (10.8%)	0.65 (0.37, 1.14)	0.1283	
Atrial Fibrillation/Flutter-No	152/3768 (4.0%)	186/3839 (4.8%)	0.82 (0.66, 1.02)	0.0706	
Nonfatal MI	237/4089 (5.8%)	332/4090 (8.1%)	0.70 (0.59, 0.82)	<0.0001	0.1481
Atrial Fibrillation/Flutter-Yes	46/ 321 (14.3%)	40/ 251 (15.9%)	0.89 (0.58, 1.36)	0.5958	
Atrial Fibrillation/Flutter-No	191/3768 (5.1%)	292/3839 (7.6%)	0.65 (0.54, 0.78)	<0.0001	
Nonfatal Stroke	85/4089 (2.1%)	118/4090 (2.9%)	0.71 (0.54, 0.94)	0.0149	0.4855
Atrial Fibrillation/Flutter-Yes	14/ 321 (4.4%)	12/ 251 (4.8%)	0.90 (0.41, 1.96)	0.7954	
Atrial Fibrillation/Flutter-No	71/3768 (1.9%)	106/3839 (2.8%)	0.67 (0.50, 0.91)	0.0095	
Coronary Revascularization	376/4089 (9.2%)	544/4090 (13.3%)	0.66 (0.58, 0.76)	<0.0001	0.1496
Atrial Fibrillation/Flutter-Yes	58/ 321 (18.1%)	54/ 251 (21.5%)	0.82 (0.57, 1.20)	0.3065	
Atrial Fibrillation/Flutter-No	318/3768 (8.4%)	490/3839 (12.8%)	0.63 (0.55, 0.73)	<0.0001	
Hospitalization for Unstable Angina	108/4089 (2.6%)	157/4090 (3.8%)	0.68 (0.53, 0.87)	0.0018	0.0831
Atrial Fibrillation/Flutter-Yes	8/ 321 (2.5%)	19/ 251 (7.6%)	0.33 (0.14, 0.76)	0.0058	
Atrial Fibrillation/Flutter-No	100/3768 (2.7%)	138/3839 (3.6%)	0.73 (0.56, 0.94)	0.0154	

Abbreviations: CI = confidence interval; CV = cardiovascular; HR = hazard ratio; ITT = Intention-to-Treat; MI = myocardial infarction.

Note: Includes all adverse events and positively adjudicated atrial fibrillation/atrial flutters

Note: The number of subjects with event (n) is the number of subjects with the event in the ITT Population within each treatment group (N).

Log-Rank p-value is reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

Overall, atrial fibrillation and/or flutter event rates in REDUCE-IT were relatively low. The incidences of atrial fibrillation and/or flutter SAEs were not different across treatment groups, but TEAEs and adjudicated endpoints were higher with icosapent ethyl than placebo. Cox regression analyses do not identify any particular baseline characteristics associated with the differences observed in patients with or without atrial fibrillation and/or flutter. Analyses comparing patients with or without atrial fibrillation and/or flutter (by history or on study), suggest patients with atrial fibrillation and/or flutter are more likely to experience an atrial fibrillation and/or flutter or bleeding event, but these differences do not appear to affect the overall CV benefit derived from icosapent ethyl as explored within the primary and key secondary composite endpoints and their individual contributing endpoint events.

Limited mechanistic data in the literature does not support a negative impact of EPA on cardiac rhythm, but the apparent increase of atrial fibrillation/flutter observed in REDUCE-IT was consistent with that observed for other omega-3 fatty acids and for Lovaza (Kowey 2010, Lovaza Prescribing Information). Stroke, MI, cardiac arrest, and sudden cardiac death can be associated with atrial fibrillation or atrial flutter, but a significantly lower risk was observed in the icosapent ethyl group versus the placebo group for the endpoints of endpoints of fatal or nonfatal stroke (HR of 0.720; $p=0.0129$), fatal or nonfatal myocardial infarction (HR of 0.688; $p<0.0001$), cardiac arrest (HR of 0.52; $p = 0.0105$), and sudden cardiac death (HR of 0.69; $p = 0.0259$) (Figure 5; Table 32). Finally, inclusion of positively adjudicated atrial fibrillation and/or flutter endpoints (and serious bleeding events) in *post hoc* analyses within broadened composites of the primary and key secondary endpoints did not alter overall study conclusions, demonstrating substantial and statistically significant risk reductions despite inclusion of atrial fibrillation and/or flutter (and bleeding) within outcome analyses (Table 12). The lack of effect in congestive heart failure, the lower rates of stroke, MI, cardiac arrest, and sudden cardiac death, and the primary and key secondary endpoint analyses including atrial fibrillation and/or flutter (and bleeding) are all consistent with the overall cardioprotective effects of icosapent ethyl demonstrated in REDUCE-IT.

In summary, the overall incidence of atrial fibrillation and/or flutter events (including non-serious and serious AE, and endpoint events) was higher with icosapent ethyl than placebo. This is a finding consistent with prior omega-3 fatty acid products. Most of the atrial fibrillation and/or flutter events observed with icosapent ethyl in REDUCE-IT were not serious and occurred in patients with a history of atrial fibrillation and/or flutter at baseline, and they can likely be clinically well managed. The incidence of patients with more consequential atrial fibrillation and/or flutter (SAEs or endpoint) was higher with icosapent ethyl than placebo, but the overall treatment difference in incidence was low over the median 4.9 year study period. Risk appeared higher in those with a history of atrial fibrillation and/or flutter, who are therefore already being managed medically for their atrial arrhythmias, perhaps mitigating further sequelae. Older patients (e.g., those > 65 years) without a history of atrial fibrillation and/or flutter may also have greater risk for experiencing atrial fibrillation and/or flutter; they should be advised to promptly consult with their health care professional if signs or symptoms of atrial fibrillation and/or flutter become apparent, as the condition can be effectively managed medically.