REDUCE-IT: accumulation of data across prespecified interim analyses to final results

B. Olshansky[1], D. Bhatt[2], M. Miller[3], P.G. Steg[4], E.A. Brinton[5], T.A. Jacobson[6], S.B. Ketchum[7], R.T. Doyle[7], R.A. Juliano[7], L. Jiao[7], C. Granowitz[7], J.-C. Tardif[8], C. Mehta[9], C.M. Ballantyne[10], M.K. Chung[11]

[1]University of Iowa College of Medicine, Iowa city, United States of America; [2]Brigham and Women's Hospital, Boston, United States of America; [3]University of Maryland, Department of Medicine, University of Maryland School of Medicine, Baltimore, United States of America; [4]University of Paris, INSERM Unité 1148; FACT Hopital Bichat, Paris, France; [5]Utah Lipid Center, Salt Lake City, United States of America; [6]Emory University School of Medicine, Lipid Clinic and Cardiovascular Risk Reduction Program, Department of Medicine, Atlanta, United States of America; [7]Amarin Pharma, Inc., Bridgewater, United States of America; [8]University of Montreal, Montreal Heart Institute, Montreal, Canada; [9]Cytel Inc., Waltham, United States of America; [10]Baylor College of Medicine, Houston, United States of America; [11]Cleveland Clinic, Cleveland, United States of America

On behalf of The REDUCE-IT Investigators

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Background: REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial), an event-driven trial, randomized 8,179 statin-treated patients with elevated triglycerides (TGs) and increased cardiovascular (CV) risk to icosapent ethyl (IPE); pure, stable prescription eicosapentaenoic acid, 4g/day or placebo. 1,612 primary endpoint events (CV death, nonfatal myocardial infarction [MI], nonfatal stroke, coronary revascularization, or hospitalization for unstable angina) projected 90% power to detect 15% relative risk reduction (5% 2-sided alpha). The key secondary composite endpoint was CV death, nonfatal MI, or nonfatal stroke. An independent data and safety monitoring committee (DMC) performed prespecified interim analyses (IAs) at ~60% (IA1 31 May 2016 data cutoff; 2.9 y median primary endpoint follow-up) and ~80% (IA2 01 May 2017; 3.7 y) of events; final analysis included 1,606 events (06 Sep 2018; 4.9 y median study follow-up).

Purpose: Explore REDUCE-IT efficacy and safety across prespecified IAs for insight into progression of robustness and consistency of conclusions.

Methods: The interim statistical analysis plan guided study continuation decisions by a prespecified decision-making process, including assessment of safety, treatment arm performance, primary composite endpoint formal analyses, and informal robustness analyses, with no futility or efficacy stopping requirements. Prior to DMC IA study continuation decisions, the need for a mature dataset to support the robustness of final efficacy and safety findings was discussed. Sponsor, Steering Committee, and Clinical Endpoint Committee were blinded throughout.

Results: Primary and key secondary endpoints achieved statistical significance at IA1 and IA2 that persisted at final analyses (p-value below final adjusted 2-sided alpha of 0.0437); hazard ratios also remained consistent and similar robustness was observed across individual endpoint components; clarity of findings across endpoints and subgroups improved with more events. Stopping for overwhelming efficacy was discussed at each IA; prior to IA study continuation recommendations, the DMC considered historical examples of failed CV outcome studies for TG-lowering and mixed omega-3 therapies, reflected on the potential for overestimating final demonstrated benefit using incomplete data, and weighed societal impacts of fuller datasets relative to patient therapy access.

Conclusions: Consistent, potent efficacy emerged early and persisted across the two prespecified interim and final analyses. The mature dataset demonstrated highly statistically significant reductions in the primary (25%; p=0.00000001) and key secondary (26%; p=0.0000006) endpoints and allowed robust analyses to support overall efficacy and safety conclusions. Allowing the REDUCE-IT dataset to fully mature provided clinicians with robust, consistent, and reliable data upon which to base clinical decisions for IPE in CV risk reduction.

Figure: REDUCE-IT Data Accumulation across Interim Analysis #1, Interim Analysis #2 and Final Results

Endpoint	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Icosapent Ethyl vs Placebo HR (95% CI)	Log-Rank P-value
Primary Composite Endpoint					
Interim Analysis 1		420/4059 (10.3)	533/4062 (13.1)	0.77 (0.68–0.87)	0.00005
Interim Analysis 2		541/4089 (13.2)	677/4090 (16.6)	0.77 (0.69–0.87)	0.0000008
Final Analysis		705/4089 (17.2)	901/4090 (22.0)	0.75 (0.68–0.83)	0.00000001
Key Secondary Composite Endpoint					
Interim Analysis 1		232/4059 (5.7)	322/4062 (7.9)	0.71 (0.60–0.83)	0.00005
Interim Analysis 2		318/4089 (7.8)	430/4090 (10.5)	0.72 (0.62–0.83)	0.000009
Final Analysis		459/4089 (11.2)	606/4090 (14.8)	0.74 (0.65–0.83)	0.0000006