How does VASCEPA[®] work in lowering cardiovascular risk?

Determining the mechanisms responsible for the benefit shown in REDUCE-IT[®] was not the focus of REDUCE-IT. Independent of REDUCE-IT, Amarin has worked to further support the REDUCE-IT thesis with published scientific findings based on various degrees of evidence that show that icosapent ethyl may interrupt the atherosclerotic processes (e.g., plaque formation and instability) by beneficially affecting cellular functions thought to contribute to atherosclerosis and cardiovascular events and by beneficially affecting lipid, lipoprotein and inflammation biomarkers.¹

As published in *Atherosclerosis* in 2015, there is evidence to support that the unique single active ingredient in VASCEPA® potentially affects multiple atherosclerotic processes.² These processes include

- Endothelial function
- Oxidative stress
- Foam cell formation
- Inflammation/cytokines
- Plaque formation/progression
- Plaque aggregation
- Thrombus formation
- Plaque rupture

The effects of this unique active ingredient on cell membranes are illustrated in this animation <u>https://www.webcargo.net/view-file/index/link-id/703709/link-key/0TNKt4nVie/file-id/16797593/</u>. This animation was created by Drs. Peter Libby and Preston Mason of Brigham & Women's Hospital and Harvard Medical School, based in part on scientific evaluation which Dr. Mason led as President of Elucida Research. Dr. Mason's work includes evaluation of the differentiated effects of eicosapentaenoic acid (EPA) relating to oxidative stress, crystal domain formations, oxidation of LDL and preservation of HDL function.

Reduction in inflammation markers in patients treated by VASCEPA was shown in multiple clinical studies of VASCEPA, including REDUCE-IT.^{1,3}

In Japan, the CHERRY⁴ study showed that eicosapentaenoic acid added to high dose statin doubled incidence of plaque regression vs. high dose statin therapy alone.⁵

Mechanistic work like that featured in this FAQ can be helpful to understand how VASCEPA may have worked to achieve the cardiovascular risk reduction demonstrated in REDUCE-IT. The degree to which each of these effects of VASCEPA contributed to the successful REDUCE-IT cardiovascular outcomes study results is unknown.

Full understanding of a drug's mechanism of action is not required for regulatory approval or commercial success, as evidenced by the success of multiple therapies, including widely used therapies for diabetes and cholesterol management. For further discussion around the mechanisms of action of VASCEPA and its active ingredient, click <u>here</u>.

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¹ Bhatt DL, Steg PG, Miller M, et al. Cardiovascular Risk Reduction with Icosapent Ethyl in Hypertriglyceridemia. *N Engl J Med*. 2019;380:11-22.

² Borow KM, Nelson JR, Mason RP. Biologic plausibility, cellular effects, and molecular mechanisms of eicosapentaenoic acid (EPA) in atherosclerosis. *Atherosclerosis*. 2015;242:357-366.

³ Bays HE, Ballantyne CM, Braeckman RA, Stirtan WG, Soni PN. Icosapent Ethyl, a Pure Ethyl Ester of Eicosapentaenoic Acid: Effects on Circulating Markers of Inflammation from the MARINE and ANCHOR Studies. *Am J Cardiovasc Drugs*. 2013;13:37–46.

⁴ Watanabe T, Ando K, Daidoji H, et al., CHERRY study investigators. A randomized controlled trial of eicosapentaenoic acid in patients with coronary heart disease on statins. *Journal of Cardiology*. 2017;70:537-544.

⁵ Budoff M, Muhlestein JB, Le VT, et al. Effect of VASCEPA (icosapent ethyl) on progression of coronary atherosclerosis in patients with elevated triglycerides (200–499 mg/dL) on statin therapy: Rationale and design of the EVAPORATE study. *Clin Cardiol*. 2018;1–7.