How Does Vascepa Work?
Potential Mechanisms of Action for Vascepa

NASDAQ: AMRN
Important Information About Mechanism of Action Studies

- Studies designed to help understand how a drug may have demonstrated an effect shown in clinical research, so-called mechanism of action studies, can lead to more informed understanding of disease and more discoveries to improve public health.

- Mechanism of action studies have different degrees of reliability and often involve evolving methods and analyses that can be difficult to independently verify.

- Due to the complexity of cardiovascular disease, mechanism of action studies and theories on the biological plausibility of mechanistic effects on the reduction of cardiovascular risk have not been reliably predictive of clinical effects (e.g., the generally recognized failure of HDL-raising drugs).

- The degree to which, if any, the mechanistic effects featured herein may have contributed to the risk reduction effects of Vascepa demonstrated in the REDUCE-IT™ cardiovascular outcomes study is not fully understood and may, in certain cases, require additional research.
Vascepa’s Mechanisms of Action Are Multifactorial

Plaque reduction, regression and stabilization as contributing mechanisms of action (MoA) of Vascepa

- Coronary heart disease is caused by the buildup of coronary plaque.
- Atherosclerosis (coronary plaque in arteries) reduces blood flow, contributing to cardiovascular (CV) events.
- Regression: EPA therapy added to high dose statin therapy doubled the incidence of coronary plaque regression compared to statin therapy alone in the Japanese clinical study, CHERRY.
- Stabilization: EPA increased fibrous cap thickness in Japanese patients with a recent coronary event, reducing the likelihood that plaque will dislodge and travel down the blood stream, block blood flow, and cause a cardiovascular event.

Stable Plaque

Lipid pool=Lipid rich plaque
The effects of EPA in conjunction with statins on atherosclerotic plaques have also been evaluated in animal models. Benefits shown in mice include a decrease in coronary plaque lesions.

Inflammation and oxidative stress

- Inflammation and oxidative stress can contribute to cardiovascular disease.  
- Clinical Data: Vascepa has anti-inflammatory effects, both systemic as well as localized. This includes significant reduction of inflammation and oxidation biomarkers such as hsCRP, Lp-PLA2, and oxLDL.
- Preclinical Data: Oxidative stress leads to cholesterol domain formation.

**EPA Inhibits Lipid Oxidation and Cholesterol Domain Formation**
EPA May Have Beneficial Effects on Multiple Atherosclerotic Processes

- **Endothelial function**
  - Nitric oxide production
  - Endothelium-dependent vasodilation
  - Reactive oxygen species

- **Anti-inflammatory effects**
  - Proinflammatory eicosanoids and cytokines
  - Inflammatory cell recruitment

- **Plaque stability**
  - Plaque formation, progression, and rupture
  - Thrombosis
  - Platelet activation
  - Fibrous cap thickness

The extent to which these so-called pleiotropic effects of EPA (eicosapentaenoic acid in stable and pure form) may have contributed to the success of Vascepa in the REDUCE-IT study relative to other effects of EPA (e.g. transcriptional gene regulation, membrane stabilization) is under evaluation.
Vascepa’s Mechanisms of Action are Multifactorial (cont’d)

Cellular transcriptional and membrane stabilizing effects

- EPA regulates genes involved in lipid metabolism and plaque stabilization \(^{19}\)
- EPA alters membrane function and stabilization \(^{20}\)

High triglyceride levels and an atherogenic lipid profile

- Vascepa, in multiple clinical studies (MARINE, ANCHOR and REDUCE-IT), has demonstrated that it lowers triglyceride (TG) levels (a type of blood fat) and improves various other markers of lipids and lipoproteins \(^7,^{17},^{21}\)
- Multiple epidemiological, genetic and clinical studies link elevated TG levels to increased cardiovascular (CV) risk [https://amarincorp.gcs-web.com/static-files/28493518-0506-43f9-91e2-a88ab47e271b](https://amarincorp.gcs-web.com/static-files/28493518-0506-43f9-91e2-a88ab47e271b)
- However, lowering TG levels alone does not fully explain the CV risk reduction demonstrated by Vascepa:
  - Studies of other agents that lower TG levels (Niacin, Fibrates) did not demonstrate cardiovascular risk reduction \(^{22},^{23}\)
  - In REDUCE-IT, Vascepa reduced CV risk rates more than it lowered TG levels (relative risk reduction of 25% in first occurrence of MACE and 30% reduction in first and recurrent MACE, with TG lowering of 20% vs. placebo) \(^{17},^{18}\)
  - JELIS (large outcomes study in Japan that used eicosapentaenoic acid, EPA, the active ingredient in Vascepa) demonstrated a 19% risk reduction in patients with essentially normal TG levels and only 5% lower TG, suggesting the effects of EPA go beyond TG lowering \(^{24}\)
Amarin has invested in extensive research regarding Vascepa’s mechanism of action (MoA)

- This document includes dozens of publication references regarding EPA’s MoA; many funded by Amarin
- These references highlight Amarin’s commitment to researching the science of Vascepa

Complete understanding of Vascepa’s MoA is not required for FDA approval

- Many drugs are approved for use and broadly used without MoA’s being fully understood
  
  Examples include:
  - Statins
  - Acetaminophen (active ingredient in Tylenol®)
  - Aspirin
  - Calcium Channel Blockers
  - General anesthesia
  - Lithium
  - Modafinil

Evidence of drug efficacy and safety from a well-controlled, well-conducted clinical development program is the most important element of a supplemental new drug application (sNDA)
References

1) CDC. https://www.cdc.gov/heartdisease/coronary_ad.htm


21) Bays HE, Ballantyne CM, Kastelein JJ, Isaacsohn JL, Braeckman RA, Soni PN. Eicosapentaenoic acid ethyl ester (AMR101) therapy in patients with very high triglyceride levels (from the Multi-center, pAlcebo-controlled, Randomized, double-blINd, 12-week study with an open-label Extension [MARINE] trial).


Summary of Publications Regarding Potential Mechanisms of Action of Vascepa’s Active Ingredient

Multiple (2 or more) Mechanisms of Action

- Video: Animation of potential mechanisms of action
- Video: Biologic Basis of EPA to Reduce Atherosclerosis Burden

Triglyceride Reduction

- See separate summary of multiple publications https://amarincorp.gcs-web.com/static-files/28493518-0506-43f9-91e2-a88ab47e271b

Endothelial Function


Note:
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- The degree to which, if any, the mechanistic effects featured herein may have contributed to the risk reduction effects of Vascepa demonstrated in the REDUCE-IT™ cardiovascular outcomes study requires additional research.
Summary of Publications Regarding Potential Mechanisms of Action of Vascepa’s Active Ingredient (cont’d)

Anti-oxidant Effects


Foam Cell Formation


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Summary of Publications Regarding Potential Mechanisms of Action of Vascepa’s Active Ingredient (cont’d)

**Inflammation**


**Plaque Formation/progression**


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Platelet Aggregation

- Suehiro EPA plus ASA or ticlid on PLTs in cerebral ischemia pts *Clinical Therapeutic Research* 1994

Thrombus Formation


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Plaque Stabilization


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### Recap of Potential Mechanistic Effects of Vascepa’s Active Ingredient on Multiple Atherosclerotic Processes

<table>
<thead>
<tr>
<th>Multiple Plaque Formation/Progression Processes Potentially Affected by EPA&lt;sup&gt;16&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Endothelial function</td>
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<tr>
<td>▪ Atherogenic lipids/lipoproteins</td>
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<td>▪ Oxidative stress</td>
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</tr>
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