ENCODE
IDEAS

Acasti Pharma Inc. (ACST)
INITIATION REPORT

November 25, 2019

Encode Ideas, L.P.
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FINANCIAL SUMMARY TABLE

Symbol	ACST
Exchange	NASDAQ
Current Price	$2.04*
52 week High	$2.95
52 week Low	$0.60
O/S	83.09mm**
Market Cap	~$169.5mm*
Average Volume (30D)	~1.2mm
Cash	~$25.8mm CAD**

*as of 11/22/2019 **as of 9/30/2019

KEY CATALYST DATES

December 2019	Topline TG Results from Ph3 Trilogy I
January 2020	Topline TG Results from Ph3 Trilogy II
Q1 2020	Secondary and exploratory endpoints for Trilogy I & II
2H 2020	AZN releases Ph3 data on Epanova

KEY DISCLOSURES

One or more of the Encode Ideas partners own stock in the covered company; Encode Ideas, L.P. partners intend to continue transacting in the securities covered therein, and we may be long, short, or neutral thereafter regardless of our initial recommendation.

HIGH-RISK INVESTMENT IDEA

Encode Ideas is initiating on Acasti Pharma, Inc. as a high-risk investment idea.

Encode Ideas is initiating coverage on Acasti Pharma, Inc. as a high-risk investment idea. Acasti is developing a krill-based omega-3 fatty acid product, CaPre, for the treatment of severe hypertriglyceridemia. Acasti is currently conducting two virtually identical Ph3 studies - Trilogy I and Trilogy II- with CaPre, and expects to report top-line data from the first in December and the second in January. If the primary TG-lowering endpoints are met in both Trilogy studies, assuming an acceptable safety profile, there is a good probability that CaPre would be approved by FDA in 2021. The theoretical timing of a CaPre launch in 2021 is ideal, with the omega-3 market thriving due to the likely label expansion for Amarin's Vascepa, based on the compelling REDUCE-IT study, and the possible commercial launch of AstraZeneca's Epanova. Even with an inferior label relative to Vascepa, and likely Epanova, we believe that CaPre can carve out a niche in what should be a vibrant omega-3 market. The size of that niche will, in our opinion, be determined by attributes of CaPre beyond its TG-lowering capability. Specifically, these include whether CaPre demonstrates a meaningful impact on other lipid parameters (LDL, HDL) and / or HbA1c, which would allow Acasti, or a partner / acquirer, to create a differentiated omega-3 brand based on cardiometabolic attributes. Later in this report, we will outline how we envision CaPre competing as a commercial omega-3 product through analysis of best and base case scenarios.

Although we are optimistic, assuming Ph3 clinical success, about CaPre's commercial potential, we recommend caution to investors heading into the first Trilogy readout in December. Acasti has run two Ph2 studies with CaPre - COLT and Trifecta - and, to be candid, we find these studies challenging to interpret, as they relate to the probability of CaPre meeting the primary TG-lowering endpoint in the Trilogy studies. It is apparent from both studies that CaPre reduces TG levels, although it remains unclear whether this is in a dose-dependent manner. Acasti has presented limited data on the 4g dose of CaPre being used in the Trilogy studies, and no data at all on how this dose has performed in patients with severe hypertriglyceridemia.

We feel that some investors are demonstrating undue faith that CaPre will work simply because it is an omega-3. In our opinion, this argument is intellectually remiss, and investors should take a closer look at the Ph2 evidence before betting too heavily on Ph3 success.

We think it is prudent to take a wait-and-see approach towards owning Acasti. The public release of the results of the two Trilogy studies, and subsequent secondary and exploratory endpoints, will occur separately over a period of three to four months, and with each data release the risk profile should improve. The first Trilogy outcome will be the most critical and de-risking announcement. Even if Acasti announces that CaPre has met the primary endpoint in Trilogy I, we feel the immediate upside may be tempered by Acasti's capital needs, uncertainty around the street's expectation for percentage TG-lowering, and a lack of key cardiometabolic data until later in 1Q20. Although remaining on the sidelines for the first Trilogy readout may lead to investors missing out on a sudden upward move in Acasti, we prefer the strategy of owning post-Trilogy I. This approach will provide investors with some clinical clarity and confidence, while still offering the potential upside of the Trilogy II readout, as well as secondary and exploratory data announcements.

Significance of Cadance of Data / Events

One of the key differentiating factors being relied upon by Acasti, as well as potential investors, is CaPre showing additional benefits beyond TG-lowering. The company has espoused CaPre's "trifecta" effect, a reference to its potential benefit on key cardiometabolic endpoints besides TGs, most notably LDL, HDL, and HbA1c. We assume that CaPre, like its omega-3 predecessors, will only need to demonstrate a statistical benefit on TGs, which for the Trilogy studies is defined as a difference of at least a 20% reduction from baseline in TGs between CaPre and placebo, in order to achieve FDA approval. However, its commercial viability, and its attractiveness to a partner or acquirer, may be more dependent on its additional attributes.

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Acasti will report on the first of its Ph3 Trilogy studies in December. This will only be a top-line data release regarding the primary TG-lowering endpoint at 12 weeks. The company has disclosed that secondary and exploratory endpoints will not be available until after the Trilogy II top-line TG results are released, which is currently scheduled for late January 2020. Significantly, the highly anticipated LDL and HbA1c results will require a pooling of subgroups, patients with mixed dyslipidemia and type II diabetes respectively, from the two Trilogy trials, and these data may not be available until March 2020. In the background, as all these data are released, Acasti will certainly be actively conducting financing discussions, given that the company has guided that its cash runway only lasts until June 2020.

There are some parallels between Amarin's situation in 2010/2011, when it announced data from its two pivotal Ph3 studies, and Acasti's current situation. Amarin was (and remains) a single-asset company with a tenuous balance sheet (although not as tenuous as Acasti's currently) when it delivered its first Ph3 study, MARINE, in Nov 2010. Amarin was $3.55 ($360mm cap) prior to data, $5.85 ($590mm cap) immediately following data, and financed two months later at $7.60 ($770mm cap). In April 2011, Amarin reported its second positive Ph3 study, ANCHOR, and traded to $17 ($1.9b cap) immediately following this announcement.

We would highlight that investors willing to take substantial clinical risk and own Amarin heading into the first Ph3 results were rewarded with a modest 60% return immediately following the first data release, but ended up with a return of close to 400% if they held through the subsequent financing and Amarin's second Ph3 study. For those with a lower appetite for risk, buying Amarin immediately after its first Ph3 readout provided substantially more clinical comfort and security, while still yielding a healthy 200% return after the second Ph3 report.

Although the cadence of events for Amarin - first Ph3, finance, then second Ph3 - are not identical to what we expect for Acasti, the trading dynamics may play out similarly. For those investors with an appetite for risk, owning in front of the first Trilogy study could yield substantial benefits, perhaps in a range similar to that experienced by Amarin shareholders in 2010/2011. For those with a lower appetite for risk, buying after the first Trilogy readout would still offer the potential upside of the second Trilogy readout, as well as of secondary and exploratory data announcements, but with the comfort of already having the success of the first Trilogy study confirmed.

We would also highlight that defining what qualifies as "success" for the Trilogy studies may not be as straightforward as some might think. The studies are powered to show a 20% reduction from baseline in TGs between CaPre and placebo. This level of TG reduction may be statistically significant, and arguably clinically meaningful, but it is uncertain whether it would be sufficient to excite investors. The CaPre data will be compared predominantly against those from Amarin's Ph3 MARINE study, where Vascepa showed a 33% TG reduction. This begs a question regarding what investors' expectations are of CaPre in terms of TG-lowering percentage. As noted above, Acasti's earlier Ph2 studies are not very insightful, offering no data on how the 4g CaPre dose has performed in patients with severe hypertriglyceridemia. It is possible that we could see a scenario where Acasti announces a "successful" Ph3 Trilogy study that has achieved its primary TG-lowering endpoint, but the percentage TG reduction underwhelms investors. If CaPre can demonstrate its "trifecta" effect, then investors (and eventually partners and prescribers) will likely look beyond a moderate TG-lowering benefit. However, results regarding CaPre's impact on LDL and HbA1c will not be available until several months after the first Trilogy TG results readout. Of course, CaPre may deliver TG reductions within or above the range seen with Vascepa, which would invalidate this kind of discussion about what defines success. Regardless, we think that investors should be cognizant that what defines success in Ph3 may not be as simple as achieving the primary endpoint.

Class Effect

Our discussion above on the cadence of Trilogy data, and the benefits and risks of owning Acasti around these events, is

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focused exclusively on the next three to four months. We now look at a slightly longer timescale, and contemplate how CaPre, as an FDA-approved product, could compete in the omega-3 market. We will outline two commercial scenarios we see as plausible for CaPre; however, in order to best frame these scenarios, some history on the omega-3 class and the potential impact of the class effect is needed first.

In 2004, Reliant Pharmaceuticals received FDA approval for the first prescription omega-3 fatty acid product (Omacor). At that time, there was little question as to whether omega-3 products were effective TG-lowering agents, but a high level of uncertainty existed as to whether the market (physicians / patients / payers) would embrace a prescription omega-3 product in the face of cheaper supplement competition. Some of the doubts around market acceptance were allayed once GlaxoSmithKline (GSK) purchased Reliant in 2007, giving the drug (now rebranded as Lovaza) the Big Pharma stamp of approval. GSK went on to sell $1b of Lovaza annually in the United States, demonstrating the market's willingness to embrace such products, and paving the way for a second generation of prescription omega-3 competitors.

Between 2012 and 2014, two new notable omega-3 products were approved by FDA: Vascepa (Amarin Corp) and Epanova (AstraZeneca). Both companies undertook large, long-term (three to five years' follow-up) cardiovascular outcome studies with their products. In 2018, Amarin reported top-line data from its >8,000 patient REDUCE-IT study, demonstrating a statistically significant mortality and morbidity benefit for patients who took Vascepa while on stable statin therapy, but with elevated TGs and high risk for cardiovascular disease, versus placebo. These data have profoundly impacted Vascepa's sales, and arguably created a halo effect for the omega-3 class as a whole. Based on the success of REDUCE-IT, Amarin has filed a supplemental New Drug Application (sNDA) with FDA to expand Vascepa's label.

AstraZeneca is following a similar pattern to REDUCE-IT for its own study, entitled STRENGTH, with the drug Epanova, which was acquired through the company's purchase of Omthera Therapeutics in 2013 (another example of Big Pharma acquiring an omega-3 product, a theme we will revisit later in the report). Enrolling over 13,000 patients, STRENGTH is due to readout top-line data in mid/late 2020. Interestingly, AstraZeneca opted not to launch Epanova pending the results of STRENGTH. If Epanova were to demonstrate similar benefits in STRENGTH as Vascepa did in REDUCE-IT, then the argument for mortality and morbidity benefits for the entire omega-3 class - a class effect - would become all the more plausible.

One of the most compelling examples of a class effect, and the benefits that can be derived from such a phenomenon, is the early commercial story of Lipitor (Pfizer). Lipitor eventually became the top-selling drug in the statin class in the US, a position it held for the better part of a decade, but its rise to such lofty sales heights was heavily influenced by trail-blazing work with predecessor drugs in the statin class, specifically Pravachol (BMS) and Zocor (Merck). By the time Lipitor was launched in 1996, the LDL-lowering benefit of statins was firmly established. A new benefit for the class in terms of mortality and morbidity was demonstrated first by Zocor, in Merck's >4,000 patient 4S study (1994), and then by Pravachol, in BMS's >6,000 WOSCOP study (1995). The benefits gained from treatment with Zocor and Pravachol, in 4S and WOSCOP respectively, were interpreted by many as deriving not from the specific attributes of the individual drugs, but from the benefits of the target / class as a whole. This created a perfect scenario for launching a new drug: Pfizer's competitors had spent years toiling away laying the groundwork for the merits of their own drugs, and had finally produced the hard mortality and morbidity evidence to drive broad adoption and grow the market; however, physicians were not convinced that these benefits were drug-specific, and viewed them rather as a class effect. It was into this environment that Pfizer and Park Davis launched Lipitor, and within a few years, even without any hard mortality and morbidity data of their own, their product overtook Zocor and Pravachol as the top-selling statin in its class.

Looking forward to 2020/2021, we believe that a similar environment to that of Lipitor's launch could be developing for CaPre. Amarin's REDUCE-IT study laid the groundwork for the broader benefits of omega-3 therapy, much like 4S did for statin therapy. Then a second study, STRENGTH, has further cemented the belief that omega-3 therapy has mortality and morbidity benefits, much like WOSCOP did for statins. Prescribing physicians are beginning to assume that the benefits seen with Vascepa and Epanova, in REDUCE-IT and STRENGTH respectively, are the result of a class effect, rather than drug-specific, much as physicians concluded during the 1990s from the Zocor and Pravachol studies.

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A new drug is now entering the class, one that does not have its own specific supporting mortality and morbidity data, but does have compelling differentiating feature(s), and is being aggressively marketed. This was a formula that worked for Lipitor, and a similar opportunity may present itself for Acasti and CaPre.

Scenario Analysis: Best case

Our best-case scenario for Acasti is predicated on the following assumptions: (1) CaPre achieves its primary TG endpoint in both Trilogy studies; (2) CaPre hits on certain key secondary lipid parameters and / or other exploratory endpoints, like LDL and/ or Hba1c; (3) CaPre is approved by the FDA for patients with severe hypertriglyceridemia; and (4) AstraZeneca reports positive results from STRENGTH, and launches Epanova in 2021.

In this scenario, we see CaPre competing in the vibrant omega-3 market with a differentiated story compared to the incumbent products. Having demonstrated meaningful benefits in one or more key secondary and/or exploratory endpoints, CaPre, once approved, should have a compelling narrative beyond TG lowering, even with an inferior label. Amarin should have its expanded label for Vascepa, and AstraZeneca will be launching Epanova after the success of STRENGTH. The omega-3 market will be dominated by Vascepa, but the success of STRENGTH could call into question whether the benefits witnessed in the two omega-3 cardiovascular outcome trials (REDUCE-IT and STRENGTH) are drug-specific or demonstrate a class effect. This class-effect phenomenon could present huge benefits to new market entrants like CaPre. There is a good probability that Acasti is acquired in this scenario, likely by a prominent pharma with an existing cardiovascular disease franchise, looking to enter the lucrative omega-3 arms race.

Base Case

Our base-case scenario for Acasti is predicated on the following assumptions: (1) CaPre achieves its primary TG endpoint in both Trilogy studies; (2) CaPre does not demonstrate meaningful benefits on key secondary and / or exploratory endpoints; (3) CaPre is approved by FDA for patients with severe hypertriglyceridemia; and (4) Epanova is unsuccessful in STRENGTH.

In this scenario, we do not believe that AstraZeneca will launch Epanova. This will leave CaPre as one of the only branded omega-3 competitors to Vascepa. Given the failing of STRENGTH, the class effect phenomenon will be non-existent, as physicians will assume the benefits seen in REDUCE-IT with Vascepa are drug-specific and not generalizable to the whole class. Commercially, CaPre will face significant headwinds as it tries to market against the powerful reputation of Vascepa. However, CaPre should still find a modest commercial niche through hitching itself to the Vascepa story as far as possible, and conducting marketing based on simplistic differentiating themes of being krill-based and having lower food effects. We would highlight that in the heady days of branded statins, Novartis's Lescol, a product that lacked the LDL-lowering punch and label of its blockbuster competitors, still managed to sell between $200mm–$300mm in the US per year for the better part of a decade, in essence picking the scraps off the blockbuster statins' table. Similarly, CaPre, even with less data and an inferior label, could still carve out a modest niche in a flourishing omega-3 market.

Notable Risks

Notable risks to our investment thesis include; (1) Clinical setback in either of ACST's Ph3 studies (2) financing risk or capital market issues, whereby capital becomes challenging and / or excessively expensive to access (3) regulatory risk, whereby FDA requires additional studies to support CaPre's approval.

Executive Summary

Heart disease is the leading cause of death for American men and women, accounting for one out of every four deaths each year. Hypertriglyceridemia is a condition in which serum triglyceride levels are elevated. In several epidemiologic and interventional studies, hypertriglyceridemia has been identified as a potential risk factor for coronary artery disease. In the US, the incidence of hypertriglyceridemia is high. According to the American Heart Association, the prevalence of hypertriglyceridemia has increased globally over the past few decades due to an aging population and a high prevalence of obesity and diabetes. In the United States, the prevalence of hypertriglyceridemia defined as a triglyceride level >150 mg/dL ranges from 25% and 33%. About 4 million people aged ≥20 years in the United States have severe hypertriglyceridemia with triglyceride concentrations of ≥500 mg/dL.

Therapeutic lifestyle changes are the first defense for treatment of hypertriglyceridemia. Statins are widely used as an adjunct to diet and exercise in the treatment of patients with lipid abnormalities. Statins substantially reduce low density lipoprotein cholesterol levels and may also help to lower triglycerides levels. However, the effects of statins on triglyceride levels are often insufficient, and therefore a triglyceride-lowering agent is sometimes needed if triglyceride levels remain high.

The main treatment options for hypertriglyceridemia include fibrates, niacin and omega-3 fatty acids. Treatment with fibrates can markedly lower triglycerides and modestly raise high density lipoprotein cholesterol levels. Niacin lowers triglyceride levels but also raise high density lipoprotein cholesterol and lower low density lipoprotein cholesterol levels. The drawback to both of these drug products is they have significant side effects which can limit their use. In April 2016, the Food and Drug Administration concluded that the benefits of the concomitant use of statins plus extended release niacin or some fibrates do not outweigh the risks, and withdrew their approvals for this indication.

It has been suggested that omega-3 fatty acids may be an effective alternative to fibrates and niacin for the treatment and management of hypertriglyceridemia. The mechanism by which omega-3 fatty acid lower triglycerides is multifactorial and is thought to involve decreased hepatic lipogenesis, increased β-oxidation of fatty acids, inhibition of key enzymes involved in hepatic triglyceride synthesis, and increased expression of lipoprotein lipase. Together with their triglyceride-lowering effects, omega-3 fatty acids are also thought to have anti-arrhythmic, anti-thrombotic, anti-atherosclerotic, and anti-inflammatory effects, as well as promoting improvements in endothelial function and lowering blood pressure. All of these effects may contribute to the cardiovascular benefits associated with omega-3 fatty acids.

Several prescription omega-3 fatty acid products have been approved for use in the United States as an adjunct to diet for reducing triglyceride levels in adult patients with severe hypertriglyceridemia (≥500 mg/dL). Prescription omega-3 fatty acid products fall into one of three formulations:

- Omega-3 fatty acid ethyl esters
  - Lovaza® - GlaxoSmithKline (approved in 2004)
  - Omtryg™ - Trygg Pharma, Inc. (approved in 2014)
  - some generics - various manufacturers
- Icosapent ethyl
  - Vascepa® - Amarin Corp (approved in 2012)
- Omega-3 carboxylic acids
  - Epanova® - AstraZeneca Pharmaceuticals LP (approved in 2014)

All of the prescription omega-3 fatty acid formulations have been shown to be well tolerated and demonstrate a lack of drug-drug interactions with other lipid-lowering drugs, such as statins and fibrates.

Omega-3 fatty acid dietary supplements are also available. However, these products do not need to comply with the rigorous regulations required for prescription formulations and do not require approval from the FDA. Dietary supplement omega-3 fatty acid content is often inconsistent and may be inadequate to effectively treat hypertriglyceridemia.

Fatty fish and other seafood are the most important sources of omega-3 fatty acids. Since fish are a limited resource, there is a growing interest in exploring alternative sources of omega-3 fatty acids. Krill (Euphausia superba) are small crustaceans that appear similar to shrimp. The oil extracted from krill is a rich source of long-chain omega-3 fatty acids. Since Krill are a dominant member of the Antarctic zooplankton community in terms of biomass, they are an attractive alternative resource for commercial harvest and use.

Acasti Pharma is a biopharmaceutical company focused on the research, development and commercialization of prescription drugs using omega-3 fatty acids derived from krill oil. Acasti Pharma is currently developing an omega-3 fatty acid product CaPre for treatment of severe hypertriglyceridemia.

CaPre, is a krill oil-derived mixture of polyunsaturated fatty acids, primarily composed of the omega-3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid) which are present as a combination of phospholipids and free fatty acids. The digestion and absorption of omega-3 fatty acids esterified to phospholipids is believed to be more efficient due to the emulsifying properties of phospholipids facilitating access to the main hydrolyzing enzyme phospholipase-A2, together with the capacity to form micelles, enhancing absorption. Unlike that of phospholipids, the hydrolysis of ethyl esters (found in other omega-3 fatty acid prescription products) is mediated by carboxyl ester lipase, a bile salt–dependent lipase. Its release into the intestinal lumen is highly dependent on co-ingested fat. Therefore, bioavailability of eicosapentaenoic acid and docosahexaenoic acid conjugated to PL, may be far less affected by the fat content of a meal compared to ethyl esters, offering a potential clinical advantage to patients with hypertriglyceridemia who are advised to follow a fat-restricted diet.

Acasti Pharma is seeking Food and Drug Administration approval for CaPre in the United States. To date Acasti Pharma has carried out six clinical trials, four of which have been completed (2 x phase 1 and 2 x 2) and two of which are ongoing (phase 3).

Summary of CaPre Clinical Trials

Name	Phase	Status
Dose Response	Phase 1	Completed
Bioavailability	Phase 1	Completed
COLT	Phase 2	Completed
TRIFECTA	Phase 2	Completed
TRILOGY 1	Phase 3	Ongoing
TRILOGY 2	Phase 3	Ongoing

CaPre is supplied in a 1 g hard capsule formulation for oral administration with each 1 g capsule contains the following 310 mg of EPA and DHA.

Results from the phase 1 bioavailability study indicate:

- The bioavailability of the phospholipid and free fatty acid forms of eicosapentaenoic acid and docosahexaenoic acid found in CaPre are far less affected when taken on an empty stomach than the ethyl ester forms found in Lovaza;
- The bioavailability of Lovaza is maximal following administration with a high fat meal but is dramatically reduced under fasting conditions.

Since patients with severe hypertriglyceridemia should adhere to a low fat diet, these findings suggest preserved exposure, and perhaps retained efficacy in patients taking CaPre in either the fasted state or with a low fat diet.

The results from the phase 2 COLT study indicate:

- CaPre had a positive impact on lowering triglycerides, although not clear if dose-dependent;
- CaPre reduced triglycerides by 18.0% at 4 weeks and by 14.4% at 8 weeks (4.0 g dose of CaPre compared to standard of care); and
- CaPre had a positive impact on multiple lipoproteins, including HDL-C and non-HDL-C, without any significant deleterious effects on LDL-C.

This study demonstrated that CaPre has triglyceride lowering properties as well as beneficial overall lipid management effects in patients with mild to high hypertriglyceridemia.

CaPre may also have several additional advantages including:

- Krill is a more abundant source of omega-3 fatty acids compared to fish,
- CaPre has no effect or has a positive effect on LDL-C (ie lowers LDL-C), and
- CaPre may have improved bioavailability, with no food effects.

Currently Acasti has two ongoing multi-center, placebo-controlled, randomized, double-blind clinical trials that are nearing completion. The results from the two TRILOGY trials should help to confirm and extend these encouraging initial observations. Enrollment for these studies has been completed and preliminary results are expected for TRILOGY 1 at the end of 2019 and in early 2020 for TRILOGY 2.

Comparison of the Therapeutic Effects of Omega-3 Fatty Acid Containing Products

Product	Therapeutic Effect				
	TG	LDL-C	HDL-C	Non-HDL-C	Food Effects
CaPre	down	- / down	- / up	down	none
Vascepa	down	-	-	down	significant
Epanova	down	up	-	down	none
Lovaza	down	up	-	down	significant
Abbreviations: HDL-C = High Density Lipoprotein; LDL-C = Low Density Lipoprotein; TG = Triglycerides.					

Epidemiological, biological, and genetic studies have provided robust evidence of a strong association between elevated triglyceride levels and higher rates of cardiovascular events. Two large outcome trials are testing the triglyceride-lowering hypothesis with prescription omega-3 fatty acid products in statin-treated patients at high cardiovascular risk (REDUCE-IT - NCT01492361; STRENGTH - NCT02104817).

In the REDUCE-IT trial, a total of 8179 patients were enrolled and followed for approximately 5 years. A primary endpoint event (composite of CV death, myocardial infarction, stroke, coronary revascularization, and hospitalization for unstable angina) occurred in 17.2% of the patients in the omega-3 fatty acid (Vascepa) group, compared to 22.0% of the patients in the placebo group. The corresponding rates of the key secondary endpoint were 11.2% and 14.8%. The rates of additional ischemic endpoints were significantly lower in the omega-3 fatty acid group than in the placebo group, including the rate of cardiovascular death (4.3% vs. 5.2%).

Based on this information the REDUCE-IT trial authors concluded that among statin-treated patients with elevated triglycerides and cardiovascular disease or diabetes, multiple statistical models demonstrated that the omega-3 fatty acid (Vascepa) substantially reduced the burden of first, subsequent and total ischemic events. Based on the REDUCE-IT results, Amarin has submitted a supplemental New Drug Application to the FDA for an expanded label for Vascepa, with a Prescription Drug User Fee Act goal date of December 28, 2019. If approved, Vascepa would be the first omega-3 fatty acid indicated to reduce residual cardiovascular risk in patients with statin-managed low density lipoprotein cholesterol, but persistent elevated triglycerides.

Enrollment for the STRENGTH trial started in October 2014 and was completed on July 12, 2017 (13,086 patients). The results of the STRENGTH trial, which are due in 2020, should hopefully confirm and extend the REDUCE-IT results and conclusions.

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1 Introduction

1.1 Hypertriglyceridemia

Heart disease is the leading cause of death for American men and women, accounting for one out of every four deaths each year. Every 34 seconds someone has a heart attack and each minute someone dies from a heart disease-related event. There are approximately 715,000 heart attacks and 600,000 deaths each year due to heart disease in the United States (CDC, 2012).

Hypertriglyceridemia (HTG) is a condition in which serum triglyceride (TG) levels are elevated. Hypertriglyceridemia is commonly observed in people with metabolic syndrome, obesity, physical inactivity, smoking, excess alcohol intake, high-carbohydrate diets, diabetes type 2, chronic renal failure, nephrotic syndrome, and people taking certain drugs like corticosteroids, estrogens and retinoids as well as individuals with genetic disorders. According to the American Heart Association (AHA), the prevalence of HTG has increased globally over the past few decades due to an aging population and a high prevalence of obesity and diabetes. In the United States (US), the prevalence of HTG defined as a TG level >150 mg/dL ranges from 25% (Carroll et al, 2015) and 33% (CDC, 1996; Ford et al, 2002). About 4 million people aged ≥20 years in the US have severe HTG with TG concentration of ≥500 mg/dL (Lapointe et al 2019).

Epidemiologic studies have demonstrated that elevated TG levels are independently associated with increased cardiovascular (CV) risk (Boullart et al, 2012). Consistent with the epidemiologic data, clinical studies have shown that reaching target TG levels correlates with reduced CV risk (Miller et al, 2011). Moreover, TG lowering has been associated with reduced CV risk in certain patients with high baseline TG levels (Miller et al, 2011). Together, these data infer that elevated TG levels are a biomarker of CV risk. However, accumulating evidence suggests that TGs and triglyceride-rich lipoproteins (TRLs) are in the causal pathway of atherosclerotic cardiovascular disease (ASCVD), indicating that they play a pathogenic role in atherosclerosis rather than simply serving as a biomarker of disease risk (Budoff, 2016).

A number of definitions of what constitutes elevated TG-levels have been proposed. The following groups have developed guidelines:

- National Cholesterol Education Program (NCEP), Adult Treatment Panel (ATP) III
- European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS)
- Endocrine Society
- EAS Consensus Panel

Table 1 summarizes the ATP III classification of human serum TG levels. This table was adapted from the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).

Table 1 Adult Treatment Panel III Serum Triglyceride Classification

Triglyceride Classification	Adult Treatment Panel III Classification	
	Plasma Levels mg/dL	Plasma Levels mmol/L
Normal	<150 mg/dL	
Borderline High	150-199 mg/dL	1.70-2.25 mmol/L
High	200-499 mg/dL	2.26-5.64 mmol/L
Very High	≥500 mg/dL	>5.64 mmol/L

1.2 Hypertriglyceridemia Treatment

Therapeutic lifestyle changes (TLC) are the first line of defense for treatment of HTG. These changes include a low saturated fat, carbohydrate-controlled diet, combined with alcohol reduction, smoking cessation, and regular aerobic exercise. Following a Mediterranean diet (which is rich in monounsaturated fatty acids) significantly reduces TGs, as well as increasing high density lipoprotein cholesterol (HDL-C) levels (Kastorini et al, 2011). Consumption of fish is also an important factor associated with CV risk reduction. It has been found that fish higher in omega-3 fatty acids have a greater TG lowering effect (von Schacky et al, 2007).

Statins are widely used as an adjunct to diet and exercise in the treatment of patients with lipid abnormalities. Statins substantially reduce low density lipoprotein cholesterol (LDL-C) levels and may also help to lower TG levels. However, the

effects of statins on TG levels are often insufficient, and therefore a triglyceride-lowering agent may need to be added to statin therapy if TG levels remain high. The main treatment options for high TG levels include fibrates, niacin and omega-3 fatty acids.

Treatment with fibrates (nuclear peroxisome proliferator activated receptor (PPAR) alpha receptor agonists) can markedly lower TG levels (40 to 60%) and modestly raise HDL-C levels (15 to 25%) (fenofibrate prescribing information). In patients with CV disease and moderately elevated TG levels and low HDL-C levels, fibrates have been shown to decrease the risk of CV events (Manninen et al, 1992; Rubins et al, 1999).
Fibrate therapy also has been shown to decrease angiographic progression of coronary heart disease in patients with type 2 diabetes (Vergès, 2005). However, fibrate-induced increases in LDL-C may occur in patients with severe HTG. Fibrate therapy is also associated with a number of adverse effects, including increases in creatinine levels, myopathy and in rare cases, rhabdomyolysis, especially when used in combination with other lipid-lowering therapies (Davidson et al, 2007).

Another potential pharmacological agent for treatment of HTG is niacin (nicotinic acid). Niacin has been shown to lower TG levels by 30 to 50%, raise HDL-C levels by 20 to 30%, and lower LDL-C levels by 5 to 25% (Bodor and Offermanns, 2008). Niacin is not as potent as fibrates for lowering TG levels but is more effective at raising HDL-C levels (Feingold et al, 2018). Niacin is known to cause flushing, which many patients find intolerable, and also has the potential to increase serum glucose and cause liver toxicity or myopathy, particularly when co-administered with a statin (Ito, 2015).

In addition to fibrates and niacin, several prescription omega-3 fatty acid products have been approved in the US as an adjunct to diet for reducing TG levels in adult patients with severe HTG (≥500 mg/dL). The mechanism by which omega-3 fatty acid lower TG is multifactorial and is thought to involve decreased hepatic lipogenesis, increased β-oxidation of fatty acids, inhibition of key enzymes involved in hepatic TG synthesis, and increased expression of lipoprotein lipase (Bays et al, 2008; Le Jossic-Corcos et al, 2005; Horton et al, 1998; Park et al, 2003; Harris et al, 2006; Khan et al, 2002). Together with their TG-lowering effects, omega-3 fatty acids are also thought to have anti-arrhythmic (Reiffel et al, 2006), anti-thrombotic, anti-atherosclerotic (Robinson et al, 2006), and anti-inflammatory effects (Mori et al, 2004), as well as promoting improvements in endothelial function (Wang et al, 2013) and lowering blood pressure (Vandongen et al, 1993). All of these effects may contribute to the CV benefits associated with omega-3 fatty acids.

A variety of novel TG-lowering agents are also in development. These include an antiviral vector approach for lipoprotein lipase inhibition (Khera et al 2017), antisense oligonucleotide approaches for apo CIII inhibition (Crosby et al, 2014; Jørgensen et al, 2014), ANGLPTL3 (Dewey et al, 2017), ANGPTL4 antibodies (Dewey et al, 2016), and diacylglycerol acyltransferase inhibitors (Watts et al, 2013; Xiao et al, 2016). However, it remains to be seen whether any of these agents will reach clinical trials for treating high TG levels (200 to 499 mg/dL) (Ganda et al, 2018).

1.3 Objective

Acasti Pharma is currently developing an omega-3 fatty acid product CaPre for treatment of severe hypertriglyceridemia. CaPre is intended to be used as a therapy in conjunction with positive lifestyle changes and is to be administered either alone or with other drug treatment regimens such as statins.

CaPre is a krill oil derived mixture containing polyunsaturated fatty acids (PUFAs), primarily composed of omega-3 fatty acids, principally eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Acasti Pharma believes that EPA and DHA are more efficiently transported by phospholipids (PLs) sourced from krill oil than the EPA and DHA contained in fish oil typically found in other prescription omega-3 drugs.

The object of this report is to review and summarize the current literature/information available on the following topics:

- Krill oil versus other sources of omega-3 fatty acids,
- Omega-3 fatty acid prescription products,
- Acasti's CaPre clinical data,
- CaPre phase 3 clinical trial designs,
- Differentiating attributes between CaPre, Vascepa and Epanova, and
- Potential market impact of the REDUCT-IT (Vascepa) and STRENGTH trials (Epanova).

This information will then be used to determine the potential future commercial prospects for CaPre and Acasti Pharma.

2 Literature Search

Pubmed searches (https://www.ncbi.nlm.nih.gov/pubmed) using the following keys words were performed by the author in mid-June of 2019:

- Triglycerides
- Hypertriglyceridemia
- Omega-3 Fatty Acids
- Krill oil Fish oil
- Eicosapentaenoic acid and EPA
- Docosahexaenoic acid and DHA
- Vascepa and icosapent ethyl and IPA
- Epanova
- CaPre
- Acasti

To refine the search and reduce the number of hits, these key words were used in various combinations.

Abstracts were reviewed for their relevance and if available free online, the full article was obtained. The pubmed searches were restricted to information available for humans. No time restrictions were imposed. Additional references identified through article review were also included if deemed relevant.

In addition to the pubmed searches, information from the following websites was reviewed:

- Acasti Pharma Inc. - https://www.acastipharma.com
- Amarin Corporation - https://amarincorp.com
- AstraZenica - https://www.astrazeneca.com
- Clinical Trials Government - https://clinicaltrials.gov
- United States Patents and Trademark Office (USPTO) - https://www.uspto.gov
- Drug Information Portal - https://druginfo.nlm.nih.gov/drugportal
- U.S. Food and Drug Administration (FDA) - https://www.fda.gov

The prescribing information (PI) for relevant omega-3 fatty acid products were also reviewed:

- Lovaza (Omacor, Zoden, Lotriga)
- Omtryg
- Epanova
- Vascepa

A comprehensive list of references used when compiling this report can be found in Section 5.

3 Discussion

3.1 Omega-3 Fatty Acids

Fatty acids are long-chain hydrocarbons with a carboxylic acid group at one end (alpha terminal) and a methyl group at the other (omega terminal). They are classified based on the number of double bonds in their side chains–saturated fatty acids (no double bond), monounsaturated fatty acids (MUFAs; single double bond), and polyunsaturated fatty acids (two or more double bonds). PUFAs can be classified further by the length of the carbon chain and the position of the first double bond from the methyl terminal into omega-6 (ω-6 or n-6) or omega-3 (ω-3 or n-3).

The most important fatty acids for humans are the essential fatty acids (EFAs), which are necessary to maintain homeostasis. These fatty acids cannot be synthesized, or cannot be synthesized sufficiently by the organism and must be supplied through a food source. The "parent essential fatty acids" linoleic acid (LA) and alpha-linolenic acid (ALA) are metabolized into other fatty acids through desaturase and elongase enzymes. However, this pathway is slow and inefficient (Bowen et al 2016) therefore, for all practical purposes, the dietary intake of eicosapentaenoic acid and docosahexaenoic acid is "essential" and crucial for human health.

Most vegetable oils and crop seeds, like corn, sunflower, soybean, and canola oils, are a rich source of LA with lesser amounts of ALA. On the other hand, flax, walnuts, and chia seeds are a rich source of ALA, as are some green leafy vegetables.

Fatty fish and other seafood are the most important dietary sources of EPA and DHA. Eicosapentaenoic acid occurs in large amounts in herring (15% of total lipids) (Shirai et al, 2006), wild sardine (13.6% of muscle total FAs) (Bandarra et al, 2018) and pollock roe (18.8%) (Shirai et al, 2004). Eicosapentaenoic acid is rare in plants. The main sources of DHA are flying fish, herring,

pollock and salmon roe (27.9%, 22.6%, 22.2%, and 17.4% of total lipids, respectively) (Shirai et al, 2004), *Cirrhinus mrigata* (18.07 g/100 g muscle tissue FAs), and *Catla catla* (17.98 g/100 g muscle tissue FAs) (Memon et al, 2011). Since fish are a restricted resource, there is a growing interest in exploring alternative sources of omega-3 fatty acids.

Krill (*Euphausia superba*) are small crustaceans that appear similar to shrimp. The oil extracted from krill is a rich source of long-chain omega-3 PUFAs. They are found in the colder waters of the ocean and primarily serve as a food source for other animals such as whales, seals, penguins, squid and fish. Krill are by far the most dominant member of the Antarctic zooplankton community in terms of biomass and, thus, attractive for commercial harvest. The krill fishery is probably unique in that the internationally recognized precautionary catch limits (totalling 8.6 million tonnes per year) set by the Commission for the Conservation of Antarctic Marine Living Resources (CCAMLR) is over 40 times the current annual catch (approximately 210 000 tonnes per year) (Nicol et al, 2011).

Both fish and krill oil contain a high proportion of EPA and DHA, but in contrast to fish oil, krill oil contains a major part of these fatty acids in the form of PLs (mainly phosphatidylcholine) (Tou et al, 2007). The digestion and absorptions of omega-3 fatty acids esterified to PL are believed to be more efficient due to the emulsifying properties of PL facilitating access to the main hydrolyzing enzyme Phospholipase A2, together with the capacity to form micelles enhancing the absorption (Schuchardt et al, 2011; Mun et al, 2007; Beckermann et al 1990).
A brief comparison of the characteristics of krill and fish oil can be found in Table 2.

Table 2 Comparison of Krill and Fish Oil

	Krill Oil	Fish Oil
Fatty Acid Composition	EPA and DHA	EPA and DHA
Fatty Acid Form	Phospholipids	Triglycerides
EPA and DHA Ratio	2:1	1:1

Studies on the bioavailability of EPA and DHA from krill and fish oil in humans are limited and interpretation of their results is difficult, since different amounts of EPA and DHA have been used, the duration of the intervention have differed, and different study groups have been included.

Ulven and Holven (2011) conducted a literature review to identify clinical trials which compared the bioavailability of krill versus fish oil. They identified seven human randomized trials including five double-blind and two open-label ones. These studies have been summarized in Table 3.

Table 3 Summary of Studies Comparing Krill and Fish Oil (Adapted from Ulven and Holven 2015)

Study	Design	Intervention	PUFA	Duration	Subjects
Laidlaw et al, 2014	Open-label, randomized, crossover study	Four groups: 1) rTG FO, 2) EE FO, 3) PL KO, 4) TG SO	Group 1: EPA, 650 mg; DHA, 450 mg. Group 2: EPA, 756 mg; DHA, 228 mg. Group 3: EPA, 150 mg; DHA, 90 mg. Group 4: EPA, 180 mg; DHA, 220 mg	28-day period, followed by a 4-week washout period	35 healthy subjects male and female 35±14 years
Ramprasath et al, 2013	Double-blinded, randomized, placebo-controlled crossover trial	Three groups: 1) KO, 2) FO, 3) CO	Three treatment groups including KO or FO providing 600 mg of n-3 PUFAs	4 weeks' treatment, with an 8-week washout period	24 healthy volunteers with BMI of 23.8±3 kg/m^2 28.2±5.4 years

Study	Design	Intervention	PUFA	Duration	Subjects
Ulven et al, 2011	Open single-center, randomized, parallel-group designed study	Three groups: 1) KO: 3.0 g/d (n=41), 2) FO: 1.8 g/d (n=40) 3) no dietary intervention (n=41)	KO: 543 mg EPA + DHA; FO: 864 mg EPA + DHA No dietary intervention	7 weeks	113 subjects with normal or slightly elevated total blood cholesterol and/or TG levels KO: 38.7±11.1 years; FO: 40.3±14.8 years; control: 40.5±12.1 years
Banni et al, 2011	Randomized, double-blind, controlled, parallel clinical trial	Three groups: 1) KO (n=21), 2) MO (n=23), 3) OO (n=19) 2 g/d dose	KO: 309 mg/d of EPA/DHA 2:1; MO: 390 mg/d of EPA/DHA 1:1	4 weeks	63 subjects: healthy overweight or obese men and women, with waist circumference of ≥102 cm (men) or ≥88 cm (women) 35–64 years of age
Schuchardt et al, 2011	Randomized, double-blind crossover trial	Three EPA + DHA formulations: 1) FO rTGs, 2) FO EEs, 3) KO (mainly PLs).	Total EPA + DHA intake: 1,680 mg for all three groups. Groups 1 and 2: EPA intake 1,080 mg and DHA intake 672 mg. Group 3: EPA intake 1,050 mg and DHA intake 630 mg	Postprandial study: measurements recorded 2 h, 4 h, 6 h, 8 h, 24 h, 48 h, and 72 h after capsule ingestion	12 healthy young men between 20 years and 50 years and with BMI between 20 kg/m^2 and 28 kg/m^2 31±5 years
Maki et al, 2009	Randomized, double-blind parallel-arm trial	Three groups: 1) 2 g/d of KO, 2) 2 g/d MO, 3) 2 g/d OO Four 500 mg capsules per day.	KO: 216 mg/d EPA and 90 mg/d DHA; MO: 212 mg/d EPA and 178 mg/d DHA	4 weeks	76 healthy overweight and obese men and women, 35–64 years of age, with waist circumference of ≥102 cm (men) or ≥88 cm (women) KO: 49.4±1.7 years; MO: 49.6±1.4 years; and placebo: 47.4±1.6 years
Bunea et al, 2004	Double-blind, randomized trial	Four groups: Group A: KO (2-3 g daily); Group B: KO (1–1.5 g daily); Group C: FO (3 g daily); Group D: placebo (3 g/d, microcrystalline cellulose).	Group A: KO 2 g/d (BMI <30 kg/m2), 3 g/d (BMI >30 kg/m2). Group B: KO 1 g/d (BMI <30 kg/m2), 1.5 g/d (BMI >30 kg/m2). Group C: FO 3 g/d (180 mg EPA +120 mg DHA/g of oil). Group D: placebo 3 g/d (microcrystalline cellulose).	12 weeks	120 patients with hyperlipidemia and with blood cholesterol levels between 194 mg/dL and 348 mg/dL (18–85 years) 51±9.46 years

Abbreviations: BMI = Body Mass Index; CO = Corn Oil; d = Days; DHA = Docosahexaenoic Acid; DPA = Docosapentaenoic Acid; EE = Ethyl Ester; EPA = Eicosapentaenoic Acid; FO = Fish Oil; h = Hours; KO = Krill Oil; MO = Menhaden Oil; OO = Olive Oil; PL = Phospholipid; PUFA = Polyunsaturated Fatty Acid; rTG =, Re-esterified Triglyceride; SO = Salmon Oil; TG = Triglyceride.

Ulven and Holven (2011) identified two human studies using the same amount of EPA and DHA from krill and fish oil, and they both showed that the bioavailability of EPA and DHA from krill oil seemed to be higher than from fish oil (Ramprasath et al, 2013; Schuchardt et al, 2011). In contrast however, Yurko-Mauro et al (2015) found no significant differences in mean fasting plasma concentrations of DHA and EPA, after four weeks of supplementation with a 1.3 g/d dose of DHA and EPA in fish oil (EE), or fish oil (TG) or krill oil. More recently Lapointe et al (2019) found that among subjects in the fasted state, omega-3 fatty acids demonstrated greater bioavailability of EPA and DHA in the form of PL esters and FFA as compared to EE. They also

found that the bioavailability of omega-3 EE was drastically reduced in the fasted state compared to administration with a high-fat meal.

3.2 Omega-3 Fatty Acid Products

Omega-3 fatty acids are available in the form of prescription drugs and non-prescription dietary supplements. Prescription omega-3 fatty acids are currently approved in the US to treat patients with very high TG levels (≥500 mg/dL). Most prescription omega-3 products contain both EPA and DHA, as do virtually all marketed dietary supplements.

There are three prescription omega-3 fatty acid formulations approved in the US:

- *Omega3 fatty acid ethyl esters - a mixture of long-chain omega-3 fatty acid ethyl esters, primarily EPA (Figure 1) and DHA* (Figure 2)
    - Lovaza - GlaxoSmithKline (approved in 2004)
    - Omtryg™ - Trygg Pharma, Inc. (approved in 2014)
    - some generics - various
- *Icosapent ethyl* (Figure 3) - EPA ethyl esters
    - Vascepa - Amarin Pharma Inc. (approved in 2012)
    - Omega-3 carboxylic acids - a mixture of long-chain omega-3 fatty acids in FFA form, primarily EPA, DHA, and docosapentaenoic acid There are three prescription omega-3 fatty acid formulations approved in the US:
- *Omega-3 carboxylic acids - a mixture of long-chain omega-3 fatty acids in FFA form, primarily EPA, DHA, and docosapentaenoic acid*
    - Epanova - AstraZeneca Pharmaceuticals LP (approved in 2014)

Please note that although Epanova and Omtryg have been FDA approved in the US, they are not currently commercially available.

Figure 1 Structural Formula for EPA Ethyl Ester

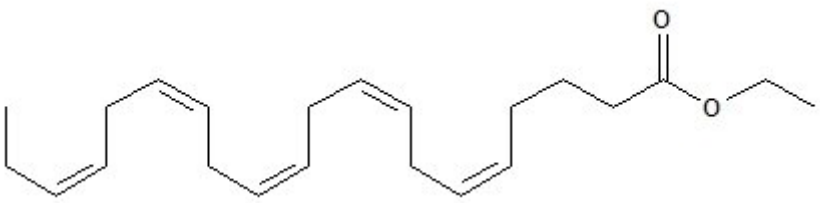


Figure 2 Structural Formula for DHA Ethyl Ester

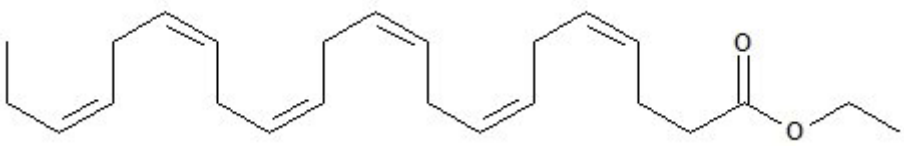
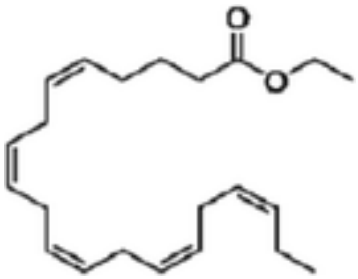


Figure 3 Structural Formula for Icosapent Ethyl



In addition to branded products, a number of omega-3 acid EE generics are also available in the US (Table 4).

Table 4 Generic Omega-3-Acid Ethyl Ester Products

ANDA Number	Company
090973	Apotex
091018	Par Pharm
091028	Teva Pharm
203893	Strides Pharma
204940	Amneal Pharms
207420	Ascent Pharms
210107	Zydus

Table 5 summarizes data from clinical studies investigating the effect of prescription omega-3 fatty acid formulations on TG, LDL-C, and HDL-C in patients with HTG. It should be noted that the placebo groups in these studies are inconsistent and therefore the results should not be directly compared (Karalis, 2017).

Table 5 Prescription Omega-3 Fatty Acids Clinical Trials (Adapted from Karalis, 2017)

Trial	Description	Treatment	Patients	Results		
				TG	LDL-C	HDL-C
Omega-3 Ethyl Esters						
Harris et al, 1997	Double-blind, placebo-controlled 16 weeks	OM3EE 4 g/day Placebo (corn oil)	n = 42 TG: 500-2000 mg/dL Baseline TG: 877 mg/dL	OM3EE: -45% Placebo: +16% (p < 0.0001)	OM3EE: +32% Placebo: -5% (p = 0.0014)	OM3EE: +13% Placebo: 0 (p < 0.014)
Pownall et al, 1999	Double-blind, placebo-controlled 6 weeks	OM3EE 4 g/day Placebo (corn oil)	n = 41 TG: 500-2000 mg/dL Baseline TG: 801 mg/dL	OM3EE: -39% Placebo: -8% (p = 0.001)	OM3EE: +17% Placebo: -4% (p = 0.013)	OM3EE: +6% Placebo: -6% (p = 0.023)
Davidson et al, 2007 (COMBOS)	Double-blind, placebo-controlled 8 weeks	OM3EE 4 g/day Placebo (vegetable oil)	n = 256 TG: 200-500 mg/dL on statin treatment (simvastatin 40 mg/day) Baseline TG: 282 mg/dL	OM3EE: -28% Placebo: -4% (p < 0.001)	OM3EE: +3% Placebo: -2% (p < 0.001)	OM3EE: +4% Placebo: -1% (p < 0.001)

Trial	Description	Treatment	Patients	Results		
				TG	LDL-C	HDL-C
Icosapent Ethyl						
Bays et al, 2011 (MARINE)	Double-blind, placebo-controlled 12 weeks	IPE 4 g/day IPE 2 g/day Placebo (light liquid paraffin)	n = 229 TG 500–2000 mg/dL Baseline TG: 680 mg/dL	IPE 2 g/day: –20% (placebo corrected) (p = 0.0051) IPE 4 g/day: –33% (placebo corrected) (p < 0.0001)	IPE 2 g/day: +5% (placebo corrected) (p = 0.30) IPE 4 g/day: –2% (placebo corrected) (p = 0.68)	IPE 2 g/day: +2% (placebo corrected) (p = 0.52) IPE 4 g/day: –4% (placebo corrected) (p = 0.22)
Ballantyne et al, 2012 (ANCHOR)	Double-blind, placebo-controlled 12 weeks	IPE 4 g/day IPE 2 g/day Placebo (not specified)	n = 663 TG ≥ 200 mg/dL on stable statin treatment with or without ezetimibe Baseline TG: 295 mg/dL	IPE 2 g/day: –10% (placebo corrected) (p < 0.001) IPE 4 g/day: –22% (placebo corrected) (p < 0.0001)	IPE 2 g/day: –4% (placebo corrected) (p = 0.087) IPE 4 g/day: –6% (placebo corrected) (p < 0.01)	IPE 2 g/day: –2% (placebo corrected) (p = 0.13) IPE 4 g/day: –5% (placebo corrected) (p < 0.01)
Omega-3 Carboxylic Acids						
Kastelein et al, 2014 (EVOLVE)	Double-blind, placebo controlled 12 weeks	OM3CA 2 g/day OM3CA 3 g/day OM3CA 4 g/day Placebo (olive oil)	n = 364 TG 500-2000 mg/dL untreated or on a stable dose of statin Baseline TG: 717 mg/dL (2 g/day group) 728 mg/dL (3 g/day group) 655 mg/dL (4 g/day group)	OM3CA 2 g/day: –26% (p < 0.01) OM3CA 3 g/day: –26% (p < 0.01) OM3CA 4 g/day: –31% (p < 0.001) Placebo: –4%	OM3CA 2 g/day: +19% (p < 0.01) OM3CA 3 g/day: +14% (p = NS) OM3CA 4 g/day: +19% (p < 0.001) Placebo: +3%	OM3CA 2 g/day: +7% (p = NS) OM3CA 3 g/day: +4% (p = NS) OM3CA 4 g/day: +6% (p = NS) Placebo: +2%
Maki et al, 2013 (ESPRIT)	Double-blind, placebo controlled 6 weeks	OM3CA 2 g/day OM3CA 4 g/day Placebo (olive oil)	n = 627 TG 200–500 mg/dL on a maximally tolerated statin or statin with ezetimibe Baseline TG: 284 mg/dL (2 g/day group) 287 mg/dL (4 g/day group)	OM3CA 2 g/day: –15% (p < 0.001) (non-HDL cholesterol: –4% (p < 0.05) OM3CA 4 g/day: –21%	OM3CA 2 g/day: +5% (p < 0.05) OM3CA 4 g/day: +1% (p = NS) Placebo: +1%	OM3CA 2 g/day: +3% (p = NS) OM3CA 4 g/day: +3% (p = NS) Placebo: +2%

Abbreviations: HDL = High-density Lipoprotein; IPE = Icosapent Ethyl; LDL = Low-density Lipoprotein; NS = Not Significant; OM3CA = Omega-3 Carboxylic Acids, OM3EE = Omega-3 Fatty Acid Ethyl Esters, TG = Triglycerides.

In addition to their TG lowering effects, prescription omega-3 fatty acids can impact other lipid parameters. EPA alone appears to minimally decrease or have a neutral effect on LDL-C, while DHA/EPA combination products have been shown to increase LDL-C, which may be an important consideration for patients with atherosclerotic disease and/or risk factors for CV disease.

In addition to the clinical trial data, a pooled analysis of 16 DHA studies showed a significant estimated increase in LDL-C compared with placebo, whereas pooled data from nine EPA studies did not show a significant change in LDL-C compared with placebo (Wei et al, 2011). In a systematic review of EPA and DHA, analysis of six studies that directly compared DHA with EPA showed that DHA increased LDL-C by 2.6% on average, while EPA minimally affected LDL-C (0.7% decrease) (Jacobson et al, 2012).

All prescription omega-3 formulations have been shown to be well tolerated. The most common adverse events (AEs) reported in the US for each formulation are diarrhea, nausea, abdominal pain or discomfort, eructation, dyspepsia, taste perversion and arthralgia (product prescribing information). Studies have shown that omega-3 fatty acids do not affect liver function (Harris et al, 1997), and do not have any known clinically significant drug–drug interactions with other commonly used lipid-modifying drugs, such as statins (McKenney et al 2006; Di Spirito et al, 2008; Kostapanos et al, 2010).

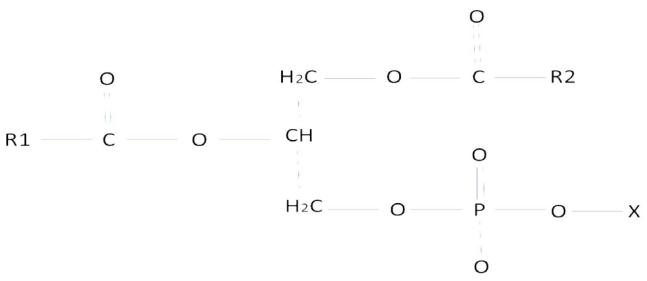
It is not known whether patients with allergies to fish and/or shellfish are at an increased risk of allergic reaction to omega-3 fatty acids, and so these formulations should be used with caution in patients with known hypersensitivity to fish and/or shellfish (product prescribing information).

Dietary-supplement omega-3 fatty acids are also widely utilized and are among the most popular dietary supplements worldwide (Barnes et al, 2008). However, dietary supplements are not subject to the rigorous regulations required for prescription drugs. Consequently, the EPA and DHA content of dietary supplements may be inconsistent (Weitz et al, 2010; Albert et al, 2015; Zargar et al, 2011). Due to an early evaluation study, practitioners typically view supplemental omega-3 fatty acids as adequate and reliable. However, a more recent analysis of individual fish oil supplements found that they contain an inadequate dose of EPA and DHA. On average, they contained only 68 % of the claimed EPA and DHA content. The same analysis also found that the majority of supplements exceeded recommended levels of oxidation markers (Albert et al, 2015). As the omega-3 fatty acids undergo oxidation, the concentration of EPA and DHA decreases, suggesting reduced efficacy. One study demonstrated that a median intake of 11 dietary fish oil supplement servings/day was required to achieve an FDA-approved dose of 3.4 g/day of omega-3 fatty acids (Zargar et al, 2011; Weintraub, 2014). This study also found that dietary-supplement omega-3 fatty acids contain other fats and cholesterol, and that the fat and cholesterol content varies widely among products (Zargar et al, 2011). In addition, as the EPA and DHA content of dietary supplements varies among products, this may cause confusion for patients and practitioners. This is likely to result in inaccurate dosing that may potentially be inadequate to effectively lower TG in patients with HTG.

Acasti and CaPre

Acasti Pharma is a biopharmaceutical innovator company focused on the research, development and commercialization of prescription drugs using omega-3 fatty acids. Acasti Pharma is currently developing CaPre, an omega-3 fatty acid product for treatment of severe HTG.

Figure 4 Phospholipids (where R1 and/or R2 is EPA or DHA)



CaPre, is a krill oil-derived mixture of PUFAs, primarily composed of the omega-3 fatty acids, EPA and DHA, which are present as a combination of PL and FFA. Approximately 60% of the omega-3 fatty acids in CaPre are naturally bound to PL and the rest are FFA. Acasti Pharma believes this gives CaPre an advantage over other prescription omega-3 fatty acids currently available on the market.

Acasti Pharma is seeking FDA approval of CaPre in the US. To date Acasti Pharma has carried out six clinical trials, four of which have beenc ompleted (2 x Phase 1 studies plus COLT and TRIFECTA) and two phase 3 studies which are currently in progress (TRILOG 1 and TRILOGY 2).

Table 6 CaPre Clinical Trials

Name	Phase	Status	Information Location
Dose Response	Phase 1	Completed	Section 3.3.1
Bioavailability	Phase 1	Completed	Section 3.3.2
COLT	Phase 2	Completed	Section 3.3.3
TRIFECTA	Phase 2	Completed	Section 3.3.4
TRILOGY 1	Phase 3	Ongoing	Section 3.3.5
TRILOGY 2	Phase 3	Ongoing	Section 3.3.6

CaPre is supplied in a 1 g hard capsule formulation for oral administration, with each 1 g capsule containing 310 mg of EPA and DHA.

Using publicy available information, the purpose, design and results of the CaPre studies have been summarized in the sections below.

3.2.1 Phase 1 Clinical Trial - Multi-dose

This phase 1 study was an open-label, randomized, multiple-dose, single-center, parallel-design study.

Forty two healthy subjects were enrolled into 3 groups (N= 14/group):

- CaPre 1 g daily x 15 days
- CaPre 2 g daily x 15 days
- CaPre 4 g daily x 15 days

Drug was administered 30 minutes from the start of low fat breakfast:

- Therapeutic lifestyle changes diet breakfast on Day 1 through Day 14
- High fat breakfast on Day 15

The results indicated that the CaPre pharmacokinetic (PK) profile for EPA+DHA appeared to be dose proportional both after a single dose (Day 1) and after multiple doses (Day 14).

3.2.2 Phase 1 Clinical Trial - Bioavailability

This phase 1 study was a single-center, open-label, randomized, 4-period, 4-treatment, 4-sequence crossover study to compare the bioavailability with CaPre (omega-3 PL/FFA) versus the FDA-approved HTG drug Lovaza (omega-3 EE). The main objective of this study was to compare the relative bioavailability of EPA and DHA after administration of a single 4 g dose of CaPre or Lovaza, in the fed and fasted states. Information from this trial was taken from a recently published article authored by Lapointe et al (2019).

Safety

The administration of CaPre or Lovaza, both with and without food, were found to be generally well tolerated by participating subjects with 13 subjects (23.2% of subjects dosed) experiencing a total of 24 treatment-emergent adverse events (TEAEs):

- 7 subjects (13.5%) reported 11 TEAEs after receiving CaPre (fasted state)
- 5 subjects (9.1%) reported 7 TEAEs after receiving Lovaza (fasted state)
- 3 subjects (5.8%) reported 4 TEAEs after receiving CaPre (fed state)
- 2 subjects (3.9%) reported 2 TEAEs after receiving Lovaza (fed state)

Headache was the most frequently reported nervous system-related TEAEs, with 4 (7.1%) subjects experiencing a total of 4 events (16.7% of total reported TEAEs). Diarrhea was the most frequently reported gastrointestinal-related TEAEs, with 5 (8.9%) subjects experiencing a total of 9 events (37.5% of the total reported TEAEs).

Pharmacokinetics

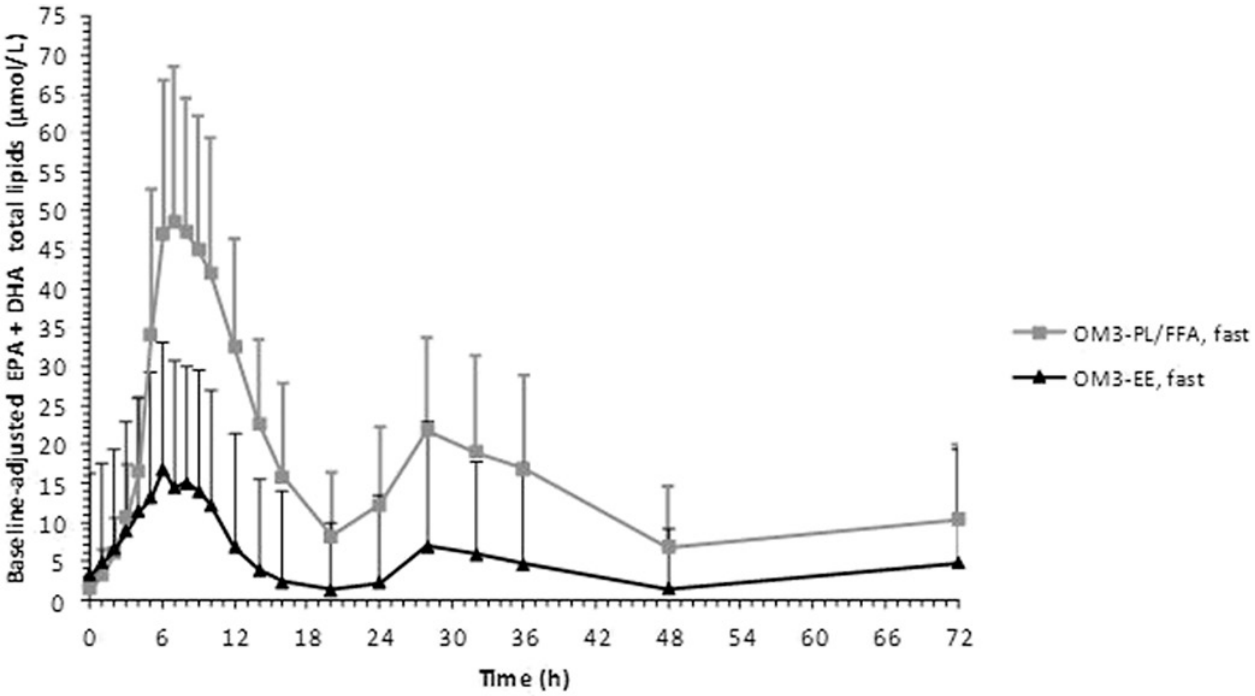
To determine the PK properties of EPA and DHA, 24 blood samples were collected prior to dosing (at −24, −16, −10, and 0 h) and up to 72 h post-dose, for a total of 24 time points. The concentrations of EPA and DHA total and free lipids in the plasma samples were determined using an LC-MS/MS analytical method.

The PK parameters measured included the area under the concentration curve 0-72 hours (AUC_{0-72}) as calculated by the linear trapezoidal method, maximum concentration (C_{max}), and time to maximum concentration (T_{max}) of total EPA, total DHA, and total EPA + DHA.

Fasted State Results

The mean plus or minus the standard deviation (SD) baseline-adjusted total EPA + DHA concentration–time profiles after a 4 g dose of the CaPre or Lovaza in the fasted state (comparative bioavailability) are shown in Figure 5. The comparative bioavailability between CaPre or Lovaza EPA + DHA in total lipids of plasma concentration–time profiles were 5-fold and 2.7-fold higher, respectively, following a 4 g dose of CaPre than with a 4 g dose of Lovaza. The median T_{max} was 7.00 hr with both treatments.

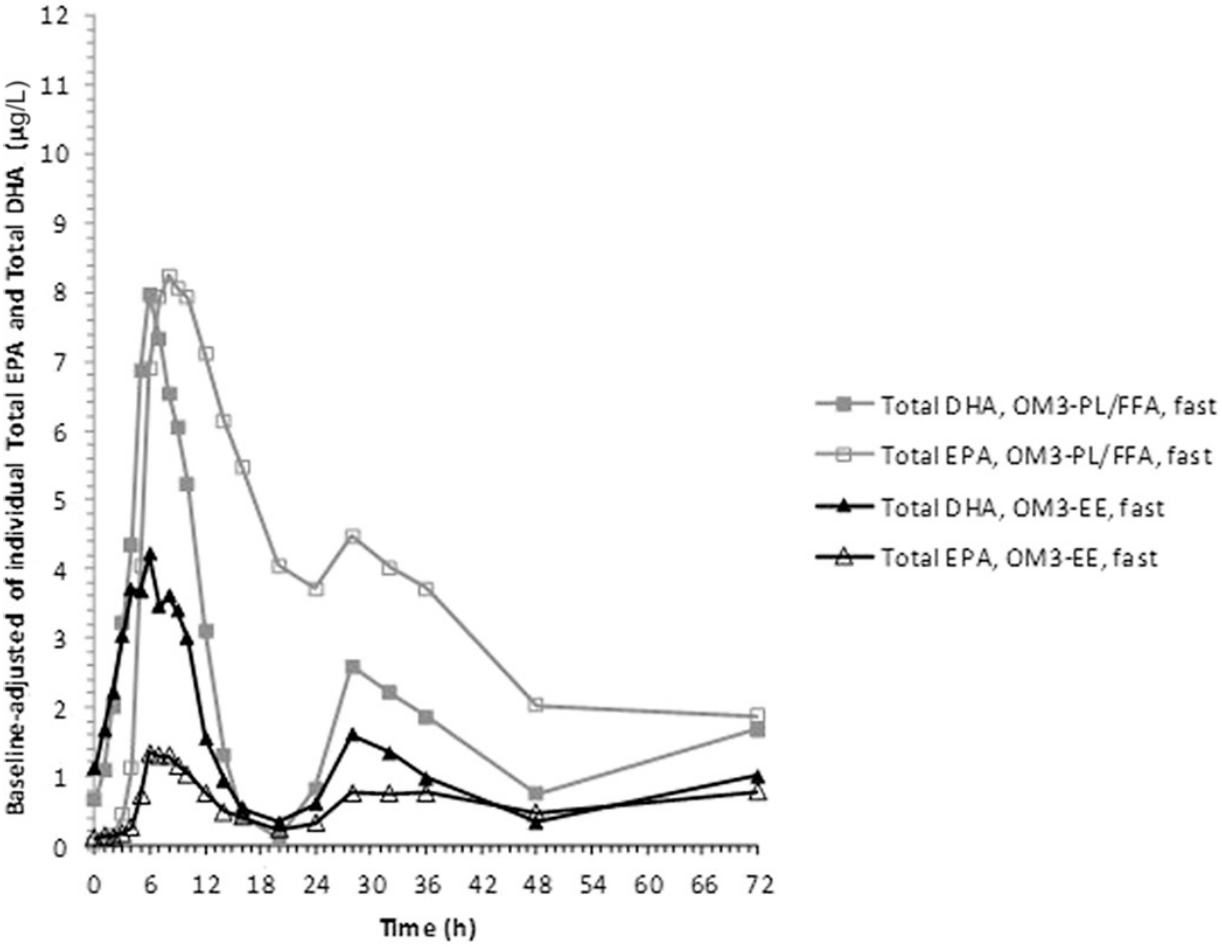
Figure 5 Comparative bioavailability (fasted state) following a single-dose of CaPre (OM3-PL/FFA) or Lovaza (OM-3EE). Data are given as mean (SD) baseline-adjusted total EPA + DHA plasma concentration–time profile values.



The total extent of exposure (as assessed by AUC_{0-72}) of baseline-adjusted EPA alone in total lipids of plasma was 6.8-fold higher following the administration of CaPre compared to Lovaza in the fasted state (Figure 6). Similarly, the peak exposure of total EPA (C_{max}) was also considerably increased (4.3-fold) following the administration of CaPre compared to Lovaza. The median T_{max} in the fasted state was similar between the two treatments (8.00 hr with CaPre, 9.00 hr with Lovaza).

The total extent of exposure of baseline-adjusted DHA alone in total lipids of plasma was 2.4-fold higher following the administration of CaPre compared to Lovaza in the fasted state (Figure 6). The increase was also observed for peak exposure, which was 1.8-fold higher following CaPre administration. The median T_{max} was 6.00 hr with both treatments in the fasted state.

Figure 6 Comparative bioavailability (fasted state) following a single-dose of CaPre (OME-PL/FFA) or Lovaza (OM3-EE). Data are given as mean (SD) baseline-adjusted total EPA and DHA total plasma concentration–time profile values.

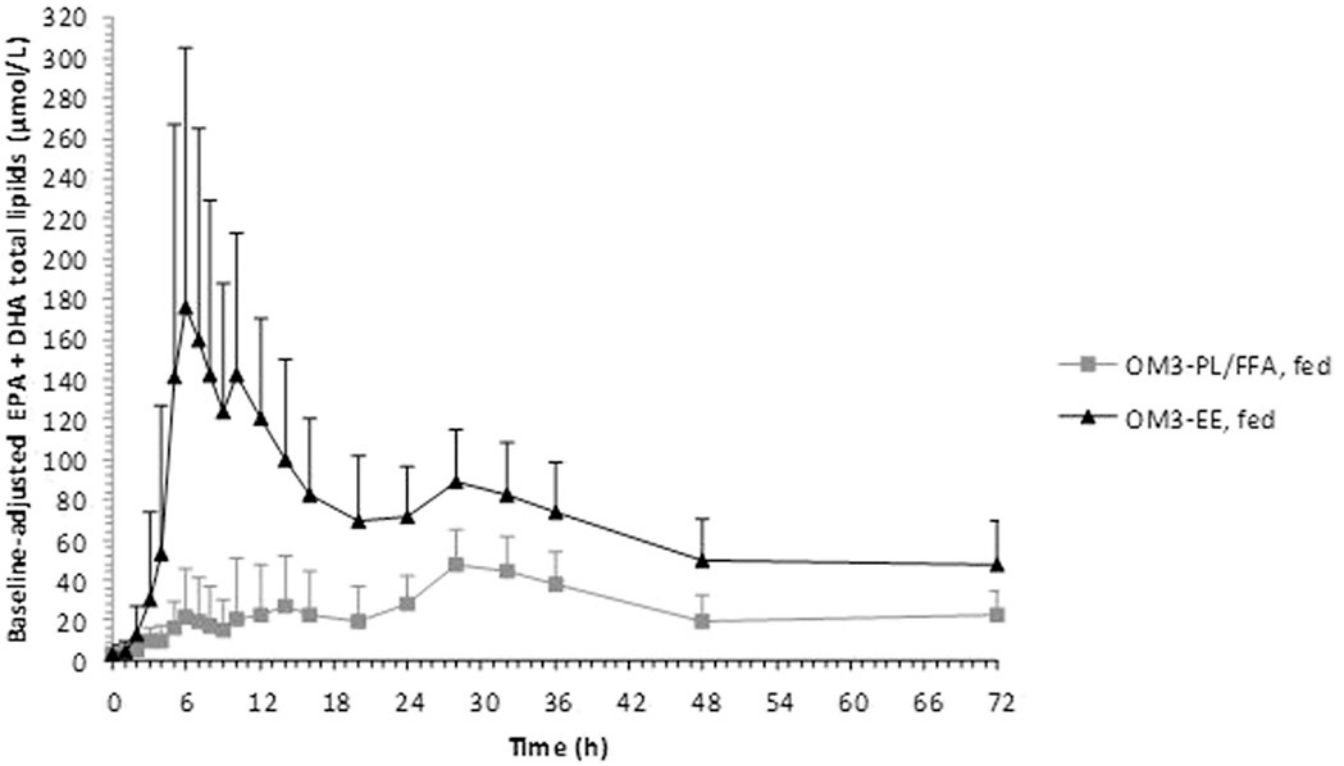


Overall, these results suggest a greater bioavailability of CaPre versus Lovaza in the fasted state, since the 90% confidence intervals (CIs) of the geometric means (GMRs) of the AUC_{0-72} and C_{max} of all analytes tested (EPA, DHA, EPA + DHA total lipids) for the two treatments were entirely contained above the standard criterion for bioequivalence of 90% CI of 80%–125%.

Fed State Results

In regards to the comparative bioavailability between CaPre and Lovaza in the fed state, CaPre displayed a longer median T_{max} compared to Lovaza (28.00 vs 7.00 hr, respectively). The total and peak exposures (AUC_{0-72} and C_{max}) of baseline-adjusted EPA + DHA in total lipids of plasma were 3-fold and 4-fold lower, respectively, with CaPre than Lovaza. The 90% CIs of the GMRs of AUC_{0-72} and C_{max} of both analytes with the two treatments were entirely contained below the standard criterion for bioequivalence of 90% CI of 80%–125%.

Figure 7 Comparative bioavailability (fed state) with single-dose CaPre (OM3-PL/FFA) or Lovaza (OMG3-EE). Data are given as mean (SD) baseline-adjusted total EPA + DHA plasma concentration–time profile values.



These results suggest higher systemic exposure to EPA and DHA with Lovaza, essentially due to the higher content of EPA/DHA per gram of Lovaza (770 mg total as FFA) versus CaPre (310 mg total as FFA) when the products are administered in the fed state. The results obtained for other baseline-adjusted analytes (EPA total lipids and DHA total lipids), along with the analysis of measured analytes, also support this.

In conclusion, this study showed that among subjects in the fasted state, CaPre demonstrated greater bioavailability of EPA and DHA in the form of PL esters and free fatty acids as compared to Lovaza. Bioavailability with Lovaza was drastically reduced in the fasted state compared to administration with a high-fat meal. Since patients with severe HTG should adhere to a low-fat diet, these findings suggest preserved exposure, and perhaps retained efficacy, in patients taking CaPre in the fasted state or with a low fat diet (Lapointe et al, 2019).

3.2.3 Phase 2 Clinical Trial - COLT

The purpose of the COLT study was to evaluate the efficacy of 0.5, 1.0, 2.0 and 4.0 g/day of CaPre on fasting serum TG over a four week period in patients with mild-to-high HTG as compared to the standard of care (SOC) alone.
A brief outline of the COLT clinical trial design can be found in Table 7.

Table 7 COLT Clinical Trial Design

COLT	
Title	A Randomized Open-label Dose-ranging, Multi-center Trial to Assess the Safety and Efficacy of NKPL66(CaPre™) in the Treatment of Mild-to-high Hypertriglyceridemia
Type	Interventional
Phase	Phase 2

COLT	
Design	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment
Condition	Hypertriglyceridemia
Intervention	Dietary Supplement: CaPre 1 capsule of 0.5 g total CaPre for 4 weeks followed by one 1.0 g capsule per day for an additional 4 weeks Dietary Supplement: CaPre 1 capsule of 1.0 g total CaPre for 4 weeks followed by two 1.0 g capsules per day for an additional 4 weeks Dietary Supplement: CaPre 2 capsules of 1.0 g total CaPre for 4 weeks followed by 4 capsules of 1.0 g total per day for an additional 4 weeks. Drug: Lipid Lowering Medication Patient will be treated as per the standard of care. Dietary Supplement: CaPre 4 capsules of 1 g total per day for 8 weeks.
Arms	Active Comparator: Group A 0.5 g total CaPre from baseline to week 4 and 1.0 g total CaPre from week 4 to week 8 Interventions: • Dietary Supplement: CaPre • Dietary Supplement: CaPre • Dietary Supplement: CaPre • Dietary Supplement: CaPre Active Comparator: Group B 1.0 g total CaPre from baseline to week 4 and 2.0 g total CaPre from week 4 to week Interventions: • Dietary Supplement: CaPre • Dietary Supplement: CaPre • Dietary Supplement: CaPre • Dietary Supplement: CaPre Active Comparator: Group C 2.0 g total CaPre from baseline to week 4 and 4.0 g total CaPre from week 4 to week 8 Interventions: • Dietary Supplement: CaPre • Dietary Supplement: CaPre • Dietary Supplement: CaPre • Dietary Supplement: CaPre Group D Standard of care Intervention: Drug: Lipid Lowering Medication Active Comparator: Group E 4.0 g total CaPre from baseline to week 8 Interventions: • Dietary Supplement: CaPre • Dietary Supplement: CaPre • Dietary Supplement: CaPre • Dietary Supplement: CaPre

COLT	
Primary Outcome	Percent change in fasting blood circulating serum TGs [Time Frame: Between baseline and 4 weeks of treatment.] The percent change in fasting blood circulating serum TGs between baseline and 4 weeks of treatment. Percent change in fasting blood circulating serum TGs [Time Frame: Between baseline and 4 and 8 weeks of treatment.] The percent change in fasting blood circulating serum TGs between baseline and 4 and 8 weeks of treatment.
Secondary Outcomes	Absolute change in fasting plasma TGs [Time Frame: Baseline, Week 4 and Week 8] Absolute change in fasting plasma TGs; Patients achieving target TG fasting plasma levels [Time Frame: Baseline] Percentage (%) of patients achieving target TG fasting plasma levels (TG<1.7 mmol/L); Change in fasting plasma LDL-C, VLDL-C, HDL-C, total cholesterol, hs-CRP and non-HDL [Time Frame: Between baseline and 4 and 8 weeks of treatment] Absolute change in fasting plasma LDL-C, VLDL-C, HDL-C, total cholesterol, hs-CRP and non-HDL Change in fasting plasma concentrations of LDL-C, VLDL-C, HDL-C, total cholesterol, hs-CRP and non-HDL [Time Frame: Between baseline and 4 and 8 weeks of treatment] Percentage (%) change in fasting plasma concentrations of LDL-C, VLDL-C, HDL-C, total cholesterol, hs-CRP and non-HDL; Calculated ratios [Time Frame: The percent change in fasting blood circulating serum TGs Between baseline and 4 and 8 weeks of treatment.] Calculated Ratios: • TC : HDL-C • LDL-C : HDL-C • TGs : HDL-C Change in fasting plasma concentrations of biomarkers [Time Frame: Between baseline and 4 and 8 weeks of treatment] Absolute and percent (%) change in fasting plasma concentrations of biomarkers; • HbA1c • Glucose • CPK
Enrollment	289
Location	Canada
Status	Completed
Sponsor	Acasti Pharma Inc
Investigator	Robert Dufour, M.D. Institut de Recherches Cliniques de Montreal
NCT	NCT01516151
Abbreviations: CPK = Creatinine Phosphokinase; HbA1c = Glycated Hemoglobin; HDL-C = High Density Lipoprotein; hs-CRP = High-sensitivity C Reactive Protein; LDL-C = Low Density Lipoprotein; NKPL66 = CaPre; TC = Total Cholesterol; TG = Triglycerides; VLDL-C = Very Low Density Lipoproteins Cholesterol.	

Results of the COLT study showed CaPre SOC-compared 4-week TG % difference was -8% (p=NS), -16% (p=0.007), -13% (p=0.025) and -18% (p=0.002), for 0.5 g, 1 g, 2 g, and 4 g, respectively, while the SOC-compared 8-week TG % difference was 2% (p=NS), 16% (p=0.021), -6% (p=NS) and -14% (p=0.038), for 0.5 g, 1 g, 2 g, and 4 g, respectively. CaPre 4 g SOC-compared 8-week TC % difference was -7% (p=0.06) and while the non-HDL-C was -10% (p=0.036). Similarly to the beneficial lipid effects, HbA1c was significantly lowered with CaPre 2 g (-18%, p=0.013) and 4 g (-15%, p=0.039).

In this study, CaPre was safe, well-tolerated, with incidence of AEs was similar to SOC.

In summary, results from the COLT study demonstrated:

- CaPre had a positive impact on lowering TGs, although not clear if dose-dependent;
- CaPre reduced triglycerides by 18.0% at 4 weeks and by 14.4% at 8 weeks with a 4.0 g dose, (SOC-compared);
- In addition to lowering triglycerides, CaPre had a positive impact on multiple lipoproteins, including HDL-C and non-HDL-C, without any significant deleterious effects on LDL-C.

This study demonstrates that CaPre has TG lowering properties as well as beneficial overall lipid management effects in patients with mild to high HTG.

3.2.4 Phase 2 Clinical Trial - TRIFECTA

The purpose of the TRIFECTA study was to determine whether CaPre, given at doses of 1.0 g or 2.0 g for 12 weeks, affected fasting plasma TGs in patients with mild to high HTG as compared to a placebo. A brief outline of the TRIFECTA trial design can be found in Table 8.

Table 8 TRIFECTA Clinical Trial Design

TRIFECTA	
Title	A Randomized, Placebo-controlled, Double-blind, Dose-ranging, Multi-centered Trial to Evaluate the Safety and Efficacy of NKPL66 (CaPre) in the Treatment of Mild-to-high Hypertriglyceridemia
Type	Interventional
Phase	Phase 2
Design	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Investigator) Primary Purpose: Treatment
Condition	Hypertriglyceridemia
Intervention	Drug: CaPre CaPre 1.0 g + Placebo 1.0 g daily for 12 weeks. Other: Placebo 2.0 g Placebo (Microcrystalline cellulose) daily for 12 weeks Drug: CaPre CaPre 2.0 g daily for 12 weeks
Arms	Experimental: CaPre 1.0 g Intervention: Drug: CaPre Experimental: CaPre 2.0 g Intervention: Drug: CaPre Placebo Comparator: Placebo Intervention: Other: Placebo
Primary Outcome	Percent (%) change in triglycerides between the baseline and the 12-week assessment visit. [Time Frame: 12 weeks]
Secondary Outcomes	Absolute change in triglycerides between the baseline and the 12-week assessment visit. [Time Frame: 12 weeks]
Enrollment	387
Location	Canada
Status	Completed
Sponsor	Acasti Pharma Inc.

TRIFECTA	
Investigator	Jacques Genest, MD, FRCP(C) Cardiology Division, MUHC
NCT	NCT01455844

Limited results from the TRIFECTA trial are publically available at this time. However, information on Acasti's website indicate that the results from the TRIFECTA trial support CaPre's TG lowering ability.

3.2.5 Phase 3 Clinical Trial – TRILOGY 1

The primary objective of the TRILOGY 1 study is to determine the efficacy of CaPre 4 g daily, compared to placebo, in lowering fasting TG levels in patients with fasting TG levels ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L) after 12 weeks of treatment.
A brief outline of the TRILOGY 1 trial design can be found in Table 9.

Table 9 TRILOGY 1 Clinical Trial Design

TRILOGY 1	
Title	A Phase 3, Multi-center, Placebo-controlled, Randomized, Double-blind 26-week Study to Assess the Safety and Efficacy of CaPre in Patients With Severe Hypertriglyceridemia
Type	Interventional
Phase	Phase 3
Design	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Investigator) Primary Purpose: Treatment
Condition	Hypertriglyceridemia
Intervention	Drug: CaPre 4 x 1 g capsules administered orally once a day for 26 weeks Drug: Placebo 4 x 1 g capsules administered orally once a day for 26 weeks
Arms	Experimental: CaPre Intervention: Drug: CaPre Placebo Comparator: Placebo Intervention: Drug: Placebo
Primary Outcome	Percent change in fasting TG levels from baseline (average of Week -2, -1, and 0) to Week 12 (average of Week 11 and 12) in patients with fasting TG levels ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L). [Time Frame: Week 12]
Secondary Outcomes	Percent change from baseline (average of Week -2, -1, and 0) to Week 12 (average of Week 11 and 12) in non-HDL-C. [Time Frame: Week 12] Percent change from baseline (Week -1 and 0) to Week 12 (average of Week 11 and 12) in VLDL-C (β-quantification). [Time Frame: Week 12] Percent change from baseline (average of Week -2, -1, and 0) to Week 12 (average of Week 11 and 12) in HDL-C. [Time Frame: Week 12] Percent change from baseline (average of Week -1 and 0) to Week 12 (average of Week 11 and 12) in LDL-C (β-quantification). [Time Frame: Week 12]
Enrollment	Estimated at 245
Location	United States

TRILOGY 1	
Status	Ongoing
Sponsor	Acasti Pharma Inc
Investigator	Dariush Mozaffarian, MD, DrPH Tufts Friedman School of Nutrition Science and Policy
NCT	NCT03398005
Abbreviations: HDL-C = High Density Lipoprotein Cholesterol; LDL-C = Low Density Lipoprotein Cholesterol; TG = Triglycerides; VLDL-C = Very Low Density Lipoprotein Cholesterol.	

At the current time the TRILOGY 1 trial has not been completed. TRILOGY 1 has achieved 100% patient randomization, with more than 90% of the patients having completed the trial. Top line results on the primary endpoint of lowering TG are expected in late 2019.

3.2.6 Phase 3 Clinical Trial – TRILOGY 2

The primary objective of the TRILOGY 2 study is to determine the efficacy of CaPre 4 g daily, compared to placebo, in lowering fasting TG levels in subjects with fasting TG levels ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L) after 12 weeks of treatment.
A brief outline of the TRILOGY 2 trial design can be found in Table 10.

Table 10 TRILOGY 2 Clinical Trial Design

TRILOGY 2	
Title	A Phase 3, Multi-center, Multi-national, Placebo-controlled, Randomized, Double-blind 26 Week Study to Assess the Safety and Efficacy of CaPre in Patients With Severe Hypertriglyceridemia
Type	Interventional
Phase	Phase 3
Design	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Investigator) Primary Purpose: Treatment
Condition	Hypertriglyceridemia
Intervention	Drug: CaPre 4 x 1 g capsules administered orally once daily for 26 weeks Drug: Placebo 4 x 1 g capsules administered orally once daily for 26 weeks
Arms	Experimental: CaPre Intervention: Drug: CaPre Placebo Comparator: Placebo Intervention: Drug: Placebo
Primary Outcome	Percent change in fasting TG levels from baseline (average of Week -2, -1, and 0) to Week 12 (average of Week 11 and 12) in patients with fasting TG levels ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L). [Time Frame: Week 12]

TRILOGY 2	
Secondary Outcomes	Percent change from baseline (average of Week -2, -1, and 0) to Week 12 (average of Week 11 and 12) in non-HDL-C. [Time Frame: Week 12] Percent change from baseline (Week -1 and 0) to Week 12 (average of Week 11 and 12) in VLDL-C (β-quantification). [Time Frame: Week 12] Percent change from baseline (average of Week -2, -1, and 0) to Week 12 (average of Week 11 and 12) in HDL-C. [Time Frame: Week 12] Percent change from baseline (average of Week -1 and 0) to Week 12 (average of Week 11 and 12) in LDL-C (β-quantification). [Time Frame: Week 12]
Enrollment	Estimated at 245
Location	Canada, Mexico, United States
Status	Ongoing
Sponsor	Acasti Pharma Inc
Investigator	Dariush Mozaffarian, MD, DrPH Tufts Friedman School of Nutrition Science and Policy
NTC	NCT03361501
Abbreviations: HDL-C = High Density Lipoprotein Cholesterol; LDL-C = Low Density Lipoprotein Cholesterol; TG = Triglycerides; VLDL-C = Very Low Density Lipoprotein Cholesterol.	

At the current time TRILOGY 2 has achieved 100% patient randomization with more than 60% of patients completing the trial. Top line results on the primary endpoint of lowering triglycerides are expected in early 2020.

3.3 CaPre Phase 3 Trial Design

Acasti Pharma's TRILOGY 1 and 2 trials are both phase 3, multi-center, placebo-controlled, randomized, double-blind 26-week studies to assess the safety and efficacy of CaPre in patients with severe hypertriglyceridemia. The clinical trial designs of TRILOGY 1 and 2 are very similar with the main difference being TRILOGY 2 includes multi-national sites in Canada, Mexico and the United States while TRILOGY 1 only includes sites in the United States.

Table 11 compares the design of the pivotal clinical trial for Vascepa (MARINE) with the TRILOGY studies. All three studies are phase 3 trials with similar study designs, primary outcomes and patient populations.

Table 11 Comparison of CaPre and Vascepa Clinical Trial Designs

	CaPre		Vascepa	
	TRILOGY 1	TRILOGY 2	MARINE	ANCHOR
Phase	3	3	3	3
Study Design	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double Primary Purpose: Treatment	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double Primary Purpose: Treatment	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Quadruple Primary Purpose: Treatment	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double Primary Purpose: Treatment

	CaPre		Vascepa	
	TRILOGY 1	TRILOGY 2	MARINE	ANCHOR
Primary Outcome	Percent change in fasting TG levels from baseline (average of Week -2, -1, and 0) to Week 12 (average of Week 11 and 12) in patients with fasting TG levels ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L). [Time Frame: Week 12]	Percent change in fasting TG levels from baseline (average of Week -2, -1, and 0) to Week 12 (average of Week 11 and 12) in patients with fasting TG levels ≥500 mg/dL and ≤1500 mg/dL (≥5.7 mmol/L and ≤17.0 mmol/L). [Time Frame: Week 12]	Difference between AMR101 and placebo treatment groups in triglyceride lowering effect [Time Frame: 12 weeks]	Difference between AMR101 and placebo treatment groups in triglyceride lowering effect [Time Frame: 12 weeks]
Condition	Hypertriglyceridemia	Hypertriglyceridemia	Hypertriglyceridemia	Hypertriglyceridemia
Enrollment	245	245	240 (actual 229)	648 (702)
Patients	Patients with triglycerides ≥500 mg/dL and <1500 mg/dL OR mixed hyperlipidemia, with serum triglycerides ≥500 and <1500 mg/dL	Patients with triglycerides ≥500 mg/dL and <1500 mg/dL OR mixed hyperlipidemia, with serum triglycerides ≥500 and <1500 mg/dL	Patients with very high levels of TG (≥500 mg/dL and ≤2000 mg/dL)	Patients with high levels of TG (≥200 mg/dL to 499 mg/dL)

Available information indicate that the TRILOGY trials are designed, to provide at least 90% power to detect at least a 20% decrease from baseline in TGs between CaPre and placebo.

3.4 Comparison of Omega-3 Fatty Acid Products

Information summarizing and comparing CaPre with prescription omega-3 fatty acid products can be found in Table 12 and Table 13 respectively.

Table 12 summarizes the new drug application number (NDA), regulatory status, company, omega-3 fatty acid type, as well as the form and source.

Table 12 Summary of Omega-3 Fatty Acid Containing Products

Product	CaPre	Vascepa	Epanova	Lovaza	Omtryg
NDA Number	TBD	202057	205060	021654	204977
Status	not yet approved	approved	approved (not yet available)	approved	approved (not yet available)
Company	Acasti	Amarin	AstraZeneca	GlaxoSmithKline	Osmotica
Omega-3	EPA & DHA	EPA (IPE)	EPA, DHA & DPA	EPA & DHA	EPA & DHA
Form	Phospholipids and free fatty acids	Ethyl ester	Free fatty acids	Ethyl ester	Ethyl ester
Source	Krill	Fish	Fish	Fish	Fish
Key Trials	COLT TRIFECTA TRILOGY 1 TRILOGY 2	MARINE ANCHOR REDUCE-IT	EVOLVE ESPRIT STRENGTH		
Abbreviations: DHA = Docosahexaenoic Acid; DPA = Docosapentaenoic Acid; EPA = Eicosapentaenoic Acid; IPE = Icosapent Ethyl; NDA = New Drug Application; TBD = To Be Determined.					

Table 13 compares the overall therapeutic effects of CaPre and other prescription omega-3 fatty acid products including their impact on TG, LDL-C, HDL-C, non-HLD-C levels as well as any food effects.

Table 13 Comparison of the Therapeutic Effects of Omega-3 Fatty Acid Containing Products

Product	Therapeutic Effect				
	TG	LDL-C	HDL-C	Non-HDL-C	Food Effects
CaPre	down	- / down	- / up	down	none
Vascepa	down	-	-	down	significant
Epanova	down	up	-	down	none
Lovaza	down	up	-	down	significant
Abbreviations: HDL-C = High Density Lipoprotein; LDL-C = Low Density Lipoprotein; TG = Triglycerides.					

Competitor information from prescription information and SEC company filings.

The primary components of omega-3 fatty acid prescription formulations, EPA and DHA, have been shown to reduce TG levels. However, they are known to have differing effects on LDL-C and HDL-C (Jacobson et al, 2012; Wei et al, 2011; Davidson et al, 2013). In a meta-analysis comparing the effects of DHA and EPA, in direct comparison studies, DHA was associated with a greater reduction in TG and a greater increase in LDL-C than EPA. DHA also raised HDL-C compared with placebo, whereas EPA did not (Wei et al, 2011). In clinical studies, CaPre showed positive effects on TGs, HDL-C and non-HDL-C, and no deleterious effects (and potentially positive effects) on LDL-C levels.

Together this information indicates that CaPre is at a minimum equivalent to the approved omega-3 fatty acids already on the market since it:

- Significantly lowers serum triglycerides in patients with hypertriglyceridemia
- Has a safety profile similar to other omega-3 fatty acid products

CaPre may have several additional advantages.

- Krill is a more abundant source of omega-3 fatty acids compared to fish, which has the potential to reduce environmental impact and improve sustainability.
- Compared to other products containing both EPA and DHA, CaPre has no effect or has a positive effect on LDL-C (ie lowers LDL-C),
- CaPre may have improved bioavailability, with no food effects.

It should be noted that Acasti will need to conduct at least one additional clinical trial to support FDA approval of a supplemental New Drug Application should Acasti want to expand CaPre's indications to include long-term cardiovascular benefits.

3.5 Triglyceride Lowering Hypothesis

Despite CV risk reduction through potent LDL-C–lowering therapies, substantial residual CV risk remains. Epidemiological, biological, and genetic studies have provided robust evidence of a strong association between elevated TG levels and higher rates of CV events. However, randomized data from large outcome studies across broad populations regarding pharmacological TG lowering and effect on CV outcomes have been mixed. Part of the reason may involve differences between the classes of drugs studied, such as fibrates, niacin, and omega-3 fatty acids.

Recent studies support the concept that add-on therapy to a statin can reduce residual risk and provide CV benefit (Cannon et al, 2015; Blom et al, 2014; Robinson et al, 2015; Sabatine et al, 2015). Two large outcome trials are testing the "triglyceride-lowering hypothesis" with prescription omega-3 fatty acid products in statin-treated patients at high CV risk.

- The Reduction of Cardiovascular Events with EPA-Intervention Trial (REDUCE-IT; NCT01492361) is evaluating 4 g/day icosapent ethyl (prescription EPA only)
- The Statin Residual Risk Reduction With Epanova in High CV Risk Patients With Hypertriglyceridemia study (STRENGTH; NCT02104817) is evaluating omega-3-carboxylic acids (prescription EPA plus DHA).

Data from these trials are expected to help elucidate whether high-dose prescription omega-3 fatty acid products reduce CVD in high-risk, statin-treated patients, such as those commonly encountered in clinical practice.

3.5.1 REDUCE-IT

Vascepa is a highly purified ethyl ester of EPA, which has been reported to improve atherogenic dyslipidemia characterized by reductions in TG, TGR, and factors involved in their metabolism, without raising LDL?C (Bays et al, 2011; Ballantyne et al 2012; Ballantyne et al 2016a; Ballantyne et al 2016b).

The REDUCE-IT trial is a Phase IIIb trial of Vascepa versus placebo. The main study objective is to evaluate whether treatment with Vascepa reduces ASCVD events in statin-treated patients with high baseline TG levels (200 to 499 mg/dl) and elevated CV risk for subsequent clinical events, and whose LDL-C levels with statins are between 40 and 100 mg/dl. A brief outline of the REDUCT-IT trial design can be found in Table 14.

Table 14 REDUCE-IT Clinical Trial Design

REDUCE-IT	
Title	Evaluation of the Effect of AMR101 on Cardiovascular Health and Mortality in Hypertriglyceridemic Patients With Cardiovascular Disease or at High Risk for Cardiovascular Disease: REDUCE-IT (Reduction of Cardiovascular Events With EPA - Intervention Trial)
Type	Interventional
Phase	Phase 3
Design	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Investigator, Outcomes Assessor) Primary Purpose: Prevention
Condition	Cardiovascular Diseases
Intervention	Drug: AMR101 Parallel Assignment Other Name: VASCEPA (icosapent ethyl) Drug: Placebo Parallel Assignment
Arms	Experimental: AMR101 Intervention: Drug: AMR101 Placebo Comparator: Placebo Intervention: Drug: Placebo
Primary Outcome	Composite of CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, and unstable angina determined to be caused by myocardial ischemia by invasive / non-invasive testing and requiring emergent hospitalization. [Time Frame: 4-6 years] Time from randomization to the first occurrence of any component of the composite of the following clinical events: CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, and unstable angina determined to be caused by myocardial ischemia by invasive / non-invasive testing and requiring emergent hospitalization.

REDUCE-IT	
Secondary Outcomes	Composite of CV death, nonfatal MI (including silent MI), or nonfatal stroke. [Time Frame: 4-6 years] Key secondary outcome measure is the time from randomization to the first occurrence of the composite of CV death, nonfatal MI (including silent MI), or nonfatal stroke. Composite of CV death or nonfatal MI (including silent MI). [Time Frame: 4-6 years] Time from randomization to the first occurrence of the composite of CV death or nonfatal MI (including silent MI). Fatal or nonfatal MI (including silent MI). [Time Frame: 4-6 years] Time from randomization to the first occurrence of fatal or nonfatal MI (including silent MI). Non-elective coronary revascularization represented as the composite of emergent or urgent classifications. [Time Frame: 4-6 years] Time from randomization to the first occurrence of non-elective coronary revascularization represented as the composite of emergent or urgent classifications. CV death. [Time Frame: 4-6 years] Time from randomization to the occurrence of CV death. Unstable angina determined to be caused by myocardial ischemia by invasive / non-invasive testing and requiring emergent hospitalization. [Time Frame: 4-6 years] Time from randomization to the first occurrence of unstable angina determined to be caused by myocardial ischemia by invasive / non-invasive testing and requiring emergent hospitalization. Fatal or nonfatal stroke. [Time Frame: 4-6 years] Time from randomization to the first occurrence of fatal or nonfatal stroke. Total mortality, nonfatal MI (including silent MI), or nonfatal stroke. [Time Frame: 4-6 years] Time from randomization to the first occurrence of the composite of total mortality, nonfatal MI (including silent MI), or nonfatal stroke. Total mortality. [Time Frame: 4-6 years.] Time from randomization to the occurrence of death from any cause.
Enrollment	8179
Location	Australia, Canada, India, Netherlands, New Zealand, Poland, Romania, Russian Federation, South Africa, Ukraine, United States
Status	Completed
Sponsor	Amarin Pharma Inc.
Investigator	Deepak L. Bhatt, MD, MPH Brigham and Women's Hospital, 75 Francis Street, Boston
NCT	NCT01492361
Abbreviations: AMR101 = Vascepa; CV = Cardiovascular; EPA = Eicosapentaenoic Acid; MI = Myocardial Infarction.	

In the REDUCE-IT trial a total of 8179 patients were enrolled and followed for a median of 4.9 years. The results showed that 1,606 (55.2%) first primary endpoint events and 1,303 (44.8%) subsequent primary endpoint events occurred (which included 762 second events, and 541 third or more events). Overall, Vascepa reduced total primary endpoint events (61 vs. 89 per 1,000 patient-years for Vascepa versus placebo, respectively; rate ratio: 0.70; 95% confidence interval: 0.62 to 0.78; $p < 0.0001$). Vascepa also reduced totals for each component of the primary composite endpoint, as well as the total key secondary endpoint events (32 vs. 44 per 1,000 patient-years for Vascepa versus placebo, respectively; rate ratio: 0.72; 95% confidence interval: 0.63 to 0.82; $p < 0.0001$) (Bhatt et al, 2019a).

Some of the key results of the REDUCE-IT trial are summarized in Table 15.

Table 15 REDUCE-IT Endpoints

Endpoint	Vascepa Rate per 1000 Patient Years	Vascepa Rate per 1000 Patient Years	Odds Ratio (95% CI)	p Value
Primary composite endpoint	61	89	0.70 (0.62-0.78)	<0.0001
Key secondary composite endpoint	32	44	0.72 (0.63-0.82)	<0.0001
Cardiovascular death	10	12	0.81 (0.66-0.99)	0.0326
Fatal or nonfatal MI	17	26	0.67 (0.56-0.80)	<0.0001
Fatal or nonfatal stroke	6	9	0.68 (0.52-0.91)	0.0078
Coronary revascularization	27	42	0.64 (0.56-0.74)	<0.0001
Hospitalization for unstable angina	7	10	0.69 (0.54-0.89)	0.0041
Abbreviations: CI = Confidence Interval; MI = Myocardial Infarction.				

A primary endpoint event (composite of CV death, myocardial infarction, stroke, coronary revascularization, and hospitalization for unstable angina) occurred in 17.2% of the patients in the Vascepa group, as compared with 22.0% of the patients in the placebo group (hazard ratio, 0.75; 95% CI, 0.68 to 0.83; P<0.001); the corresponding rates of the key secondary endpoint were 11.2% and 14.8% (hazard ratio, 0.74; 95% CI, 0.65 to 0.83; P<0.001). The rates of additional ischemic end points, as assessed according to a pre-specified hierarchical schema, were significantly lower in the Vascepa group than in the placebo group, including the rate of cardiovascular death (4.3% vs. 5.2%; hazard ratio, 0.80; 95% CI, 0.66 to 0.98; P=0.03). A larger percentage of patients in the Vascepa group than in the placebo group were hospitalized for atrial fibrillation or flutter (3.1% vs. 2.1%, P=0.004). Serious bleeding events occurred in 2.7% of the patients in the Vascepa group and in 2.1% in the placebo group (P=0.06) (Bhatt et al, 2019b).

The REDUCE-IT trail authors concluded that among statin-treated patients with elevated TG and CV disease or diabetes, multiple statistical models demonstrate that Vascepa substantially reduced the burden of first, subsequent and total ischemic events.

3.5.2 STRENGTH

Epanova is a formulation of omega-3 fatty acid that has undergone an additional manufacturing step to hydrolyze and distill the ethyl esters into omega-3 free fatty acids (omega-3 carboxylic acids) with a final concentration of 75% EPA and DHA. Given the free fatty acid formulation, Epanova does not require hydrolysis by pancreatic lipase that conventional omega-3 ethyl ester do to maximize intestinal absorption.

A Long‐Term Outcomes Study to Assess Statin Residual Risk Reduction with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia (STRENGTH) trial is currently underway to test the hypothesis that administration of EPA/DHA at a higher dose than typically employed in clinical trials, in addition to conventional medical therapy, affects risk for CV events in patients with high vascular risk.

The STRENGTH study is a randomized, double-blind, placebo-controlled (corn oil), parallel group design that will enroll approximately 13,000 patients with HTG and low HDL and high risk for CVD to be randomized 1:1 to either corn oil + statin or Epanova + statin, once daily, for approximately 3-5 years as determined when the number of MACE outcomes is reached. MACE components include: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, emergent/elective coronary revascularization, or hospitalization for unstable angina.

A brief outline of the STRENGTH trial design can be found in Table 16.

Table 16 STRENGTH Clinical Trial Design

STRENGTH	
Title	A Long-Term Outcomes Study to Assess STatin Residual Risk Reduction With EpaNova in HiGh Cardiovascular Risk PatienTs With Hypertriglyceridemia (STRENGTH)
Type	Interventional
Phase	Phase 3
Design	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Investigator, Outcomes Assessor) Primary Purpose: Treatment
Condition	Eligible Men or Women Considered High Risk for Atherosclerotic Cardiovascular Disease (CVD)
Intervention	Drug: Epanova® (omega-3 carboxylic acids) Adjunct to statin therapy and diet in high risk adult patients for the prevention and reduction of major adverse cardiovascular events (MACE) Other Name: omega-3 carboxylic acids Drug: corn oil control corn oil control arm
Arms	Experimental: EPANOVA Epanova + statin, once daily Intervention: Drug: Epanova® (omega-3 carboxylic acids) Active Comparator: Corn oil Corn oil + Statin Intervention: Drug: corn oil control
Primary Outcome	The primary outcome measure is the time to the first occurrence of any component of the composite of MACE. [Time Frame: Patients will remain in the study until the required number of MACE has occurred. We anticipate that patients will be in the study for up to 5 years.] MACE components include: cardiovascular death, nonfatal MI, nonfatal stroke, emergent/elective coronary revascularization, or hospitalization for unstable angina.
Secondary Outcomes	The composite measure of CV events that include the first occurrence of cardiovascular death, non-fatal MI and non-fatal stroke. [Time Frame: We anticipate that patients will be in the study for up to 5 years. Same for all outcome measures.] The secondary outcome measures will be analyzed the same as outlined above for the primary outcome measures. The composite measure of coronary events that include the first occurrence of cardiac death. [Time Frame: Up to 5 years] The composite measure of coronary events that include the first occurrence of cardiac death (including death due to acute myocardial infarction, sudden cardiac death and death due to cardiovascular procedures), nonfatal MI, emergent/elective coronary revascularization, or hospitalization for unstable angina. The first occurrence of individual components of MACE: cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, emergent/elective coronary revascularization, or hospitalization for unstable angina. [Time Frame: Up to 5 years] Time to CV death [Time Frame: Up to 5 years] Cardiovascular death includes death resulting from: an acute MI, sudden cardiac death, death due to heart failure (HF), death due to stroke, death due to cardiovascular (CV) procedures, death due to CV hemorrhage, and death due to other CV causes.
Enrollment	13086

STRENGTH	
Location	Australia, Belgium, Canada, China, Czechia, Denmark, Estonia, Hungary, Italy, Japan, Korea, Republic of Lithuania, Mexico, Netherlands, New Zealand, Poland, Russian Federation, South Africa, Taiwan, Ukraine, United Kingdom, United States
Status	Estimated completion date September 30, 2020
Sponsor	AstraZeneca
Investigator	Steven Nissen, MD - The Cleveland Clinic Michael Lincoff, MD - The Cleveland Clinic Stephen Nicholls, MD - Adelaide Clinical Research
NCT	NCT02104817
Abbreviations: CVD = Cardiovascular Disease; MACE = Major Adverse Cardiovascular Event; MI = Myocardial Infarction.	

Enrollment for the STRENGTH trial started in October 2014 and was completed on July 12, 2017 (enrolled 13,086 patients). The results of the trial should be available in 2020.

In conclusion, the data from these clinical outcome trials are helping to elucidate whether high-dose prescription omega-3 fatty acid products reduce CVD in high-risk, statin-treated patients, such as those commonly encountered in clinical practice. If the results from the REDUCE-IT trial hold true in the STRENGTH trial, it could have a significant positive impact on the future omega-3 fatty acid commercial market.

4 Conclusions

Heart disease is the leading cause of death for American men and women, accounting for one out of every four deaths each year. In several epidemiologic and interventional studies, HTG has been identified as a potential risk factor for CVD. Therapeutic lifestyle changes are the first line of HTG treatment. Statins can lower TG levels but are often insufficient. Additional treatment is often needed with options including fibrates, niacin and omega-3 fatty acids however, fibrates and niacin have significant side effects which limit their use.
Omega-3 fatty acids may be an effective alternative to fibrates and niacin for the treatment and management of HTG. Several prescription omega-3 fatty acid products have been FDA approved for use in the US as an adjunct to diet for reducing TG levels in adult patients with severe HTG (≥500 mg/dL).

The prescription omega-3 fatty acid products fall into one of three formulations:

- Omega-3 fatty acid ethyl esters (Lovaza®, Omtryg™, and some generics)
- Icosapent ethyl (Vascepa®)
- Omega-3 carboxylic acids (Epanova®)

All prescription omega-3 formulations have been shown to be safe and well tolerated, and demonstrate a lack of drug-drug interactions with other lipid-lowering drugs.

Acasti Pharma is a biopharmaceutical company focused on the research, development and commercialization of prescription drugs using omega-3 fatty acids. Acasti Pharma is currently developing an omega-3 fatty acid product CaPre for treatment of severe HTG. CaPre, is a krill oil-derived mixture of PUFA, primarily composed of the omega-3 fatty acids, EPA and DHA, which are present as a combination of PLs and FFAs.

Acasti Pharma is seeking FDA approval of CaPre in the US. To date Acasti Pharma has carried out six clinical trials, four of which have been completed (2 x Phase 1 studies plus COLT and TRIFECTA) and two phase 3 studies which are currently in progress (TRILOGY 1 and TRILOGY 2).

Results from a phase 1 bioavailability study indicate:

- The bioavailability of the phospholipid and free fatty acid forms of eicosapentaenoic acid and docosahexaenoic acid found in CaPre are far less affected when taken on an empty stomach than the ethyl ester forms found in Lovaza
- The bioavailability of Lovaza is maximal following administration with a high fat meal but is dramatically reduced under fasting conditions

Since patients with severe hypertriglyceridemia should adhere to a low fat diet, these findings suggest preserved exposure, and perhaps retained efficacy in patients taking CaPre in either the fasted state or with a low fat diet.

The results from a phase 2 study indicate:

- CaPre had a positive impact on lowering triglycerides, although not clear if dose-dependent;
- CaPre reduced triglycerides by 18.0% at 4 weeks and by 14.4% at 8 weeks (4.0 g dose of CaPre compared to standard of care); and
- CaPre had a positive impact on multiple lipoproteins, including HDL-C and non-HDL-C, without any significant deleterious effects on LDL-C.

This study demonstrated that CaPre has triglyceride lowering properties as well as beneficial overall lipid management effects in patients with mild to high hypertriglyceridemia.

CaPre may also have several additional advantages including:

- Krill is a more abundant source of omega-3 fatty acids compared to fish,
- CaPre has no effect or has a positive effect on LDL-C (ie lowers LDL-C), and
- CaPre may have improved bioavailability, with no food effects.

The results from the two upcoming CaPre TRILOGY trials should help to confirm and extend these encouraging initial results.

Epidemiological, biological, and genetic studies have provided robust evidence of a strong association between elevated TG levels and higher rates of CV events. Two large outcome trials are testing the triglyceride-lowering hypothesis with prescription omega-3 fatty acid products in statin-treated patients at high CV risk (REDUCE-IT and STRENGTH).

In the REDUCE-IT trial, a total of 8179 patients were enrolled and followed for approximately 5 years. A primary end-point event (composite of CV death, myocardial infarction, stroke, coronary revascularization, and hospitalization for unstable angina) occurred in 17.2% of the patients in the omega-3 fatty acid (Vascepa) group, compared to 22.0% of the patients in the placebo group. The corresponding rates of the key secondary end point were 11.2% and 14.8%. The rates of additional ischemic end points were significantly lower in the omega-3 fatty acid group than in the placebo group, including the rate of cardiovascular death (4.3% vs. 5.2%).

Based on this information the REDUCE-IT trial authors concluded that among statin-treated patients with elevated triglycerides and cardiovascular disease or diabetes, multiple statistical models demonstrate that the omega-3 fatty acid (Vascepa) substantially reduced the burden of first, subsequent and total ischemic events.

Enrollment for the STRENGTH trial started in October 2014 and was completed on July 12, 2017 (13,086 patients). The results of the STRENGTH trial, which are due in 2020, should hopefully confirm and extend the REDUCE-IT results and conclusions.

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