AMARIN CORP PLC\UK
Form 10-K
February 28, 2013
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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form 10-K

þ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the fiscal year ended December 31, 2012

OR

¨ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the transition period from to

Commission File No. 0-21392

Amarin Corporation plc

(Exact name of registrant as specified in its charter)

England and Wales	**Not applicable**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**

2 Pembroke House

Upper Pembroke Street 28-32, Dublin 2, Ireland

(Address of principal executive offices)

+353 (0) 1 6699 020

(Registrant s telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act:

Title of Each Class	Name of Each Exchange on Which Registered
American Depositary Shares, each representing one Ordinary Share	
Ordinary Shares, 50 pence par value per share	The NASDAQ Stock Market LLC

Securities registered pursuant to Section 12(g) of the Act:

None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. YES þ NO ¨

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. YES ¨ NO þ

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. YES þ NO ¨

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). YES þ NO ¨

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant s knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ¨

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of large accelerated filer, accelerated filer and smaller reporting company in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer þ	Accelerated filer ¨
Non-accelerated filer ¨ (Do not check if a smaller reporting company)	Smaller reporting company ¨

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). YES ¨ NO þ

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant as of June 30, 2012 was approximately $1.92 billion, based upon the closing price on the NASDAQ Capital Market reported for such date.

149,991,187 shares held as American Depository Shares (ADS), each representing one Ordinary Share, 50 pence par value per share, and 380,694 Ordinary Shares, were outstanding as of February 20, 2013.

DOCUMENTS INCORPORATED BY REFERENCE

Certain information required to be disclosed in Part III of this report is incorporated by reference from the registrant s definitive proxy statement to be filed not later than 120 days after the end of the fiscal year covered by this report.

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PART I

SPECIAL NOTE REGARDING

FORWARD-LOOKING STATEMENTS AND INDUSTRY DATA

This Annual Report on Form 10-K contains forward-looking statements. All statements other than statements of historical fact contained in this Annual Report on Form 10-K are forward-looking statements, including statements regarding the progress and timing of our clinical programs, regulatory filings and commercialization activities, and the potential clinical benefits, safety and market potential of our product candidates, as well as more general statements regarding our expectations for future financial and operational performance, regulatory environment, and market trends. In some cases, you can identify forward-looking statements by terminology such as may, would, should, could, expects, aim plans, anticipates, believes, estimates, predicts, projects, potential, or continue ; the negative of these terms; or other comparable ter These statements include but are not limited to statements regarding the commercial success of Vascepa in its first approved indication, the MARINE indication, the potential for, and timing of, approval of the Vascepa Supplemental New Drug Application, or sNDA, by the United States Food and Drug Administration, or FDA, in its potential second indication, the ANCHOR indication; the safety and efficacy of our product candidates; the scope of our intellectual property protection and the likelihood of securing additional patent protection and regulatory exclusivity; estimates of the potential markets for our product candidates; the likelihood of qualifying additional third party manufacturing suppliers and estimates of the capacity of manufacturing and other facilities to support our products; our operating and growth strategies; our industry; our projected cash needs, liquidity and capital resources; and our expected future revenues, operations and expenditures.

Forward-looking statements are only current predictions and are subject to known and unknown risks, uncertainties, and other factors that may cause our or our industry s actual results, levels of activity, performance, or achievements to be materially different from those anticipated by such statements. These factors include, among other things, those listed under Risk Factors in Item 1A of Part I of this Annual Report on Form 10-K and elsewhere in this Annual Report on Form 10-K. These and other factors could cause results to differ materially from those expressed in these forward-looking statements.

Although we believe that the expectations reflected in the forward-looking statements contained in this Annual Report on Form 10-K are reasonable, we cannot guarantee future results, performance, or achievements. Except as required by law, we are under no duty to update or revise any of such forward-looking statements, whether as a result of new information, future events or otherwise, after the date of this Annual Report on Form 10-K.

Unless otherwise indicated, information contained in this Annual Report on Form 10-K concerning our product candidates, the number of patients that may benefit from these product candidates and the potential commercial opportunity for our product candidates, is based on information from independent industry analysts and third-party sources (including industry publications, surveys, and forecasts), our internal research, and management estimates. Management estimates are derived from publicly available information released by independent industry analysts and third-party sources, as well as data from our internal research, and based on assumptions made by us based on such data and our knowledge of such industry, which we believe to be reasonable. None of the sources cited in this Annual Report on Form 10-K has consented to the inclusion of any data from its reports, nor have we sought their consent. Our internal research has not been verified by any independent source, and we have not independently verified any third-party information. While we believe that such information included in this Annual Report on Form 10-K is generally reliable, such information is inherently imprecise. In addition, projections, assumptions, and estimates of our future performance are necessarily subject to a high degree of uncertainty and risk due to a variety of factors, including those described in Risk Factors in Item 1A of Part I of this Annual Report on Form 10-K and elsewhere in this Annual Report on Form 10-K. These and other factors could cause results to differ materially from those expressed in the estimates made by the independent parties and by us.

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Item 1. ***Business***

References in this report to Amarin, the Company, we, our and us refer to Amarin Corporation plc and its subsidiaries, on a consolidated basis, unless otherwise indicated.

This Annual Report on Form 10-K includes the registered and unregistered trademarks and service marks of other parties.

Amarin Corporation plc (formerly Ethical Holdings plc) is a public limited company incorporated under the laws of England and Wales. Amarin Corporation plc was originally incorporated in England as a private limited company on March 1, 1989 under the Companies Act 1985, and re-registered in England as a public limited company on March 19, 1993.

Our registered office is located at One New Change, London EC4M 9AF, England. Our principal offices are located at 2 Pembroke House, Upper Pembroke Street 28-32, Dublin 2 Ireland. Our primary office in the United States is located at 1430 Route 206, Bedminster, NJ 07921, USA. Our telephone number at that location is (908) 719-1315.

For purposes of this Annual Report on Form 10-K, our ordinary shares may also be referred to as common shares or common stock.

Overview

We are a biopharmaceutical company focused on the commercialization and development of therapeutics to improve cardiovascular health. On July 26, 2012, we received approval from the U.S. Food and Drug Administration, or FDA, to market and sell our lead product Vascepa® (icosapent ethyl) capsules (formerly known as AMR101) as an adjunct to diet to reduce triglyceride, or TG, levels in adult patients with severe (TG ³500mg/dL) hypertriglyceridemia, which we sometimes refer to as the MARINE indication. Vascepa became commercially available in the United States by prescription in January 2013, when we commenced sales and shipments to our network of U.S.-based wholesalers. On January 28, 2013, we commenced our full commercial launch of Vascepa in the United States for the MARINE indication.

We are also developing Vascepa for the treatment of patients with high (TG ³ 200 mg/dL and <500 mg/dL) triglyceride levels who are also on statin therapy for elevated low-density lipoprotein cholesterol, or LDL-C, levels which we refer to as mixed dyslipidemia. We refer to this second proposed indication for Vascepa as the ANCHOR indication. In late February 2013, we submitted a Supplemental New Drug Application, or sNDA, for the ANCHOR indication with the FDA. If our sNDA is accepted by the FDA, assuming a ten-month FDA review period, we expect the FDA to assign a Prescription Drug User Fee Act, or PDUFA, action date which is not later than the end of 2013.

In December 2011, we announced commencement of patient dosing in our cardiovascular outcomes study of Vascepa, titled REDUCE-IT (Reduction of Cardiovascular Events with EPA Intervention Trial), that is designed to evaluate the efficacy of Vascepa in reducing major cardiovascular events in a high risk patient population on statin therapy. Based on communications with the FDA, we believe that we are required to be substantially underway with a cardiovascular outcomes study at the time of the submission of our sNDA seeking approval of the ANCHOR indication. We believe that we achieved this requirement prior to submitting the sNDA. However, there can be no assurance that the FDA will agree with our assessment or that they will accept our sNDA for the ANCHOR indication. We do not believe the final results of the REDUCE-IT study will be required for FDA approval of Vascepa for the ANCHOR indication.

Hypertriglyceridemia refers to a condition in which patients have high levels of triglycerides in the bloodstream. Triglycerides are fats in the blood. It is estimated that over 40 million adults in the United States

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have elevated triglyceride levels greater than 200mg/dL and approximately 4.0 million people in the United States have severely high (TG ³500mg/dL) triglyceride levels, commonly known as very high triglyceride levels. According to *The American Heart Association Scientific Statement on Triglycerides and Cardiovascular Disease* (2011), triglycerides also provide important information as a marker associated with the risk for heart disease and stroke, especially when an individual also has low high-density lipoprotein, or HDL-C (often referred to as good cholesterol), and elevated levels of LDL-C (often referred to as bad cholesterol). Guidelines for the management of very high triglyceride levels suggest that reducing triglyceride levels is the primary goal in patients to reduce the risk of acute pancreatitis. The effect of Vascepa on cardiovascular mortality and morbidity in patients with hypertriglyceridemia has not been determined. The effect of Vascepa on the risk for pancreatitis in patients with hypertriglyceridemia has not been determined.

The potential efficacy and safety of Vascepa was studied in two Phase 3 clinical trials, the MARINE trial and the ANCHOR trial. At a daily dose of 4 grams of Vascepa, the dose at which Vascepa is FDA approved, these trials showed favorable clinical results in their respective patient populations in reducing triglyceride levels without increasing LDL-C levels in the MARINE trial and with a statistically significant decrease in LDL-C levels in the ANCHOR trial. These trials also showed favorable results, particularly with the 4-gram dose of Vascepa, in other important lipid and inflammation biomarkers, including apolipoprotein B (apo B), non-high-density lipoprotein cholesterol (non-HDL-C), total-cholesterol (TC), very low-density lipoprotein cholesterol (VLDL-C), lipoprotein-associated phospholipase A2 (Lp-PLA2), and high sensitivity C-reactive protein (hs-CRP). In these trials, the most commonly reported adverse reaction (incidence >2% and greater than placebo) in Vascepa-treated patients was arthralgia (joint pain) (2.3% for Vascepa vs. 1.0% for placebo).

Commercialization of Vascepa

Vascepa became commercially available in the United States by prescription in January 2013, when we commenced sales and shipments to our network of U.S.-based wholesalers. On January 28, 2013, we commenced our full commercial launch of Vascepa in the United States for use in the MARINE indication. In preparation for our commercial launch, we recently hired and trained a direct sales force of approximately 275 sales representatives. We also employ various marketing and medical affairs personnel to support our commercialization of Vascepa. Our clinical and commercial supply is provided to us under agreements with various third-party suppliers. As of the date of this Annual Report, we have announced that 18 patent applications in the United States have been either issued or allowed and more than 30 additional patent applications are pending in the United States. We are also pursuing patent applications related to Vascepa in multiple jurisdictions outside the United States. These patent applications are part of our strategy to protect the commercial potential of Vascepa, which generally includes obtaining and maintaining intellectual property rights, maintaining trade secrets, seeking regulatory exclusivity and taking advantage of manufacturing barriers to entry.

We believe that our sales and marketing teams are well positioned to support the commercialization of Vascepa for the MARINE indication. We also believe that a larger sales effort will be required to best support the commercialization of Vascepa for the ANCHOR indication, assuming FDA approval of the ANCHOR indication. To support the continued commercialization of Vascepa, we intend to consider strategic opportunities with larger pharmaceutical companies. From time to time we have held discussions with larger pharmaceutical companies on potential collaborations and other strategic opportunities, and we intend to continue having discussions regarding such opportunities in the future. These strategic opportunities may include licensing or similar transactions, joint ventures, partnerships, strategic alliances, business associations, or a sale of the company. However, we cannot estimate the timing of any such potential strategic transaction, and no assurance can be given that we will enter into any such strategic transaction. Until such time when we enter into such a strategic transaction, if ever, we plan to continue to execute on our plans to market and sell Vascepa on our own.

The U.S. market is currently our primary focus for Vascepa. Opportunities to seek regulatory approval and to market and sell Vascepa outside of the United States are also under evaluation.

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Financial Position

We believe that our cash balance of $260.2 million at December 31, 2012 is sufficient to fund our projected operations for at least the next twelve months, including commercialization of Vascepa in the United States for the MARINE indication, preparations for commercialization of Vascepa in the United States for the ANCHOR indication and the advancement of the REDUCE-IT cardiovascular outcomes study. In order to fund our commercialization plans, in particular to fully support the launch, marketing and sale of Vascepa in the ANCHOR indication, we will likely need enter into a strategic collaboration or raise additional capital.

Lipid Disorders and Cardiovascular Disease

Heart attacks, strokes and other cardiovascular events represent the leading cause of death and disability among men and women in western societies. According to the *2012 At-A-Glance Report* from the U.S. Center for Disease Control, more than 1 out of every 3 adults in the U.S. (approximately 83 million) currently lives with one or more types of cardiovascular disease; an estimated 935,000 heart attacks and 795,000 strokes occur each year; an estimated 71 million adults have high cholesterol (i.e. high levels of low-density lipoprotein cholesterol, or LDL-C); and only 1 out of 3 adults with high LDL cholesterol has the condition under control.

Hypertriglyceridemia refers to a condition in which patients have high levels of triglycerides in the bloodstream and has been recognized as an independent risk factor for cardiovascular disease. Triglyceride levels provide important information as a marker associated with the risk for heart disease and stroke, especially when an individual also has low HDL-C and elevated levels of LDL-C. The effect of Vascepa on cardiovascular mortality and morbidity in patients with hypertriglyceridemia has not been determined.

Guidelines for the management of very high triglyceride levels (≥500 mg/dL) suggest that reducing triglyceride levels is the primary goal in patients to reduce the risk of acute pancreatitis. Under these guidelines, targeting LDL-C goal for all patients remains important. Other important parameters to consider in patients with very high TGs include levels of apo B, non HDL-C, VLDL-C, TC, and HDL-C. The effect of Vascepa on the risk for pancreatitis in patients with hypertriglyceridemia has not been determined.

It is estimated that over 40 million adults in the United States have elevated triglyceride levels >200mg/dL and approximately 4.0 million people in the United States have very high triglyceride levels (≥500 mg/dL). Since 1976, mean triglyceride levels have increased, in concert with the growing epidemic of obesity, insulin resistance, and type 2 diabetes mellitus. In contrast, mean LDL-C levels have decreased.

Mixed dyslipidemia refers to a condition in which patients have a combination of two or more lipid abnormalities including elevated triglycerides, low HDL-C, and/or elevated LDL-C. Both hypertriglyceridemia and mixed dyslipidemia are components of a range of lipid disorders collectively referred to as dyslipidemia. Dyslipidemia has been linked to atherosclerosis, commonly referred to as hardening of the arteries.

Limitations of Current Therapies

It is estimated that fewer than 4% of U.S. adults with triglyceride levels ³ 200 mg/dL are currently receiving prescription medication for lowering triglycerides. Many of these patients are taking statin therapy directed primarily at lowering their LDL-C levels.

The leading treatments to lower triglyceride levels are fibrates (fenofibrate and gemfibrozil), statins and a prescription only omega-3 fatty acid, known as Lovaza® in the United States, and as Omacor® in Europe. The use of fenofibrates can lead to abnormal liver function tests (an increase in ALT (alanine transaminase) or AST (aspartate transaminase), which are liver enzymes, and are commonly measured clinically as a part of a diagnostic liver function test to determine liver health), especially when used with statins. The use of gemfibrozil can lead to rhabdomyolysis (severe breakdown of muscles), especially when used with a statin. Lovaza is comprised of omega-3 ethyl esters, which the FDA has described as a complex mixture of eicosapentanoic acid,

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or EPA, docosahexaenoic acid, or DHA, and other fatty acids. We believe that DHA may increase LDL-C levels and thereby partially offset one of the typically desired benefits of lipid-lowering therapies, which is lowering LDL-C. Also, in 2012, the FDA required an update to Lovaza product labeling to reflect the risk that Lovaza may increase the frequency of a heart rhythm problem known as atrial fibrillation, or heart flutter.

Potential Benefits and Market Opportunity for Vascepa

Vascepa is comprised of not less than 96% pure icosapent ethyl, or ethyl-EPA, and contains no DHA. We believe that the removal of DHA mitigates against the LDL-C raising effect observed in omega-3 formulations that include DHA, as well removing the fishy taste and smell that is sometimes associated with DHA. Based on the results of the MARINE trial, Vascepa was the first omega-3 based product to demonstrate statistically significant triglyceride reduction without a statistically significant increase in LDL-C in this very high triglyceride population.

We believe that the results of the MARINE trial and Vascepa s EPA only/DHA-free composition suggest that Vascepa has the potential to become a best-in-class triglyceride-lowering agent in the United States and the European Union. In addition, currently no omega-3 based product is approved in the United States for lowering high triglycerides in patients with mixed dyslipidemia. We believe that Vascepa has the potential to become first-in-class in the prescription-only omega-3 market for lowering triglycerides in patients with mixed dyslipidemia.

We believe the potential market for Vascepa is large and growing. We estimate that drug treatment for hypercholesterolemia patients exceeds $53 billion per year in the United States, with sales dominated by statin therapies. U.S. sales of fibrates as a class of products were approximately $3.1 billion in 2012 with Tricor and Trilipix leading the class. U.S. gross sales of Lovaza in 2012 were over $1.3 billion.

Commercialization of Vascepa

Vascepa became commercially available in the United States by prescription in January 2013, when we commenced sales and shipments to our network of U.S.-based wholesalers. On January 28, 2013, we commenced our full commercial launch of Vascepa in the United States for use in the MARINE indication. In preparation for our commercial launch, we recently hired and trained a direct sales force of approximately 275 sales representatives. We also employ various marketing and medical affairs personnel to support our commercialization of Vascepa. We continue to conduct the REDUCE-IT trial and will consider additional trials to further expand the potential indications of use for Vascepa. We do not believe the final results of our REDUCE-IT cardiovascular outcomes study will be required for FDA approval of Vascepa for use in the ANCHOR indication.

We believe that our sales and marketing teams are well positioned to support the commercialization of Vascepa for the MARINE indication. We also believe that a larger sales force will be required to best support the commercialization of Vascepa for the ANCHOR indication, assuming FDA approval for the ANCHOR indication. To support the continued commercialization of Vascepa, we intend to consider strategic opportunities with larger pharmaceutical companies. From time to time we have held discussions with larger pharmaceutical companies on potential collaborations and other strategic opportunities, and we intend to continue having discussions regarding such opportunities in the future. These strategic opportunities may include licensing or similar transactions, joint ventures, partnerships, strategic alliances, business associations, or a sale of the company. However, we cannot estimate the timing of any such potential strategic transaction and no assurance can be given that we will enter into any such strategic transaction. Until such time when we enter into such a strategic transaction, if ever, we plan to continue to execute on our plans to market and sell Vascepa on our own.

The U.S. market is currently our primary focus for Vascepa. Opportunities to seek regulatory approval of, and market and sell, Vascepa outside of the United States are also under evaluation.

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Clinical Trials

The MARINE Trial

The MARINE trial, the largest study ever conducted with the omega-3 fatty acid ethyl EPA in treating patients with very high triglycerides (³500 mg/dL), was a Phase 3, multi-center, placebo-controlled, randomized, double-blind, 12-week study. Patients were randomized into three treatment arms for treatment with Vascepa 4 gram/day, 2 gram/day or placebo. Patient enrollment in this trial began in December 2009, and enrollment and randomization was completed in August 2010 at 229 patients. The primary endpoint in the trial was the percentage change in triglyceride level from baseline compared to placebo after 12 weeks of treatment. The MARINE study was required to meet a stringent level of statistical significance of 1% ($p < 0.01$) in our Special Protocol Assessment, or SPA, agreement with the FDA.

On November 29, 2010, we reported top-line data for the MARINE trial. In the trial, Vascepa met its primary endpoint at doses of 4 grams and 2 grams per day with median placebo-adjusted reductions in triglyceride levels of 33% ($p < 0.0001$) compared to placebo for 4 grams and 20% ($p = 0.0051$) compared to placebo for 2 grams. The median baseline triglyceride levels were 703 mg/dL, 680 mg/dL and 657 mg/dL for the patient groups treated with placebo, 4 grams of Vascepa and 2 grams of Vascepa, respectively.

In a pre-specified secondary analysis in the subgroup of patients with baseline triglyceride > 750 mg/dL, representing 39% of all patients, the effect of Vascepa in reducing triglyceride levels compared to placebo was 45% for 4 grams and 33% for 2 grams, both statistically significant ($p = 0.0001$ for 4 grams and $p= 0.0016$ for 2 grams, respectively). The median baseline triglyceride levels in this subgroup were 1052 mg/dL, 902 mg/dL and 948 mg/dL for placebo, 4-gram and 2-gram groups, respectively. Twenty-five percent of patients in this trial were also on background statin therapy. These patients had greater median reduction in triglyceride levels, which was also statistically significant.

Importantly, the significant reduction in triglycerides was not associated with a statistically significant increase in median LDL-C compared to placebo at either dose (-2.3% for the 4-gram group and +5.2% for the 2-gram group [both p=NS]). In addition, there was a statistically significant decrease in median non-HDL-C (total cholesterol less so-called good cholesterol) compared to placebo with both of the Vascepa treated groups (-18% for the 4-gram group [$p < 0.001$] and -8% for the 2-gram group [$p < 0.05$]).

The MARINE trial results also included statistically significant reductions compared to placebo in several important lipid and inflammatory biomarkers, including apo B (apolipoprotein B) (8.5%), Lp-PLA2 (lipoprotein-phospholipase A2) (13.6%), VLDL-C (very low-density lipoprotein cholesterol) (28.6%), Total Cholesterol (16.3%), and hsCRP (high-sensitivity C-reactive protein) (36.0%) at the 4-gram dose. For these achieved endpoints, p-values were <0.01 for most and <0.05 for all. Apo B (apolipoprotein B) is believed to be a sensitive biomarker of cardiovascular risk and may be a better predictor of cardiovascular risk than LDL-C. Lp-PLA2 is an enzyme found in blood and atherosclerotic plaque; high levels have been implicated in the development and progression of atherosclerosis.

In the MARINE trial, patients treated with 4 grams per day of Vascepa experienced a significant reduction in median placebo-adjusted lipoprotein particle concentrations of total LDL and small LDL. When looking at lipoprotein particle concentrations and sizes as measured with nuclear magnetic resonance spectroscopy, Vascepa 4 grams per day, compared with placebo, significantly reduced median total LDL particle count by 16.3% ($p=0.0006$), which is an important factor in atherogenesis. LDL particle count and apo B are important risk markers for the prediction of cardiovascular events. Small LDL particle count, which is a common risk factor for cardiovascular events in patients with diabetes, was reduced by 25.6% ($p<0.0001$) compared with placebo. Vascepa 2 grams per day, compared with placebo, significantly reduced median small LDL particle count by 12.8% ($p <0.05$) and reduced median total LDL particle count by 1.1% (NS). LDL particle size did not change significantly for the 2 or 4 grams doses.

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Vascepa was well tolerated in the MARINE trial, with a safety profile comparable to placebo and there were no treatment-related serious adverse events observed. No significant changes in fasting blood glucose, hemoglobin A1C, vital signs, electrocardiograms, or liver or kidney function were observed with either Vascepa dose.

Patients enrolled in the MARINE trial were given the option to be treated with Vascepa for a period of up to 40 weeks after their last dose in the double-blind portion of the trial. Once participants completed the randomized, double blind, placebo-controlled 12-week MARINE registration trial, patients in all three randomized groups (4 grams, 2 grams and placebo) were offered the opportunity to participate in the open label extension, or OLE, phase. Patients in the OLE phase received 4 grams per day of Vascepa for a period of up to an additional 40 weeks. As is typical of such extension phases, the OLE phase was not a controlled trial, as differentiated from the randomized, double blind, placebo-controlled 12-week MARINE registration trial. In the OLE phase, participants were not randomized at entry, Vascepa administration was open-label (and thus not blinded), and no placebo group was maintained. Also, once patients entered in the OLE phase, investigators were free to add or modify other lipid-altering nutritional, lifestyle and drug treatment regimens. Given the lack of randomization, the open-label design, the addition of various other lipid-altering drugs and changes to doses of existing lipid-altering drugs, as well as the lack of placebo control, neither we nor our independent advisors were able to draw efficacy conclusions from the data. However, we have concluded that the MARINE OLE phase revealed no new safety signals after an additional 40 weeks of exposure to Vascepa, whether used alone or in combination with other lipid-altering regimens.

The ANCHOR Trial

The ANCHOR trial was a multi-center, placebo-controlled, randomized, double-blind, 12-week pivotal study in patients with high triglycerides (³ 200 and <500 mg/dL) who were also receiving optimized statin therapy. Patients were randomized into three arms for treatment with Vascepa 4 gram/day, 2 gram/day or placebo. Patient enrollment in this trial began in January 2010, and enrollment and randomization was completed in February 2011 at 702 patients. The primary endpoint in the trial was the percentage change in triglyceride level from baseline compared to placebo after 12 weeks of treatment.

In April 2011, we reported top-line results from the ANCHOR trial. The ANCHOR trial met its primary endpoint at doses of 4 grams and 2 grams per day with median placebo-adjusted reductions in triglyceride levels of 21.5% (p<0.0001 value) for 4 grams and 10.1% (p=0.0005) for 2 grams. The median baseline triglyceride levels were 259 mg/dL, 265 mg/dL and 254 mg/dL for the patient groups treated with placebo, 4 grams and 2 grams of Vascepa per day, respectively. The analysis of subgroups by baseline triglyceride tertiles showed that higher baseline triglycerides resulted in greater triglyceride reductions.

One of the trial s secondary endpoints was to demonstrate a lack of elevation in LDL-C, the primary target of cholesterol lowering therapy. The trial s non-inferiority criterion for LDL-C was met at both Vascepa doses. The upper confidence boundaries for both doses were below the pre-specified +6% LDL-C threshold limit. At the 4-gram dose the upper confidence boundary was below zero (-1.7%) and at the 2-gram dose the upper confidence boundary was close to zero (0.5%). For the 4 grams per day group, LDL-C decreased significantly by 6.2% from baseline versus placebo, demonstrating superiority over placebo (p=0.0067). For the 2-gram group, LDL-C decreased by 3.6% from baseline versus placebo (p=0.0867), which is not a statistically significant decrease.

Other secondary efficacy endpoints included the median placebo-adjusted percent change in non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (apo B), and lipoprotein-associated phospholipase A2 (Lp-PLA2). The 4-gram dose was associated with statistically significant reductions in non-HDL-C (13.6%, p<0.0001), apo B (9.3%, p<0.0001), Lp-PLA2 (19%, p<0.0001) and high-sensitivity C-reactive protein (hsCRP) (22%, p<0.001), at week 12 compared to placebo. In addition to the previously reported favorable lipid effects of Vascepa on hypertriglyceridemic patients in the MARINE and ANCHOR studies, a recently published analysis of these studies showed that the Vascepa 4-gram daily dose also significantly decreased levels of the inflammatory marker oxidized low-density lipoprotein relative to placebo.

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Vascepa was well tolerated in the ANCHOR trial with a safety profile comparable to placebo and there were no treatment-related serious adverse events observed. No significant changes in fasting blood glucose, hemoglobin A1C, vital signs, electrocardiograms, or liver or kidney function were observed with either Vascepa dose.

Observed Efficacy of Ethyl-EPA

In Japan, ethyl-EPA is marketed under the product name of Epadel by Mochida Pharmaceutical Co. and is indicated for hyperlipidemia and peripheral vascular disease. Clinical data from Japan suggests that Epadel is effective in reducing triglycerides. In addition, in an outcomes study called the Japan EPA Lipid Intervention Study, or JELIS study, which consisted of more than 18,000 patients followed over multiple years, Epadel, when used in conjunction with statins, was shown to reduce cardiovascular events by 19% compared to the use of statins alone. In this study, cardiovascular events decreased by approximately 53% compared to statins alone in the subset of patients with triglyceride levels of ³ 150 mg/dL (average 269 mg/dL at entry) and HDL-C <40 mg/dL.

Observed Clinical Safety of Vascepa

Prior to commencing the MARINE and ANCHOR trials, we conducted a pre-clinical program for Vascepa, including toxicology and pharmacology studies. In addition, we previously investigated Vascepa in central nervous system disorders in several double-blind, placebo-controlled studies, including Phase 3 trials in Huntington s disease. Over 1,000 patients have been dosed with Vascepa in these studies, with over 100 receiving continuous treatment for a year or more. In all studies performed to date, Vascepa has shown a favorable safety and tolerability profile. In both the MARINE and ANCHOR trials, patients dosed with Vascepa demonstrated a safety profile similar to placebo. There were no treatment-related serious adverse events in the MARINE study or in the ANCHOR study. In the MARINE and ANCHOR trials, the most commonly reported adverse reaction (incidence >2% and greater than placebo) in Vascepa treated patients was arthralgia (joint pain) (2.3% for Vascepa vs. 1.0% for placebo).

In addition to the MARINE and ANCHOR trials, we completed a 28-day pharmacokinetic study in healthy volunteers, a 26-week study to evaluate the toxicity of Vascepa in transgenic mice and multiple pharmacokinetic drug-drug interaction studies in healthy subjects in which we evaluated the effect of Vascepa on certain common prescription drugs. All findings from these studies were consistent with our expectations and confirmed the overall safety profile of Vascepa.

The REDUCE-IT Study

In August 2011, we reached agreement with the FDA on an SPA for the design of the REDUCE-IT (Reduction of Cardiovascular Events with EPA Intervention Trial) cardiovascular outcomes study. An SPA is an evaluation by the FDA of a protocol with the goal of reaching an agreement that the Phase 3 trial protocol design, clinical endpoints, and statistical analyses are acceptable to support regulatory approval. The FDA agreed that, based on the information we submitted to the agency, the design and planned analysis of the REDUCE-IT study adequately addressed the objectives necessary to support a regulatory submission. An SPA is generally binding upon the FDA unless a substantial scientific issue essential to determining safety or efficacy is identified after the testing begins. Moreover, any change to a study protocol can invalidate an SPA. There can be no assurance that the FDA will ultimately consider our SPA to be binding. If the FDA does not consider the SPA to be binding or makes a determination that we did not follow the SPA appropriately, the agency could assert that additional studies or data are required to support a regulatory submission.

In September 2011, we engaged a clinical research organization, or CRO, and began initial trial and clinical site preparation for REDUCE-IT. In December 2011, we announced that the first patient was dosed in the study.

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The study duration is dependent on the rate of clinical events in the study which rate may be affected by the number of patients enrolled in the study and the epidemiology of the patients enrolled in the study. Based on preliminary assumptions for patient enrollment rates and the clinical profile of these patients, it is assumed that fewer than 10,000 patients will be required to complete the study with an optimized target in which the study is completed in approximately six years of 8,000 patients.

The REDUCE-IT study is designed to evaluate the efficacy of Vascepa in reducing major cardiovascular events in an at-risk patient population also receiving statin therapy. REDUCE-IT is a multi-center, prospective, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the effectiveness of Vascepa, as an add-on to statin therapy, in reducing first major cardiovascular events in an at-risk patient population compared to statin therapy alone. The control arm of the study is comprised of patients on optimized statin therapy. The active arm of the study is comprised of patients on optimized statin therapy plus Vascepa. All subjects enrolled in the study will have elevated triglyceride levels and either coronary heart disease or risk factors for coronary heart disease. This study will be conducted internationally. Based on the results of REDUCE-IT, we may seek additional indications for Vascepa beyond the indication studied in the ANCHOR and MARINE trials such as a potential indication for prevention of cardiovascular events, although there can be no assurance as to whether the results of the study will support any such indication.

New Lipid Compounds and other Preclinical Programs

We are also considering development of other next generation compounds based on our internal lipid science expertise, including potential combination and derivative therapies.

In December 2012, we completed dosing and pharmacokinetic sampling in a study to test a fixed-dose combination of Vascepa capsules and a leading statin. The clinical name for this combination product candidate is AMR102. The purpose of the AMR102 study is to determine the bioavailability of the Vascepa and statin components when taken as a fixed-dose combination product, relative to the individual reference agents taken concomitantly. We anticipate reviewing the results of this study in the first half of 2013.

We believe that Vascepa and other lipid-based compositions may have an impact on a number of biological factors in the body such as anti-inflammatory mechanisms, cell membrane composition and plasticity, triglyceride levels and regulation of glucose metabolism. Currently all other clinic developments are in formulative or pre-clinical stages.

Manufacturing and Supply for Vascepa

We currently use third party manufacturers and suppliers to manufacture clinical and commercial quantities of ethyl-EPA, which constitutes the only active pharmaceutical ingredient, or API, within Vascepa, to encapsulate, bottle and package Vascepa and to maintain inventory of Vascepa. The approval of Vascepa in July 2012 included the approval of one active pharmaceutical ingredient, or API, manufacturer, Nisshin Pharma, Inc., and one API encapsulator, Patheon, Inc. (formerly Banner Pharmacaps Europe BV). Nisshin and Patheon are the API manufacturer and API encapsulator, respectively, with which we have had the longest working relationships. Their facilities were inspected by regulatory authorities as part of the process that led to the FDA s July 2012 approval of Vascepa, and we believe that the facilities are qualified to support our commercial launch of Vascepa. In October 2012, a second API encapsulator, Catalent Pharma Solutions LLC, was qualified to encapsulate API for Vascepa.

The API material that constitutes ethyl-EPA is a naturally occurring substance which is sourced from qualified producers of fish oil. A limited number of other manufacturers have the ability, know-how and suitable facilities to produce ethyl-EPA to a similar level of purity. Among the conditions for FDA approval of a pharmaceutical product is the requirement that the manufacturer s quality control and manufacturing procedures conform to current Good Manufacturing Practice, or cGMP, which must be followed at all times. The FDA typically inspects manufacturing facilities before regulatory approval of a product candidate, such as Vascepa,

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and on an ongoing basis. In complying with cGMP regulations, pharmaceutical manufacturers must expend resources and time to ensure compliance with product specifications as well as production, record keeping, quality control, reporting, and other requirements.

Our goal is to expand our supply chain to provide greater capacity to meet anticipated demand, enable supply diversification and flexibility and introduce cost competition. We have defined with the FDA our plan and specifications for qualifying the additional API suppliers. We intend to submit sNDAs for the use of additional API suppliers after the suppliers successfully complete the specified process and facility qualifications. However, Nisshin is currently our only supplier of Vascepa API. In 2011, after conducting an extensive global search for manufacturers capable of producing Vascepa API to our technical specifications, we entered into limited exclusivity, long-term agreements with two additional API suppliers, Chemport, Inc. and BASF (formerly Equateq Limited). In December 2012, we announced an agreement with an exclusive consortium of companies led by Slanmhor Pharmaceutical, Inc. Slanmhor was spun-out from Ocean Nutrition Canada (ONC) prior to the May 2012 acquisition of ONC by Royal DSM N.V., a global leader in life sciences and materials sciences.

In December 2012, we announced our submissions of two sNDAs to the FDA seeking approval for Chemport and BASF as additional Vascepa API suppliers. We intend to submit an additional sNDA for Slanmhor after it successfully completes the qualification process. Subject to appropriate regulatory approvals, the addition of Slanmhor would give us a total of four qualified worldwide suppliers of API for Vascepa to utilize in supporting the global commercialization of Vascepa.

Our agreements with our API suppliers include annual purchase levels to enable Amarin to maintain exclusivity with each respective supplier and to prevent potential termination of the agreements. Certain of these agreements also contain provisions under which the cost of supply to us decreases as we purchase increased product volume. The agreements with each of our API suppliers that have not yet been approved by the FDA also contemplate phased capacity expansion aimed at creating sufficient capacity to meet anticipated demand for API material for Vascepa. Accordingly, these suppliers are currently working to expand their production capabilities to manufacture the API for Vascepa. These API suppliers are self-funding these expansion and qualification plans with contributions from Amarin. There can be no assurance that additional suppliers will fully-fund the capital costs of our engagement or that these additional suppliers will successfully qualify with the FDA.

We intend to purchase increasing amounts of API to support the commercial launch of Vascepa. Our supply agreement with Nisshin contains minimum purchase commitments for metric tons of API, and we may purchase more than the minimum requirement. We received the majority of this API during 2012, in advance of our planned commercial launch of Vascepa. During 2013, we intend to further increase our purchases of API and finished capsules of Vascepa. These purchases are generally made on the basis of rolling twelve-month forecasts which in part are binding on us and the balance of which are subject to adjustment by us subject to certain limitations. We may elect to make certain of these purchases prior to sNDA approval of our added suppliers after we are satisfied that the material they produce and their facilities are qualified. However, in the event that we make such purchases, we will not be able to use such material for commercial sale until the sNDA for the applicable supplier is approved by the FDA. Similarly, if we are not compliant with other regulations with regard to this intended purchase of supply, the supply of product may be delayed.

Our strategy is to expand capacity and to mitigate risk by having multiple API suppliers. Our aggregate capacity to produce API is dependent upon the qualification of our API suppliers. Each of our API suppliers has outlined plans for potential further capacity expansion. We anticipate purchasing qualified API from multiple suppliers for our first year of commercial sales of Vascepa, including purchases from BASF, Chemport and/or Slanmhor prior to FDA approval of the respective sNDAs for these suppliers. If an sNDA for any of these three API suppliers is not approved, we will not be able to use the supply from such supplier for commercial product. Also, if no additional API supplier is approved by the FDA, our API supply will be limited to the API we purchase from Nisshin. We believe that our overall API manufacturing plan provides a pathway to the production of API in sufficient quantities to meet anticipated demand, subject to API supplier capacity expansion,

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qualification and regulatory approval. There can be no assurance that these expansion plans will be successful. If our third party manufacturing capacity is not expanded and compliant with application regulatory requirements, we may not be able to supply sufficient quantities of Vascepa to meet anticipated demand. Our purchase of supply may be insufficient to meet, or exceed, actual demand for Vascepa.

Our Marketing Plans

We are currently expanding our marketing, sales and distribution capabilities. In early 2013 we hired and trained approximately 275 sales representatives in the United States. Vascepa became commercially available in the United States by prescription in January 2013, when we commenced sales and shipments to our network of U.S.-based wholesalers. On January 28, 2013, we commenced our full commercial launch of Vascepa for use in the MARINE indication. We are initially targeting clinicians who are top prescribers of lipid regulating therapies.

Historical Product Development Programs

Prior to October 2009, the majority of Amarin s product development activities were focused on central nervous system and other non-cardiovascular disorders. In October 2009, we completed a private placement resulting in gross proceeds of $70.0 million. These proceeds were used primarily to fund the MARINE and ANCHOR studies for Vascepa. In connection with this private placement, our board of directors and executive management underwent significant change, and our research and development activities, as well as certain executive functions, were consolidated from multiple offices to our research and development headquarters in the United States. In connection with these changes, we re-focused our efforts on developing improved treatments for cardiovascular disease and ceased development of all product candidates outside of our cardiovascular disease focus. In particular, this decision resulted in our ceasing all direct development of product candidates on central nervous system disorders, which included product candidates for the treatment of Huntington s disease, Myasthenia gravis and Parkinson s disease.

Competition

The biotechnology and pharmaceutical industries are highly competitive. There are many pharmaceutical companies, biotechnology companies, public and private universities and research organizations actively engaged in the research and development of products that may be similar to our products. It is probable that the number of companies seeking to develop products and therapies similar to our products will increase. Many of these and other existing or potential competitors have substantially greater financial, technical and human resources than we do and may be better equipped to develop, manufacture and market products. These companies may develop and introduce products and processes competitive with or superior to ours. In addition, other technologies or products may be developed that have an entirely different approach or means of accomplishing the intended purposes of our products, which might render our technology and products noncompetitive or obsolete.

Our potential competitors both in the United States and Europe include large, well-established pharmaceutical companies, specialty pharmaceutical sales and marketing companies and specialized cardiovascular treatment companies. These companies include GlaxoSmithKline plc, which currently markets Lovaza, a prescription-only omega-3 fatty acid indicated for patients with very high triglycerides, and Abbott Laboratories, which currently markets Tricor, Trilipix and Niaspan for the treatment of very high triglycerides and mixed dyslipidemia and Niaspan, which is primarily used to increase HDL-C, but which is also used to lower triglycerides. In March 2011, Pronova BioPharma Norge AS, which owns the patents for Lovaza, entered into an agreement with Apotex Corp. and Apotex Inc. to settle their patent litigation in the United States related to Lovaza. Pursuant to the terms of the settlement agreement, Pronova granted Apotex a license to enter the U.S. market with a generic version of Lovaza in the first quarter of 2015, or earlier, depending on circumstances. We expect Apotex to compete against us as well. Other companies are also seeking to introduce generic versions of Lovaza.

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In addition, we are aware of other pharmaceutical companies that are developing products that, if approved, would compete with Vascepa. These include a free fatty acid form of omega-3 (comprised of 55% EPA and 20% DHA) which is being developed by Omthera Pharmaceuticals which in April 2012 announced its top-line Phase 3 clinical trial results and indicated that it plans to submit an NDA during 2013 for the treatment of hypertriglyceridemia. In addition, Acasti Pharma, a subsidiary of Neptune Technologies & Bioresources Inc., announced in December 2012 that it intends to conduct a Phase 3 clinical program to assess the safety and efficacy of its omega-3 prescription drug candidate derived from krill oil for the treatment of hypertriglyceridemia. We believe Resolvyx Pharmaceuticals and Catabasis Pharmaceuticals are also developing potential treatments for hypertriglyceridemia based on omega-3 fatty acids, but we believe that neither has initiated a Phase 2 clinical trial of its product. In addition, we are aware that Essentialis, Inc is developing a controlled release diazoxide product for the treatment of hypertriglyceridemia. Essentialis, Inc. has reported that they have completed Phase 2 clinical studies with this product.

Vascepa will also face competition from dietary supplement companies marketing naturally occurring omega-3 fatty acids as nutritional supplements. We cannot be sure physicians and pharmacists will view the FDA-approved prescription-only status, EPA-only purity of Vascepa and stringent regulatory oversight as significant advantages versus naturally occurring omega-3 fatty acid dietary supplements.

In addition, other drug companies, known as generic drug companies, may challenge the validity, enforceability or both of our patents and seek to design products around our issued patent claims and, after a period of FDA-granted regulatory exclusivity gain marketing approval for generic versions of Vascepa or gain marketing approval for branded competitive products based on new clinical studies.

Regulatory Matters

Government Regulation and Regulatory Matters

Any product development activities related to Vascepa or products that we may develop or acquire in the future will be subject to extensive regulation by various government authorities, including the FDA and comparable regulatory authorities in other countries, which regulate the design, research, clinical and non-clinical development, testing, manufacturing, storage, distribution, import, export, labeling, advertising and marketing of pharmaceutical products and devices. Generally, before a new drug can be sold, considerable data demonstrating its quality, safety and efficacy must be obtained, organized into a format specific to each regulatory authority, submitted for review and approved by the regulatory authority. The data is generated in two distinct development stages: pre-clinical and clinical. Our drugs must be approved by the FDA through the NDA process before they may be legally marketed in the United States. For new chemical entities, the pre-clinical development stage generally involves synthesizing the active component, developing the formulation and determining the manufacturing process, as well as carrying out non-human toxicology, pharmacology and drug metabolism studies which support subsequent clinical testing.

The clinical stage of development can generally be divided into Phase 1, Phase 2 and Phase 3 clinical trials. In Phase 1, generally, a small number of healthy volunteers are initially exposed to a single dose and then multiple doses of the product candidate. The primary purpose of these studies is to assess the metabolism, pharmacologic action, side effect tolerability and safety of the drug. Phase 2 trials typically involve studies in disease-affected patients to determine the dose required to produce the desired benefits. At the same time, safety and further pharmacokinetic and pharmacodynamic information is collected. Phase 3 trials generally involve large numbers of patients at multiple sites, in multiple countries and are designed to provide the pivotal data necessary to demonstrate the effectiveness of the product for its intended use, its safety in use, and may include comparisons with placebo and/or other comparator treatments. The duration of treatment is often extended to mimic the actual use of a product during marketing.

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United States Drug Development

In the United States, the process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local, and foreign statutes and regulations require the expenditure of substantial time and financial resources. Failure to comply with the applicable United States requirements at any time during the product development process, approval process or after approval, may subject an applicant to administrative or judicial sanctions. These sanctions could include the FDA s refusal to approve pending applications, withdrawal of an approval, a clinical hold, warning letters, product recalls, product seizures, total or partial suspension of production or distribution injunctions, fines, refusals of government contracts, restitution, disgorgement, or civil or criminal penalties. Any agency or judicial enforcement action could have a material adverse effect on us.

Prior to the start of human clinical studies for a new drug in the United States, preclinical laboratory and animal tests are often performed under the FDA s Good Laboratory Practices regulations, or GLP, and an investigational new drug application, or IND, is filed with the FDA. Similar filings are required in other countries; however, data requirements and other information needed for a complete submission may differ in other countries. The amount of data that must be supplied in the IND depends on the phase of the study. Phase 1 studies typically require less data than larger Phase 3 studies. A clinical plan must be submitted to the FDA prior to commencement of a clinical trial. If the FDA has concerns about the clinical plan or the safety of the proposed studies, they may suspend or terminate the study at any time. Studies must be conducted in accordance with good clinical practice and regular reporting of study progress and any adverse experiences is required. Studies are also subject to review by independent institutional review boards, or IRBs, responsible for overseeing studies at particular sites and protecting human research study subjects. An independent IRB may also suspend or terminate a study once initiated.

NDA and FDA Review Process

Following trial completion, trial data is analyzed to determine safety and efficacy. Data is then filed with the FDA in an NDA along with proposed labeling for the product and information about the manufacturing and testing processes and facilities that will be used to ensure product quality. The NDA must contain proof of safety, purity, potency and efficacy, which entails extensive pre-clinical and clinical testing. FDA approval of an NDA must be obtained before marketing a drug in the United States. In addition, in order to seek approval for a potentially expanded indication based on the ANCHOR study, we are required to have been substantially enrolled subjects in our REDUCE-IT cardiovascular outcomes study at the time of our NDA submission for the ANCHOR indication. Based upon feedback from the FDA and in accordance with the SPA for the ANCHOR study, we do not believe that the results of the REDUCE-IT outcomes study are required for approval of the indication studied in the ANCHOR trial.

The FDA will likely re-analyze the clinical trial data, which could result in extensive discussions between the FDA and us during the review process. The review and evaluation of applications by the FDA is extensive and time consuming and may take longer than originally planned to complete. The FDA may conduct a pre-approval inspection of the manufacturing facilities for the new product to determine whether they comply with current good manufacturing practice requirements and may also audit data from clinical and pre-clinical trials.

There is no assurance that the FDA will ultimately approve a drug product for marketing in the United States. Even if future indications for Vascepa are approved, the FDA s review will be lengthy and we may encounter significant difficulties or costs during the review process. After approving any drug product, the FDA may require post-marketing testing and surveillance to monitor the effects of approved products or it may place conditions on approvals including potential requirements or risk management plans that could restrict the commercial promotion, distribution, prescription or dispensing of products. Product approvals may be withdrawn for non-compliance with regulatory standards or if problems occur following initial marketing.

European Union Drug Development

In the European Union, or E.U., our future products may also be subject to extensive regulatory requirements. As in the United States, the marketing of medicinal products has been subject to the granting of

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marketing authorizations by regulatory agencies. Particular emphasis is also being placed on more sophisticated and faster procedures for reporting of adverse events to the competent authorities.

Similar to the United States, the various phases of pre-clinical and clinical research in the E.U. are subject to significant regulatory controls. Although the regulatory controls on clinical research are currently undergoing a harmonization process following the adoption of the Clinical Trials Directive 2001/20/EC, there are currently significant variations in the member state regimes. However, all member states currently require independent institutional review board approval of interventional clinical trials. With the exception of U.K. Phase 1 studies in healthy volunteers, all clinical trials require either prior governmental notification or approval. Most regulators also require the submission of adverse event reports during a study and a copy of the final study report.

European Union Drug Review and Approval

In the E.U., approval of new medicinal products can be obtained through one of three processes: the mutual recognition procedure, the centralized procedure and the decentralized procedure.

Mutual Recognition Procedure

An applicant submits an application in one E.U. member state, known as the reference member state. Once the reference member state has granted the marketing authorization, the applicant may choose to submit applications in other concerned member states, requesting them to mutually recognize the marketing authorizations already granted. Under this mutual recognition process, authorities in other concerned member states have 55 days to raise objections, which must then be resolved by discussions among the concerned member states, the reference member state and the applicant within 90 days of the commencement of the mutual recognition procedure. If any disagreement remains, all considerations by authorities in the concerned member states are suspended and the disagreement is resolved through an arbitration process. The mutual recognition procedure results in separate national marketing authorizations in the reference member state and each concerned member state.

Centralized Procedure

This procedure is currently mandatory for products developed by means of a biotechnological process and optional for new active substances and other innovative medicinal products with novel characteristics. Under this procedure, an application is submitted to the European Agency for the Evaluation of Medical Products. Two European Union member states are appointed to conduct an initial evaluation of each application. These countries each prepare an assessment report that is then used as the basis of a scientific opinion of the Committee on Proprietary Medical Products. If this opinion is favorable, it is sent to the European Commission, which drafts a decision. After consulting with the member states, the European Commission adopts a decision and grants a marketing authorization, which is valid throughout the European Union and confers the same rights and obligations in each of the member states as a marketing authorization granted by that member state.

Decentralized Procedure

The most recently introduced of the three processes for obtaining approval of new medicinal processes in the E.U., the decentralized procedure is similar to the mutual recognition procedure described above, but with differences in the timing that key documents are provided to concerned member states by the reference member state, the overall timing of the procedure and the possibility of clock stops during the procedure, among others.

Post-Marketing Requirements

Following approval of a new product, a pharmaceutical company generally must engage in numerous specific monitoring and recordkeeping activities and continue to submit periodic and other reports to the

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applicable regulatory agencies, including any cases of adverse events and appropriate quality control records. Modifications or enhancements to the products or labeling or changes of site of manufacture are often subject to the approval of the FDA and other regulators, which may or may not be received or may result in a lengthy review process.

Prescription drug advertising is subject to federal, state and foreign regulations. In the United States, the FDA regulates prescription drug promotion, including direct-to-consumer advertising. Prescription drug promotional materials must be submitted to the FDA in conjunction with their first use. Any distribution of prescription drug products and pharmaceutical samples must comply with the U.S. Prescription Drug Marketing Act, or the PDMA, a part of the U.S. Federal Food, Drug, and Cosmetic Act.

In the United States, once a product is approved, its manufacture is subject to comprehensive and continuing regulation by the FDA. The FDA regulations require that products be manufactured in specific approved facilities and in accordance with current good manufacturing practices, or cGMPs, and NDA holders must list their products and register their manufacturing establishments with the FDA. These regulations also impose certain organizational, procedural and documentation requirements with respect to manufacturing and quality assurance activities. NDA holders using contract manufacturers, laboratories or packagers are responsible for the selection and monitoring of qualified firms, and, in certain circumstances, qualified suppliers to these firms. These firms and, where applicable, their suppliers are subject to inspections by the FDA at any time, and the discovery of violative conditions, including failure to conform to cGMPs, could result in enforcement actions that interrupt the operation of any such facilities or the ability to distribute products manufactured, processed or tested by them.

Federal and State Fraud and Abuse Laws

In addition to FDA restrictions on marketing of pharmaceutical products, several other types of state and federal laws restrict certain marketing practices in the biopharmaceutical industry. These laws include anti-kickback statutes and false claims statutes.

The federal anti-kickback statute prohibits, among other things, knowingly and willfully offering, paying, soliciting, or receiving remuneration to induce or in return for a referral or the purchasing, leasing, ordering, or arranging for or recommending the purchase, lease, or order of any healthcare facility, item or service reimbursable under Medicare, Medicaid, or other federal healthcare programs. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on one hand and prescribers, purchasers, and formulary managers on the other. Although there are a number of statutory exemptions and regulatory safe harbors protecting certain activities from prosecution, the exemptions and safe harbors are drawn narrowly, and practices that involve remuneration intended to induce prescribing, purchases, or recommendations may be subject to scrutiny if they do not qualify for an exemption or safe harbor. Our practices may not in all cases meet all of the criteria for safe harbor protection from anti-kickback liability.

Federal false claims laws prohibit any person from knowingly presenting, or causing to be presented, a false claim for payment to the federal government, or knowingly making or using, or causing to be made or used, a false statement to get a false claim paid. Recently, several pharmaceutical and other healthcare companies have been prosecuted under these laws for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. Other companies have been prosecuted for causing false claims to be submitted because of the company s marketing of the product for unapproved, and thus non-reimbursable, uses. The majority of states also have statutes or regulations similar to the federal anti-kickback law and false claims laws, which apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payer. Sanctions under these federal and state laws may include civil monetary penalties, exclusion of a manufacturer s products from reimbursement under government programs, criminal fines, and imprisonment.

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Because of the breadth of these laws and the narrowness of the safe harbors, it is possible that some of our business activities could be subject to challenge under one or more of such laws. Such a challenge could have a material adverse effect on our business, financial condition and results of operations. As a company marketing an FDA-approved product in the United States, our operations may be directly, or indirectly through our customers, subject to various federal and state fraud and abuse laws, including, without limitation, the federal anti-kickback statute. These laws may impact, among other things, our proposed sales, marketing and education programs. In addition, we may be subject to patient privacy regulation by both the federal government and the states in which we conduct our business. The laws that may affect our ability to operate include:

- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created new federal criminal statutes that prohibit executing a scheme to defraud any healthcare benefit program and making false statements relating to healthcare matters;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and its implementing regulations, which imposes certain requirements relating to the privacy, security and transmission of individually identifiable health information; and

- state law equivalents of each of the above federal laws, such as anti-kickback and false claims laws which may apply to items or services reimbursed by any third-party payer, including commercial insurers, and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

If our operations are found to be in violation of any of the laws described above or any other governmental regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, damages, fines and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

In the United States and foreign jurisdictions, there have been a number of legislative and regulatory changes to the healthcare system that could affect our future results of operations. In particular, there have been and continue to be a number of initiatives at the United States federal and state levels that seek to reduce healthcare costs. The Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the MMA, imposed new requirements for the distribution and pricing of prescription drugs for Medicare beneficiaries. Under Part D, Medicare beneficiaries may enroll in prescription drug plans offered by private entities which will provide coverage of outpatient prescription drugs. Part D plans include both stand-alone prescription drug benefit plans and prescription drug coverage as a supplement to Medicare Advantage plans. Unlike Medicare Part A and B, Part D coverage is not standardized. Part D prescription drug plan sponsors are not required to pay for all covered Part D drugs, and each drug plan can develop its own drug formulary that identifies which drugs it will cover and at what tier or level. However, Part D prescription drug formularies must include drugs within each therapeutic category and class of covered Part D drugs, though not necessarily all the drugs in each category or class. Any formulary used by a Part D prescription drug plan must be developed and reviewed by a pharmacy and therapeutic committee. Government payment for some of the costs of prescription drugs may increase demand for our products for which we receive marketing approval. However, any negotiated prices for our products covered by a Part D prescription drug plan will likely be lower than the prices we might otherwise obtain. Moreover, while the MMA applies only to drug benefits for Medicare beneficiaries, private payers often follow Medicare coverage policy and payment limitations in setting their own payment rates. Any reduction in payment that results from the MMA may result in a similar reduction in payments from non-governmental payers.

The American Recovery and Reinvestment Act of 2009 provides funding for the federal government to compare the effectiveness of different treatments for the same illness. A plan for the research will be developed by the Department of Health and Human Services, the Agency for Healthcare Research and Quality and the National Institutes for Health, and periodic reports on the status of the research and related expenditures will be made to Congress. Although the results of the comparative effectiveness studies are not intended to mandate

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coverage policies for public or private payers, it is not clear what effect, if any, the research will have on the sales of any product, if any such product or the condition that it is intended to treat is the subject of a study. It is also possible that comparative effectiveness research demonstrating benefits in a competitor s product could adversely affect the sales of our product candidates. If third-party payers do not consider our products to be cost-effective compared to other available therapies, they may not cover our products as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow us to sell our products on a profitable basis.

Most recently, in March 2010 the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively the PPACA, was enacted, which includes measures to significantly change the way healthcare is financed by both governmental and private insurers. Among the provisions of the PPACA of greatest importance to the pharmaceutical and biotechnology industry are the following: