UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

AMARIN PHARMA, INC., DR. JONATHAN HERBST, DR. ERIC RISHE, DR. PETER GOTTESFELD, and DR. RALPH YUNG, Plaintiffs, v. UNITED STATES FOOD & DRUG ADMINISTRATION 10903 New Hampshire Avenue Silver Spring, Maryland 20993, UNITED STATES OF AMERICA Serve to: U.S. Attorney General 950 Pennsylvania Avenue NW Washington, DC 20530, STEPHEN OSTROFF, M.D., in his official capacity as Acting Commissioner of Food and Drugs 10903 New Hampshire Avenue Silver Spring, Maryland 20933, and SYLVIA MATHEWS BURWELL, in her official capacity as Secretary of the Department of Health & Human Services 200 Independence Avenue SW Washington, DC 20201, Defendants.	)	Civil Action No. _____

COMPLAINT

Plaintiffs Dr. Jonathan Herbst, Dr. Eric Rishe, Dr. Peter Gottesfeld, and Dr. Ralph Yung (collectively, the "Doctor Plaintiffs"), and Amarin Pharma, Inc. ("Amarin") allege as follows:

1. This Complaint presents an as-applied First Amendment challenge to FDA regulations that prohibit Amarin, a pharmaceutical company, from making completely truthful and non-misleading statements about its product to sophisticated healthcare professionals, including Doctor Plaintiffs.

2. Every day, doctors across America, including Doctor Plaintiffs, prescribe drugs to patients at risk for cardiovascular disease and who have persistently high triglyceride[1] levels in their blood (i.e., high despite statin therapy) to lower those patients' triglycerides and/or non-HDL cholesterol.[2] This is a medically-accepted practice supported by numerous national and international cardiovascular treatment guidelines and position statements.[3] These doctors do so because, in their medical judgment, drug therapy is the best course of treatment for these patients.

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[1] Triglyceride is fat and, like cholesterol, is a type of lipid in the blood. Triglyceride is carried through the body with cholesterol, on the same lipoproteins.

[2] HDL cholesterol refers to high-density lipoprotein cholesterol, which is often referred to as "good cholesterol." Non-HDL cholesterol refers to all other kinds of cholesterol.

[3] *See* T.A. Jacobson et al., *National Lipid Association recommendations for patient-centered management of dyslipidemia*, 8 J. Clin. Lipidol. 473 (2014); P.S. Jellinger et al., *American Association of Clinical Endocrinologists' guidelines for management of dyslipidemia and prevention of atherosclerosis*, 1 Endocr. Pract. 1 (2012); R. A. Hegele et al., *The polygenic nature of hypertriglyceridaemia: implications for definition, diagnosis, and management*, 2 Lancet Diabetes Endocrinol. 655, Table 3 (2014); Expert Dyslipidemia Panel of the International Atherosclerosis Society, *An International Atherosclerosis Society Position Paper: global recommendations for the management of dyslipidemia – full report*, 8 J. Clin. Lipidol. 29 (2014); L. Berglund et al., *Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline*, 97 J. Clin. Endocrinol. Metab. 2969 (2012); M. J. Chapman et al., *Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management*, 32 Eur. Heart J. 1345 (2011); Z. Reiner, et al., *ESC/EAS Guidelines for the management of dyslipidaemias: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS)*, 32 Eur. Heart J. 1769 (2011); National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment on High Blood Cholesterol in Adults (Adult Treatment Panel III), *Third report of the National Cholesterol Education Program (NECP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report*, 106 Circulation 3143 (2002).

3. These doctors need truthful and non-misleading information about these drugs to make informed decisions about what is best for their patients. The U.S. Food & Drug Administration's ("FDA's") current regime for regulating the flow of "off-label" information to doctors about prescription drugs, however, severely restricts medical professionals' access to information from the source most knowledgeable about the drugs: the drug manufacturers—in this case, Amarin.

4. Amarin manufactures the prescription drug at issue in this case: Vascepa®, which consists of pure EPA (eicosapentaenoic acid), an omega-3 fatty acid. Vascepa® has a safety profile comparable to a placebo.

5. Based on a clinical trial conducted by Amarin, FDA has approved the marketing of Vascepa® for use as an adjunct to diet to reduce triglyceride levels in adult patients with *very* high triglycerides—defined as triglyceride levels of 500 mg/dL of blood or above.[4] Because FDA has approved Vascepa® for this use, doctors are lawfully permitted to prescribe Vascepa® for *any* use that, in their medical judgment, is in the best interests of their patients. Accordingly, many doctors, including Doctor Plaintiffs, prescribe Vascepa® to treat patients with persistently high triglycerides (i.e., 200-499 mg/dL of blood, despite the use of statins) to lower those patients' triglycerides and/or non-HDL cholesterol.

6. Not only is this practice lawful, it is commonplace: prescribing drugs such as Vascepa® to treat patients with persistently high triglycerides is recommended by numerous car-

[4] Throughout this Complaint, the terms "very high triglycerides" or "very high triglyceride levels" will refer to triglyceride levels of 500 mg/dL or above. The terms "high triglycerides" or "high triglyceride levels" will refer to triglyceride levels in the range from and including 200 mg/dL to and including 499 mg/dL. FDA refers to the condition of high triglycerides as hypertriglyceridemia and to that of very high triglycerides as severe hypertriglyceridemia. References to the use of Vascepa® to treat patients with "persistently high triglycerides" or "persistently high triglyceride levels" will refer to the use of Vascepa® as an adjunct to diet to treat patients on statin therapy with mixed dyslipidemia (one or more lipid disorders) and high triglyceride levels (i.e., 200-499 mg/dL).

diovascular treatment guidelines and position statements that are based on strong scientific and clinical support linking high triglycerides, high non-HDL cholesterol, and cardiovascular disease. This is the case, even though there is not yet definitive clinical evidence affirmatively demonstrating that lowering triglyceride and/or non-HDL cholesterol levels in such patients ultimately reduces cardiovascular risk.

7. Amarin has conducted a double-blind, placebo-controlled clinical trial demonstrating that Vascepa® reduces triglyceride levels and has other favorable effects in adult patients with persistently high triglycerides. FDA does not dispute the success of this trial, but has nonetheless recently advised Amarin that it refuses to approve the promotion of Vascepa® for use in treating this patient population.

8. In light of FDA's refusal, Amarin now finds itself in a bind. Using pharmaceuticals like Vascepa® in the treatment of patients with persistently high triglyceride levels is commonplace in medical practice. However, because FDA has refused to approve Vascepa® for patients with persistently high triglycerides, Amarin may not freely communicate truthful and non-misleading information about Vascepa® to healthcare professionals such as the Doctor Plaintiffs without fear of criminal prosecution and civil liability. That is because FDA regulations forbid promotion of drugs for unapproved or "off-label" uses, even if such promotion is entirely truthful and presented in a non-misleading manner.

9. FDA's treatment of Vascepa® therefore operates to keep doctors, such as the Doctor Plaintiffs, and consequently their patients, in the dark about all of the options for drug therapy they are legally empowered to prescribe to treat persistently high triglyceride levels. This is especially problematic, since fenofibrate and niacin drugs, which are widely used for treatment of patients with persistently high triglycerides, have failed in cardiovascular outcomes studies that included some patients with persistently high triglycerides, and all other triglyceride-lowering drugs have significant safety concerns and side effects not associated with Vascepa®.

This is also especially problematic since available scientific evidence reflects that EPA may have benefits in treating cardiovascular disease beyond triglyceride lowering not evident with other drugs. Moreover, for years and until recently, FDA has permitted manufacturers of other triglyceride-lowering drugs, such as fenofibrates, niacin, and another omega-3 fatty acid-based drug, to market their drugs for treatment of persistently high triglycerides. FDA's actions prevent the communication of important information to inform clinical practice and prevent doctors and patients from getting information about a potentially better treatment alternative.

10. Although, upon information and belief, while FDA has recently acted to remove the indication and labeling from these other triglyceride-lowering drugs concerning treatment of persistently high triglycerides, FDA has done little, if anything, to address the effect of permitting these drugs to be marketed for many years to healthcare professionals for treatment of adults with persistently high triglycerides. As a result, upon information and belief, many doctors who, consistent with clinical guidelines, treat patients with persistently high triglycerides with drug therapy know the clinical profile of these other drugs and that they are effective in lowering triglycerides in those patients, but do not know similar information about Vascepa®. These doctors need complete information about their treatment options to make fully-informed decisions about what is best for their patients.

11. Moreover, for more than a decade, FDA has permitted dietary supplement manufacturers that sell supplements containing EPA and/or DHA (docosahexaenoic acid, another omega-3 fatty acid) to make the following qualified health claim directly to lay consumers:

> Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease.

12. But if Amarin's pharmaceutical sales representatives made this same truthful and non-misleading statement to sophisticated doctors about Vascepa®, which consists of pure EPA, those pharmaceutical sales representatives (and Amarin) would be subject to criminal charges and/or massive civil liability under FDA's regulatory structure. The same would be true if the sales representatives made truthful and non-misleading statements to doctors detailing scientific evidence that supports the qualified health claim. If FDA allows lay consumers to be told about the state of research concerning the potential effects of EPA on reducing the risk of coronary heart disease, it must permit sophisticated doctors to be told about it too.

13. Although Amarin disagrees with FDA's ruling denying an indication for Vascepa® in treating patients with persistently high triglycerides, this case does not challenge that ruling. Nor does this case require the Court to evaluate whether FDA's scientific conclusions about Vascepa® are right or wrong. Finally, this case does not require the Court to sanction any false or misleading speech about Vascepa® or otherwise challenge the government's ability to prohibit pharmaceutical companies, including Amarin, from disseminating false or misleading information about their products.

14. Rather, this Complaint asks this Court to hold that FDA's prohibitions on "off-label" promotion, as applied to the truthful and non-misleading speech Amarin wishes to make, are unconstitutional under the First Amendment, and to declare that Amarin may engage in its proposed speech about Vascepa®. Such a holding falls squarely within Second Circuit precedent. *See United States* v. *Caronia*, 703 F.3d 149 (2d Cir. 2012) (reversing on First Amendment grounds criminal conviction based on truthful and non-misleading off-label promotion).

15. The speech Amarin proposes to engage in consists of carefully-circumscribed, truthful, and scientifically-accurate statements. In a nutshell, Amarin wishes to make specific statements about the double-blind, placebo-controlled clinical trial that demonstrated Vascepa®'s effectiveness in lowering triglycerides in patients with persistently high triglycerides. It

wishes to state to medical professionals—as dietary supplement manufacturers already do to the general public—that supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease. And it wishes to provide peer-reviewed scientific publications relevant to the potential effect of EPA on the reduction of the risk of coronary heart disease.

16. To ensure that this speech is not misleading, Amarin would also contemporaneously disclose to healthcare professionals detailed disclaimers, including that FDA has not approved Vascepa® to treat patients with persistently high triglyceride levels and that FDA has not approved Vascepa® to reduce the risk of coronary heart disease.[5]

17. In summary, Plaintiffs seek a declaration that FDA regulations promulgated under the Federal Food, Drug, and Cosmetic Act (the "FDCA") (including 21 C.F.R. § 202.1(*l*)(2), 21 C.F.R. § 202.1(e)(4)(i)(a), and 21 C.F.R. §§ 201.5 and 201.100), and FDA's interpretations of the provisions thereof (including 21 U.S.C. § 352(a) and 21 U.S.C. § 352(n)), are unconstitutional, that Amarin has a First Amendment right to engage in truthful and non-misleading speech about Vascepa®, even if that speech is off-label promotion, and that the Doctor Plaintiffs have a First Amendment right to receive such truthful and non-misleading information about Vascepa® from Amarin, without fear of (a) criminal prosecution of Amarin or its directors, officers, employees, or agents through application of FDA regulations promulgated under the FDCA or (b) civil liability of Amarin or its directors, officers, employees, or agents under the False Claims Act.

18. Alternatively, Plaintiffs seek a declaration that, as-applied here, FDA's regulatory regime is unconstitutionally vague in violation of the Due Process Clause of the Fifth Amend-

[5] The precise contours of the speech in which Amarin wishes to engage is set forth at paragraph 124.

ment because it does not provide Amarin with fair notice of what off-label promotion is permitted and what off-label promotion is forbidden under FDA regulations.

19. Amarin and the Doctor Plaintiffs also seek injunctive relief to ensure their ability to engage in truthful and non-misleading speech free from the risk of criminal and civil liability.

II. THE PARTIES

20. Dr. Jonathan Herbst is a physician practicing internal medicine in Rye Brook, New York 10573 and a resident of Westchester County, New York. Dr. Herbst has been practicing medicine continuously for over 36 years. He regularly prescribes Vascepa® for both on- and off-label uses, but the majority of the Vascepa® prescriptions he writes are for off-label use by patients with high, but not very high, triglyceride levels with the goal of reducing cardiovascular disease. Dr. Herbst wants to receive truthful and non-misleading information from Amarin about Vascepa®, including evidence relevant to its potential effect on the risk of coronary heart disease and about the efficacy of using Vascepa® to treat patients with persistently high triglycerides.

21. Dr. Eric Rishe is a board-certified physician specializing in internal medicine, hematology, and oncology in Riverdale, New York 10463 and is a resident of New York County, New York. Dr. Rishe has been practicing medicine for 13 years. Like Dr. Herbst, Dr. Rishe regularly prescribes Vascepa® for on- and off-label uses, but a significant number of the Vascepa® prescriptions he writes are for off-label use by patients with high, not very high, triglyceride levels with the goal of reducing cardiovascular risk. Dr. Rishe wants to receive truthful and non-misleading information from Amarin about Vascepa®, including evidence relevant to its potential effect on the risk of coronary heart disease and about the efficacy of using Vascepa® to treat patients with persistently high triglycerides.

22. Dr. Peter Gottesfeld is a board-certified physician specializing in family medicine. Dr. Gottesfeld has offices in Mt. Kisco, New York and Cortlandt Manor, New York and is a resident of Westchester County, New York. Dr. Gottesfeld has been practicing medicine for almost

30 years. Like Drs. Herbst and Rishe, Dr. Gottesfeld regularly prescribes Vascepa® for on- and off-label uses. Many of the Vascepa® prescriptions he writes are with the goal of reducing the risk of developing cardiovascular heart disease for patients with high, but not very high, triglycerides with the goal of reducing cardiovascular risk. Dr. Gottesfeld wants to receive truthful and non-misleading information from Amarin about Vascepa®, including evidence relevant to its potential effect on the risk of coronary heart disease and about the efficacy of using Vascepa® to treat patients with persistently high triglycerides.

23. Dr. Ralph Yung is a board-certified physician specializing in internal medicine and endocrinology in Bronx, New York 10469 and is a resident of Bronx County, New York. Dr. Yung has been practicing medicine for over 50 years and specializes in treating patients who have diabetes, many of whom also have high or very high triglycerides. Like Drs. Herbst, Rishe, and Gottesfeld, Dr. Yung regularly prescribes Vascepa® for on- and off-label uses, but the majority of the Vascepa® prescriptions he writes are for off-label use by patients with high, not very high, triglyceride levels with the goal of reducing cardiovascular risk. Dr. Yung wants to receive truthful and non-misleading information from Amarin about Vascepa®, including evidence relevant to its potential effect on the risk of coronary heart disease and about the efficacy of using Vascepa® to treat patients with persistently high triglycerides.

24. Amarin is a Delaware corporation with its principal place of business at 1430 Route 206, Bedminster, New Jersey 07921. Amarin is a biopharmaceutical company focused on the commercialization and development of therapeutics to improve cardiovascular health.

25. Defendant FDA is the federal agency within the United States Department of Health & Human Services ("HHS") responsible for approving, disapproving, and otherwise regulating food, drugs, medical devices, and biologics under the FDCA. FDA's headquarters are in Silver Spring, Maryland.

26. Defendant Dr. Stephen Ostroff is sued in his official capacity as the Acting Commissioner of Food and Drugs, the most senior official at FDA. As Acting Commissioner, Dr. Ostroff is directly responsible for execution and administration of the FDCA.

27. Defendant Sylvia Mathews Burwell is sued in her official capacity as the Secretary of HHS. Secretary Burwell is Acting Commissioner Ostroff's immediate superior and, as such, Secretary Burwell is responsible for the execution and administration of the FDCA.

III. JURISDICTION AND VENUE

28. This action seeks declaratory relief under the Federal Declaratory Judgment Act, 28 U.S.C. § 2201.

29. This Court has subject matter jurisdiction over this action under 28 U.S.C. § 1331 because all causes of action arise under the Constitution and laws of the United States.

30. Venue is proper in this judicial district under 28 U.S.C. § 1391(e) because an agency of the United States and officers of an agency of the United States are defendants, several plaintiffs reside in this district, and there is no real property involved in this action. In addition, a substantial part of the events that give rise to the claim occurred and will continue to occur in this district.

31. An actual, justiciable controversy exists between the parties regarding the constitutionality and meaning of the statutes and FDA regulations applied by FDA to Amarin and the Doctor Plaintiffs to restrict and penalize truthful and non-misleading speech.

32. Declaratory relief will resolve this controversy and eliminate the chill of such statutes and regulations on Amarin and the Doctor Plaintiffs in violation of the First and Fifth Amendments.

33. A preliminary injunction against Defendants, preventing them from enforcing the challenged statutes and regulations against Amarin and the Doctor Plaintiffs, will shield Plaintiffs' First and Fifth Amendment rights from ongoing harm while this litigation is pending.

34. A permanent injunction against Defendants, preventing them from enforcing the challenged statutes and regulations against Amarin and the Doctor Plaintiffs, will protect Plaintiffs' First and Fifth Amendment rights prospectively after the final resolution of this matter.

IV. FACTUAL ALLEGATIONS

35. Amarin's leading product is Vascepa®, a pharmaceutical-grade, single-molecule product, that consists of the ethyl-ester form of the single omega-3 acid commonly known as "EPA." Vascepa® is one of many prescription drugs that doctors, including the Doctor Plaintiffs, have prescribed to lower triglyceride levels and improve other relevant biomarkers in patients with persistently high or very high triglycerides. Upon information and belief, the majority of prescriptions written for Vascepa® are for treatment of patients with high triglycerides.

36. Vascepa® is one of numerous drugs doctors prescribe for lowering triglyceride levels among at-risk patients in the United States.[6] Many of these other drugs, however, have significant labeled safety and tolerability limitations not associated with Vascepa®, which has a safety profile comparable to placebo. Unlike Vascepa®, some of these other drugs also have failed outcomes trials in studies that included patients with persistently high triglycerides that showed no additional reduction of cardiovascular risk when taken with statins. Upon information and belief, many doctors, including the Doctor Plaintiffs, often prefer to use Vascepa® rather than these other drugs to bring down high triglyceride levels and improve other lipid parameters because of the safety and tolerability limitations associated with these other drugs and

[6] These drugs include at least eight fenofibrate-based drugs (Trilipix®, Tricor®, Triglide®, Antara®, Fibricor®, Lofibra®, Fenoglide®, Lipofen®), niacin-based drugs, such as Niaspan®, and other omega-3 drugs, such as Lovaza®.

because of the other drugs' failed outcomes trials.

Reducing Triglyceride Levels in the Treatment of Cardiovascular Health

37. Over a decade ago, the National Cholesterol Education Program's Third Adult Treatment Panel, based on an extensive review of available clinical data, formally recognized a relationship between elevated triglycerides and coronary heart disease. Since that time, National Cholesterol Education Program Adult Treatment Panel III guidelines, epidemiological studies, genetic studies, and additional clinical studies have continued to support a correlation between high triglyceride levels (greater than approximately 200 mg/dL) and the risk of cardiovascular events. Clinical studies have suggested that reducing triglycerides or reaching triglyceride treatment goals results in reductions of cardiovascular events.

38. Numerous national and international cardiovascular treatment guidelines counsel doctors to use drug therapy to treat patients with persistent elevated triglycerides above 200 mg/dL despite statin therapy to lower those patients' triglycerides and/or non-HDL cholesterol.[7]

39. When high triglyceride levels are reduced, non-HDL cholesterol levels are also reduced due to the interrelation of lipid processing in the body. Epidemiological studies support a positive association between elevated triglyceride levels and risk of cardiovascular events and the possibility that abnormal atherogenic lipoproteins reflected by high triglycerides or non-HDL cholesterol may independently contribute to residual cardiovascular risk. Further, findings from human genetic studies announced in 2014 continue to provide strong evidence for causally implicating triglycerides and triglyceride-rich lipoproteins in the development of cardiovascular risk.[8]

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7 *See* footnote 3 above.

8 S.A. Khetarpal, *Triglyceride-Rich Lipoproteins and Coronary Artery Disease Risk: New Insights From Human Genetics*, 35 Arterioscler. Thromb. Vasc. Biol. E3 (2015).

40. Although FDA takes the position that scientific evidence is inconclusive as to whether pharmacologically lowering triglyceride levels ultimately reduces a patient's risk of cardiovascular disease, upon information and belief, a significant number of doctors, including the Doctor Plaintiffs, regularly prescribe medications to lower triglyceride levels in at-risk patients. It is common in the practice of medicine for doctors to make medical decisions based on the current state of medical science without waiting for conclusive long-term studies.

EPA and DHA Consumption and Potential Reduction of Cardiovascular Risk

41. In 2004, FDA first permitted dietary supplement manufacturers that sell fish oil and other supplements containing the omega-3 fatty acids EPA and/or DHA to make the following qualified health claim directly to lay consumers:

> Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease.

Upon information and belief, FDA approved this qualified health claim because it was true in 2004, and FDA continues to permit this qualified health claim because it still believes it to be true.

42. A qualified health claim, which applies to conventional foods and dietary supplements, is available when credible scientific evidence is supportive of a claim but it does not rise to the level of the "significant scientific agreement" required in Section 343(r)(3)(B)(i) of the FDCA for FDA approval of a health claim. FDA assessed this particular claim in 2004 "based on a systematic evaluation of the available scientific data" and found that the research in this area was "not conclusive." Nevertheless, FDA recognized the public benefit of communicating the information in the qualified claim to lay consumers. In the press release announcing the claim, FDA's Acting Commissioner stated, "Coronary heart disease is a significant health problem that causes 500,000 deaths annually in the United States. This new qualified health claim for omega-

3 fatty acids should help consumers as they work to improve their health by identifying foods that contain these important compounds."

43. The physiological effects of EPA and DHA on the body that may contribute to reduction of cardiovascular risk are explored in the scientific literature but have not been fully elucidated. The physiological effects of EPA go beyond lowering triglycerides. For example, hardening of the arteries, or atherosclerosis, is a primary underlying process of cardiovascular disease involving oxidative stress, inflammation, cell dysfunction, and cholesterol accumulation within the arterial wall, followed by the formation and progression of plaque, which can eventually become unstable and rupture, leading to heart attack and stroke. EPA therapy may reduce atherosclerotic burden by improving many aspects of the lipid profile and by improving various parameters within an atherosclerotic plaque. For example, atherosclerotic plaques readily incorporate EPA and DHA, and higher EPA in plaque is associated with decreased inflammation and increased plaque stability. In addition, intervention with EPA-only therapy in combination with statin therapy may reduce markers of oxidative stress and inflammation in plasma and in plaque and may stabilize vulnerable plaques better than statins alone. Beyond the atherosclerotic processes discussed above, studies have also suggested that EPA may have beneficial effects on arterial function, heart rate and blood pressure, blood-clotting, and cardiac function and rhythm.

44. Over the decade since FDA first permitted the qualified health claim, additional cardiovascular outcomes studies and analyses have been conducted to examine the connection between the consumption of EPA and DHA omega-3 fatty acids in the risk of coronary heart disease. If anything, as to EPA, support for the qualified health claim has only increased in that time.[9]

[9] *See* Exhibit A for a list of representative samples of peer-reviewed scientific publications relevant to the potential effect of EPA on the reduction of the risk of coronary heart disease.

45. JELIS is one such study and the only completed cardiovascular outcomes study of a pure-EPA (i.e., no DHA) pharmaceutical product. JELIS was a randomized, open-label outcomes study of Japanese patients that showed cardiovascular-risk-reduction benefit from EPA on top of statin therapy. JELIS showed a 19% reduction in major coronary events in the studied population when EPA was added to a statin, over statin therapy alone. JELIS did not select patients considered to be at high risk based on high triglyceride levels. Average triglyceride levels were elevated (151 mg/dL), not high. An even greater, 53% reduction, in the incidence of major coronary events was observed in a JELIS sub-analysis of patients with both elevated triglycerides ($\geq$ 150 mg/dL) and low levels of HDL-C ("HDL cholesterol" or "good cholesterol"). Thus, JELIS results continue to support a showing of cardiovascular benefit from EPA therapy in the studied population. It is not known if the effects demonstrated in JELIS are related to EPA's triglyceride-lowering effect, which was more modest in JELIS. The putative protective effects of EPA are potentially due not to a single mode of action, but rather to multiple mechanisms working together.

46. In regulatory dialogue with Amarin, FDA acknowledged the encouraging cardiovascular event-lowering effects seen in JELIS, while noting that trial's publicly-known limitations. The details and limitations of JELIS are outlined in the peer-reviewed publications of its results.

Failed Outcomes Studies in Other Triglyceride-Lowering Drugs

47. A number of outcomes studies have been done in connection with other triglyceride-lowering drugs, such as fenofibrates and niacin, that have shown that those other drugs do not reduce the risk of cardiovascular events when used in combination with statins. Unlike these other drugs, Vascepa® has no failed outcomes studies.

The ACCORD-Lipid Study

48. In 2005, the National Heart, Lung, and Blood Institute sponsored what is now known as the "ACCORD-Lipid" study to evaluate the effectiveness of Trilipix®, a fenofibrate-based drug manufactured and marketed by Abbott Laboratories (now Abbvie, Inc.), in treating patients with type-2 diabetes who had a high-risk of cardiovascular events. ACCORD-Lipid was a sub-study within the larger ACCORD study, and ACCORD-Lipid results were published in March 2010 and subsequently evaluated by the Endocrinologic and Metabolic Drugs Advisory Committee convened by FDA on May 19, 2011. The ACCORD-Lipid study showed that, when used in combination with statins, Trilipix® did not reduce the risk of a major adverse cardiovascular event when compared to statin therapy alone.

49. After extensive discussion of the ACCORD-Lipid study, the Advisory Committee ultimately determined that the trial was not specifically designed to ascertain the clinical benefit of treating patients with high triglyceride levels and therefore could not adequately evaluate the benefits of Trilipix® as an add-on to statin therapy to help reduce the risk of cardiovascular events in patients with elevated triglycerides despite statin therapy. Because Tricor®, Triglide®, Antara®, Fibricor®, Lofibra®, Fenoglide®, and Lipofen® also regulate lipids through fenofibrate, the ACCORD-Lipid study results apply to them as well.

The AIM-HIGH Study

50. In 2006, the National Heart, Lung, and Blood Institute and Abbott Laboratories, the manufacturer of Niaspan®, initiated what is now known as the "AIM-HIGH" study to test whether adding high-dose, extended-release niacin to a statin is better than using a statin alone to reduce long-term cardiovascular events in participants whose "bad" cholesterol was controlled and who had a history of cardiovascular disease, low levels of "good" cholesterol, and in some cases—though not the majority—high triglyceride levels.

51. The AIM-HIGH study concluded in May 2011. It was stopped early for lack of efficacy at reducing serious heart and/or vascular events and because of possible safety concerns

due to an increase in the number of strokes in the patients taking extended-release niacin. Its results were published in December 2011. The results suggested that, although niacin raised "good" cholesterol and lowered triglyceride levels, it did not reduce the risk of cardiovascular events in a statistically significant way when combined with statins any more than statin therapy alone. The study results suggested that niacin did not have even an incremental clinical benefit as an add-on to statin therapy.

The HPS2-THRIVE Study

52. In 2007, the pharmaceutical company Merck Sharp & Dohme Corp. sponsored a study called "HPS2-THRIVE" to evaluate the effects of raising HDL-C (i.e., "good" cholesterol) with extended-release niacin plus the anti-flushing agent laropiprant, as an add-on to statin therapy, on various major vascular outcomes. Patients in the study were not selected based on their lipid profiles. Based on information available, approximately 74% of patients in the HPS2-THRIVE trial had normal (<150 mg/dL) triglyceride levels and very few—if any—patients had triglyceride levels above 200 mg/dL. The study, which was completed in 2012, reflected that the addition of extended-release naicin plus laropiprant, as an add-on to statin therapy, did not significantly reduce the risk of major vascular events but did increase the risk of serious adverse events.

Vascepa® and its History at FDA

53. On July 26, 2012, FDA approved Vascepa® for use as a treatment in adults with very high triglyceride levels. Roughly four million Americans are afflicted by this condition, which FDA refers to as severe hypertriglyceridemia. Patients with severe hypertriglyceridemia are at increased risk of getting pancreatitis and cardiovascular disease. As a result, doctors routinely prescribe drug therapy to reduce the triglyceride levels of such patients.

54. Although heathcare professionals now frequently use Vascepa® to treat adult patients with very high triglyceride levels, the same professionals often also prescribe Vascepa®—

as they are legally permitted to do—for treatment of patients on statin therapy who have persistently high triglyceride levels. Upon information and belief, most Vascepa® prescriptions are written to treat patients with high, but not very high, triglyceride levels.

55. The prescription of Vascepa® for persistently high triglycerides qualifies as an "off-label" use under FDA regulations, because Vascepa® has been approved by FDA only for patients with very high triglyceride levels. Doctors who prescribe Vascepa®, including the Doctor Plaintiffs, write these prescriptions based on their own medical judgments, as they may legally do. They do so because, in their medical judgment, even though the effect of Vascepa® on coronary heart disease has not yet been determined, the benefits of prescribing Vascepa® for many of their patients with high triglycerides outweigh any risks.

56. Each of the Doctor Plaintiffs prescribes Vascepa® to adult patients who have high triglyceride levels when, in their medical judgment, it is in their patients' best interest to do so. A significant portion, if not a majority of the prescriptions each of the Doctor Plaintiffs writes for Vascepa® are for this unapproved or "off label" use.

57. Despite being approved to treat patients with very high triglyceride levels, Vascepa® is still considered an unapproved "new drug" under FDA's regulatory regime regarding other uses, including the treatment of patients with high triglyceride levels. *See* 21 U.S.C. § 321(p). To obtain FDA approval for Vascepa®'s use in these patients, Amarin had to submit a "supplemental new drug application" that included detailed reports of pre-clinical and clinical trials demonstrating safety and efficacy and proposed labeling for the new use. 21 U.S.C. § 355(b).

58. The pre-clinical and clinical trials required to establish the safety and efficacy of a new drug typically cost millions of dollars and take years to complete. Prior to 1997, drug manufacturers sometimes spent years and millions of dollars preparing a new drug application, only to have FDA change its advice about the requirements for approval in the middle of the process.

To eliminate this "moving target syndrome," Congress enacted the Special Protocol Assessment ("SPA") mechanism in the FDA Modernization Act of 1997.

59. Under the FDA Modernization Act, drug manufacturers and FDA may now enter into written "SPA agreements" that lay out the design and size parameters for clinical trials of a new drug and define FDA drug claim approval requirements. A SPA agreement "constitutes an agreement between the FDA and the drug developing entity (the "sponsor") that, if the sponsor follows the procedure agreed upon in the protocol and the drug proves efficacious, then it will be approved."[10]

60. In enacting the SPA program, Congress limited FDA's discretion to change the criteria for approving a drug application after a SPA agreement has been entered into. A SPA agreement can be rescinded by FDA only if "a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun," and that issue rises to the level of a "public health concern." FDA has described the function of this collaboration as follows:

> The fundamental agreement here is that having agreed to the design, execution, and analyses proposed in protocols reviewed under this process, the Agency will not later alter its perspective on the issues of design, execution, or analyses unless public health concerns unrecognized at the time of protocol assessment under this process are evident.

FDA, PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, at § VI p. 17.

61. After completing the Vascepa® study that led to FDA approval for Vascepa® for treatment of very high triglycerides (known as the "MARINE" study), Amarin also undertook to examine the effect of Vascepa® in treating persistently high, but not very high, triglyceride levels of 200-499 mg/dL in patients on statin therapy (known as the "ANCHOR" study). Both the

[10] *Lauria* v. *Biosante Pharm., Inc.*, 968 F. Supp. 2d 951, 955 n.2 (N.D. Ill. 2013).

MARINE and ANCHOR studies were successful; they showed that Vascepa® reduced triglycerides (and other lipid, lipoprotein, and inflammatory biomarkers) in the targeted patient populations to a statistically-significant degree.

62. Historically, FDA has approved drugs designed to address abnormalities in lipid profiles based on available scientific evidence suggesting that favorable changes in lipid parameters likely translate to reduced cardiovascular risk. Based on this, and in reliance on the procedures in the FDA Modernization Act, Amarin, in good faith, entered into a SPA agreement with FDA in July 2009.

63. The ANCHOR SPA agreement set forth the precise evidentiary objectives for a clinical trial designed to demonstrate Vascepa®'s effectiveness at lowering triglycerides in patients with persistently high triglyceride levels. The study was also designed to show the effect of Vascepa® on other lipid, lipoprotein, and inflammatory parameters relevant to cardiovascular health, such as non-HDL cholesterol.[11] FDA committed that the study as designed, executed, and analyzed would provide the required clinical data for approval of Vascepa® for treatment of patients with persistently high triglyceride levels if those objectives were met, subject to narrow statutory bases for rescission.

64. At the time of the ANCHOR SPA agreement, FDA was willing to consider Amarin's proposed trial designs to approve Vascepa® to reduce triglyceride levels in patients with persistently high triglycerides, despite the fact that, due to the absence of definitive outcomes study data, the effect of triglyceride reduction in patients with persistently high triglyceride levels could not be considered what is known as a "validated" surrogate for cardiovascular risk re-

[11] Consistent with labeling for other lipid-modifying drugs, the drug label would also be expected to show the effect of Vascepa® on other studied lipid, lipoprotein, and inflammatory parameters relevant to cardiovascular health.

duction, like LDL-C (low-density lipoprotein cholesterol or "bad cholesterol") is for cardiovascular risk reduction.

65. As part of the ANCHOR SPA agreement regulatory dialogue, Amarin also undertook the planning, design, and implementation of a cardiovascular outcomes clinical study called "REDUCE-IT" to evaluate whether Vascepa® would help prevent major cardiovascular events in high risk patients (including patients with persistently high triglyceride levels) on statin therapy. FDA required that Amarin enroll at least 50% of planned patients in the REDUCE-IT study before FDA would accept for review Amarin's application for approval of Vascepa® for patients with high triglycerides under the ANCHOR SPA agreement. This requirement was designed to ensure that the clinical study investigating Vascepa®'s effect on cardiovascular risk reduction would be well underway before FDA would make a determination to approve the expanded use for Vascepa® in patients with high triglyceride levels.

66. The 50% enrollment requirement was a tremendous expense for Amarin (over $100 million) and delayed Amarin's submission of its high triglyceride application by over 16 months. In return, the SPA agreement was supposed to minimize development risk for Amarin because of the regulatory predictability thought to be provided by the SPA program.

67. The REDUCE-IT study was 50% enrolled when Amarin submitted to FDA its supplemental new drug application to treat patients with persistently high triglyceride levels. The REDUCE-IT study is ongoing. It is expected to be completed at the end of 2017 and the results are expected to be available in 2018. Amarin, a small company, is fully funding the cost of this outcomes study without financial support from The National Institutes of Health or any other government agency.

68. Amarin and FDA amended the ANCHOR SPA agreement in May 2010. At the time of the amendment, the ACCORD-Lipid study results had been published. FDA again agreed, through the amendment, that that the design, execution, and analysis in the SPA agree-

ment would provide the required clinical data for approval of Vascepa® for adult patients with high triglyceride levels if the ANCHOR study met its pre-specified endpoints.

69. The ANCHOR study met each of the primary and secondary endpoints specified in its SPA agreement. The study results showed statistically significant differences from baseline to end-of-study between placebo and Vascepa® with respect to triglyceride levels, the primary endpoint, and other lipid, lipoprotein, and inflammatory biomarkers, or secondary endpoints, including non-HDL-C (non-high density lipoprotein cholesterol or non-"good cholesterol."). Notably, the reduction in triglycerides observed with Vascepa® was not associated with elevations in LDL-C (low-density lipoprotein cholesterol or "bad cholesterol") relative to placebo. There is a strong and graded correlation between LDL-C and the risk of cardiovascular disease. These secondary clinical benefits favorably distinguish Vascepa® from other triglyceride-lowering medications on the market that have been shown in some patients to increase LDL-C, while lowering triglyceride levels and/or have other negative side effects detailed in their FDA-approved labeling.

70. Based on the ANCHOR trial results and in reliance on the amended ANCHOR SPA agreement, Amarin submitted a supplemental new drug application to FDA on February 21, 2013 that requested approval for Vascepa® for use by adult patients on statin therapy with persistently high triglyceride levels. As required by the regulatory dialogue related to the ANCHOR SPA, FDA's acceptance for review of Amarin's supplemental new drug application confirmed that Amarin had obtained at least 50% enrollment in the REDUCE-IT trial. In short, Amarin had satisfied all of the requirements for FDA approval in the amended ANCHOR SPA agreement and related regulatory dialogue. Thus, it was anticipated that FDA would approve Vascepa® for use by patients with high triglyceride levels, barring a public health concern resulting from a substantial scientific issue that was not evident when testing had begun.

71. On October 16, 2013, as part of its supplemental new drug application review, FDA convened a public Advisory Committee to consider the efficacy of Vascepa® in light of other studies that assessed the relationship between lowering triglyceride levels and the risk of cardiovascular disease "[b]ecause [FDA] recognized that there may be differing opinions regarding the interpretation and relevance [of other studies]." FDA asked the committee to focus on whether the changes in triglyceride levels demonstrated by the ANCHOR study would translate into a meaningful reduction *in cardiovascular risk* among Vascepa®'s proposed target population.

72. The ANCHOR study was not intended or designed to measure the impact of Vascepa® on cardiovascular risk. By agreement with FDA, the ANCHOR study measured the effectiveness of Vascepa® in lowering triglyceride levels and other lipid, lipoprotein, and inflammatory biomarkers in patients with high triglycerides. And that, along with 50% enrollment of the REDUCE-IT trial, is all FDA required of Amarin in the amended ANCHOR SPA agreement.

73. During its review, the Advisory Committee discussed the ACCORD-Lipid, AIM-HIGH, and HPS2-THRIVE studies, each of which evaluated the respective effects of fenofibrates and niacin on the risk of cardiovascular events in patients on statin therapy. Like Vascepa®, these drugs have been shown to reduce triglyceride levels. But fenofibrates and niacin are in different drug classes than Vascepa®, work differently in the body, and showed less favorable safety profiles than Vascepa® in their clinical trials. The three cited studies examined different patient populations than those in Vascepa®'s ANCHOR and REDUCE-IT studies; they did not focus on patients with high triglycerides—the target patient population for Vascepa®; they did not test whether reduction of triglycerides in patients with persistently high triglycerides would translate into a reduction in cardiovascular risk; and they did not address what effect Vascepa®'s

triglyceride-lowering and other effects would have on the risk of cardiovascular disease in patients with persistently high triglycerides.

74. Throughout the Advisory Committee meeting, FDA representatives emphasized that FDA had no concern about Vascepa®'s safety, which had already been established. In fact, current FDA-approved labeling of Vascepa® reflects not only safety data from patients studied in support of the approved indication, but also reflects safety data from the ANCHOR trial. Instead, FDA representatives focused primarily on whether Amarin had demonstrated that Vascepa® lowers the risk of cardiovascular disease. Both FDA and the Advisory Committee members acknowledged that Amarin had satisfied its obligations under the ANCHOR SPA agreement, and that Vascepa® unquestionably lowered triglyceride levels in adult patients with high triglyceride levels.

75. At the end of the Advisory Committee meeting, the committee concluded that, even though Amarin had fully satisfied the ANCHOR SPA, "substantial uncertainty" existed regarding "whether Vascepa®'s induced reductions in serum triglyceride levels would significantly reduce the *risk for cardiovascular events*" in patients with persistently high triglyceride levels.

76. But there was no definitive long-term outcomes study establishing the connection between triglycerides and cardiovascular risk reduction when Amarin and FDA entered into the ANCHOR SPA agreement and when they agreed to amend it. That was why FDA required Amarin to do more than prior drug sponsors in this field by beginning to enroll the REDUCE-IT study before Amarin could avail itself of the purported benefits of the SPA program.

77. On October 29, 2013, based on the Advisory Committee outcome, FDA purported to rescind the ANCHOR SPA agreement on the ground that a "substantial scientific issue" had arisen as to whether the reduction of triglyceride levels alone established an effective reduction in overall cardiovascular risk in subjects with triglyceride levels below 500 mg/dL.

78. FDA's purported rescission negated the very purpose of the SPA agreement, which is to ensure that companies like Amarin are not subject to a "moving target syndrome," whereby they spend several years and, in Amarin's case, well over $100 million on inherently risky clinical trials that FDA initially endorses but later deems inadequate for drug approval.

79. Amarin sought reconsideration and appealed the SPA agreement's rescission and urged in its submissions to FDA that the Agency had unlawfully rescinded the SPA agreement and unfairly inserted a new condition for FDA approval of the triglyceride-lowering claim by evaluating the ANCHOR study's results against a scientific objective never identified in the trial's agreed design—namely, the reduction of cardiovascular risk.

80. The SPA rescission reconsideration and appeal process within FDA involved three levels of FDA and senior FDA officials and lasted nearly a year. In its most recent, September 2014 appeal denial, FDA re-articulated its basis for rescission of the SPA agreement as follows:

> . . . the accumulation and totality of the scientific data and information, including reevaluation and improved understanding of the relevant scientific knowledge, that have become available since the ANCHOR trial began, raises a substantial scientific issue essential to determining the safety or effectiveness of Vascepa; i.e., whether a controlled trial(s) using reductions of [triglycerides] in patients on statin therapy as the primary endpoint can serve as the primary basis for demonstration of efficacy.

81. But when FDA entered into the ANCHOR SPA agreement, it exercised its discretion under the FDCA and the SPA program to commit to use the ANCHOR study's results as the primary basis for approval. FDA made this commitment, even though triglycerides were not then definitively shown to be a valid surrogate for cardiovascular risk reduction and FDA could not have been confident of the effects of Vascepa® on cardiovascular risk due to the absence of Vascepa® cardiovascular outcomes study data.

82. Based on FDA's review of Amarin's appeal at senior levels and its repeated position during the appeal process consistent with that stated above, Amarin determined that further appeal would be futile.

83. Amarin had proposed multiple alternative indications, data presentations, disclaimers, and other regulatory approval pathways to FDA under the supplemental new drug application. With ANCHOR safety data already reflected in Vascepa®'s drug labeling, Amarin asked FDA to approve including the ANCHOR efficacy results in the Vascepa® label with a disclaimer stating that using Vascepa® has not been demonstrated to reduce cardiovascular risk.

84. For years, FDA permitted other triglyceride-lowering drugs, such as fenofibrates and niacin, to be marketed with such disclaimers, even though those drugs—unlike Vascepa®—had *failed* outcomes studies that concluded that they provided no added benefit to statins in reducing cardiovascular risk.

85. Inclusion of such a disclaimer in the Vascepa® label, though not as strong an endorsement as an FDA-approved indication, would have permitted Amarin to communicate truthful and non-misleading information to doctors about the ANCHOR study results without fear of criminal and/or civil liability.

86. On April 27, 2015, FDA issued the Complete Response Letter ("CRL"), which (i) refused to approve a new indication for Vascepa® for patients with persistently high triglyceride levels from 200 to 499 mg/dL and (ii) refused to approve Amarin's request to include the ANCHOR efficacy results in the Vascepa® label, even with the proposed disclaimer language.

87. In the CRL, FDA explained its decision to refuse to approve a new indication for Vascepa® as follows:

> [T]he clinical rationale for reducing serum TG [triglycerides] (or modifying other lipid/lipoprotein parameters) with Vascepa among statin-treated patients with TG 200-499 mg/dL would be to reduce CV [cardiovascular] risk further. We have concluded that, at present, there are insufficient data to support a drug-induced

> change in serum TG as a surrogate for reducing CV risk this population. The ACCORD-Lipid, AIM-HIGH, and HPS2-THRIVE trials provide the most contemporary information regarding the potential CV benefits of modulating TG (or other lipoprotein parameters such as non-HDL-C and HDL-C), among statin-treated patients, with drugs that predominantly affect lipids other than LDL-C. Instead of confirming a hypothesis that further lowering of TGs or non-HDL-C (or raising HDL-C) in statin-treated patients reduces residual CV risk, these trials failed to demonstrate any additional benefit of lipid-altering drugs that target these lipid parameters in the overall trial populations.

88. FDA did not maintain in the CRL that Vascepa® was unsafe or ineffective in reducing triglyceride levels in patients with high triglycerides. FDA instead stated that, because there was a "current level of uncertainty regarding the benefit of drug-induced changes in lipid/lipoprotein parameters on CV risk among statin-treated patients with residually high TG [triglycerides] (200-499 mg/dL)," Amarin would need to provide evidence of a reduction in cardiovascular risk before approval would be granted. FDA noted that "the final results from the REDUCE-IT trial could be submitted to satisfy this deficiency."

89. In the CRL, FDA provided no rationale for denying Amarin's request for expanded labeling, but stated only that it would decide on Amarin's proposed expanded labeling after Amarin completed the REDUCE-IT trial.

90. The CRL concluded with a warning that any effort by Amarin to market Vascepa® for the proposed supplemental use could constitute "misbrand[ing] under the Federal Food, Drug, and Cosmetic Act." As explained below at paragraphs 134-35, violation of the FDCA's "misbranding" provision would expose Amarin to criminal liability, including imprisonment and significant collateral consequences, and massive civil liability.

91. Upon information and belief, the decision to deny Amarin's application was reviewed by at least the same three levels of FDA senior officials that had denied Amarin's SPA agreement rescission appeal. Upon information and belief, the issues presented by the expanded drug indication application denial, such as the decision to remove indications and labeling from fibrate and niacin products, also included consultation with FDA's Medical Policy Council,

which consists of even higher and interdisciplinary authorities at FDA. Based on FDA's actions to revise other products' labeling and FDA repeated positions at high levels in the SPA rescission appeal on issues directly relevant to the outcome of the CRL, Amarin determined that appeal of the FDA's decision in the CRL would be futile.

92. Under FDA's interpretation and application of regulations, the effect of FDA's CRL is to continue to prohibit Amarin from engaging in promotion of Vascepa® for treatment of patients with persistently high triglycerides, including the communication of the truthful non-misleading data generated by a successful study design to which FDA itself agreed.

93. Despite having done everything it could to design, pre-approve with FDA, and conduct a successful clinical trial that would establish the evidentiary requirements for approval, Amarin now finds itself unable to engage in a full and truthful dialogue with healthcare professionals about the success of the ANCHOR trial and the effectiveness of Vascepa® in lowering triglycerides and improving other parameters relevant to cardiovascular health in patients with persistently high triglycerides, even if Amarin states that Vascepa® has not been shown to reduce the risk of cardiovascular disease.

94. Due to Amarin's continued efforts to meet FDA's requirements for drug claim approval, it has now been over four years since April 2011 when Amarin demonstrated the effect of Vascepa® on patients with persistently high triglycerides and Amarin still cannot freely communicate the results of the ANCHOR trial in a truthful and non-misleading manner without fear of criminal prosecution and civil liability due to FDA's regulatory regime.

The Prescription of Triglyceride-Lowering Drugs Without Essential Available Data

95. FDA did not conclude in the CRL that Vascepa® fails to reduce cardiovascular risk, but only that it will require more evidence before approving Vascepa® for use to reduce triglycerides in patients with persistently high triglycerides. As FDA stated in the CRL, there

simply is "uncertainty" about the scientific link between triglyceride-lowering drugs and reduction in cardiovascular risk.

96. Despite this uncertainty, many doctors, including Doctor Plaintiffs, continue to prescribe triglyceride-lowering drugs to treat patients at risk for cardiovascular disease. Lacking definitive scientific proof that lowering triglycerides reduces the risk of cardiovascular disease, these doctors instead rely on available scientific data and clinical guidelines that recommend using these drugs for that purpose.

97. As FDA has acknowledged in its correspondence with Amarin, different standards apply to the development of clinical guidelines and FDA drug approval. In FDA's own words:

> [T]he data supporting clinical guidelines is of a different quality than what is required for drug approval by FDA. Clinical guideline development consists of gathering whatever evidence is available, evaluating what data exists, summarizing that data and translating it into a clinical practice guidelines based on opinion. Opinion is used to interpret evidence and also to derive recommendations in the absence of evidence. This can involve values, theory, and clinical experience in deriving the recommendations. This is much different from the regulatory standard for drug approval. . . .

98. Given the different standards for FDA drug approval and clinical guidelines, it is not surprising that, despite FDA's views on whether Vascepa® should be approved to reduce triglycerides in patients with persistently high triglycerides, many doctors still follow clinical guidelines advising to treat such patients with triglyceride-lowering drugs. Particularly given FDA's acknowledged "uncertainty" in the science, these doctors need more, not less, information about the current state of the science to make fully-informed clinical decisions about what is best for their patients. Yet FDA's effective all-out ban on any discussion initiated by Amarin of off-label use of Vascepa® prevents doctors from receiving essential information.

99. To make matters worse, by prohibiting Amarin from discussing the ANCHOR study and its results with doctors, FDA is actually *misleading* doctors and the public. For years,

other triglyceride-lowering drugs, such as fenofibrates and niacin, have been approved by FDA for treatment of persistently high triglycerides in adult patients on statin therapy. To get that approval, those drugs were required only to show that they were effective in lowering triglycerides in such patients, not that they reduced cardiovascular risk.

100. In light of FDA approval for this indication, manufacturers of fenofibrate and niacin have for years been able to freely promote their drugs to healthcare professionals for treatment of persistently high triglycerides. Even after these drugs had *failed* outcomes trials, and even though these drugs are associated with certain negative side effects, FDA still permitted their manufacturers to freely promote the drugs for treatment of persistently high triglycerides for years with disclaimers on their label, including disclaimers stating that they had not been demonstrated to reduce the risk of cardiovascular disease.[12]

101. Likewise, since 2008, FDA-approved labeling allowed the manufacturer of Lovaza®, which is a partially-purified fish oil concentrate that includes the omega-3 fatty acids EPA and DHA,[13] to tell healthcare professionals that Lovaza® is effective in lowering triglycerides in patients with persistently high triglycerides, even though FDA denied approval to Lovaza® for that indication after a study evaluating the effects of the drug also showed that it unacceptably

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12 For example, Trilipix® and Niaspan® were required to carry disclaimers on their labeling stating that "no incremental benefit" of these drugs "on cardiovascular morbidity and mortality" over and above that demonstrated for statin monotherapy has been established. On the same day that FDA issued the CRL, FDA removed the indications for fenofibrates and niacin in treating adult patients with persistently high triglycerides on statin therapy and strengthened the disclaimer language for these drugs to require disclosure of the failed ACCORD-Lipid and AIM-HIGH outcomes studies. The effect of FDA's removal of the indication for treatment of persistently high triglycerides despite statin use in fenofibrates and niacin was to prevent the manufacturers of those drugs from further promoting their drugs for that purpose.

13 Vascepa® is different than Lovaza®. Vascepa® consists of the single molecule, EPA. According to FDA, Lovaza® contains a naturally derived, partially-purified fish oil concentrate mainly consisting of a mixture of fatty acids, predominantly EPA and DHA. That difference is significant, as DHA is associated with increases in LDL-C (i.e., "bad" cholesterol") in patients at high risk characterized by high and very high triglyceride levels.

raised LDL-C (i.e., "bad" cholesterol) when compared to placebo.[14] Amarin's similar clinical trial of Vascepa®, the ANCHOR trial, showed no elevation of LDL-C relative to placebo.

102. Vascepa® has not failed an outcomes trial. (In fact, FDA has "strongly urge[d]" Amarin to continue with the REDUCE-IT trial.) Available scientific evidence reflects that beyond triglyceride lowering EPA may have multiple other benefits relevant to cardiovascular disease. Vascepa® has shown a more favorable safety profile than these other drugs (e.g., it is not associated with elevations in LDL-C relative to placebo). Nonetheless, FDA has for years precluded Amarin from engaging in a full and truthful dialogue with doctors about the success of the ANCHOR trial and the effectiveness of Vascepa® in lowering triglycerides and improving other parameters relevant to cardiovascular health in patients with persistently high triglycerides, even if Amarin acknowledges that Vascepa® has not been shown to reduce the risk of cardiovascular disease.

103. Upon information and belief, because manufacturers of other triglyceride-lowering drugs have for years been able to freely promote their drugs to healthcare professionals for treatment of persistently high triglycerides and Amarin has not, many healthcare professionals have incomplete information about available treatment options to consider as they determine how best to treat their patients at risk for cardiovascular disease.

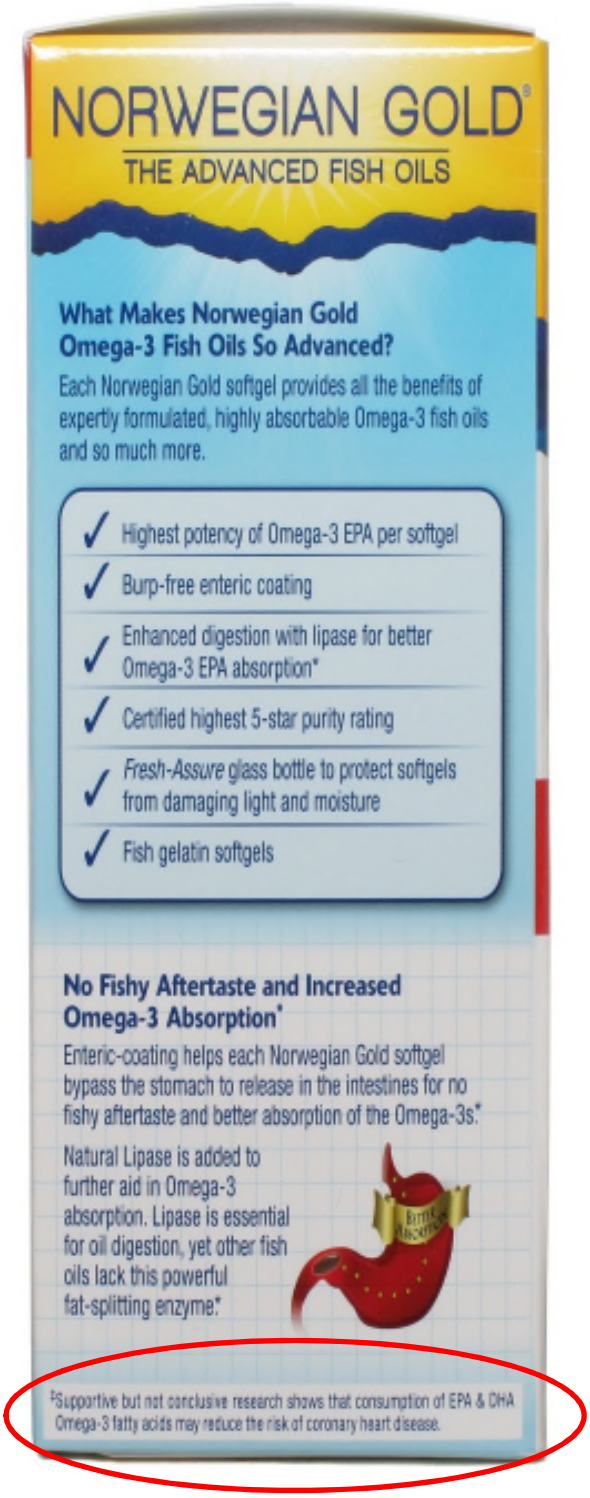
FDA-Permitted Health Claims for Omega-3 Supplements

104. Inconsistently, FDA permits—albeit under a different regulatory standard—the following qualified health claim to be used by dietary supplement manufacturers who market dietary supplements that include EPA, the single ingredient in Vascepa®, and/or DHA, another omega-3 fatty acid, directly to consumers:

[14] In May 2014, FDA removed the information from the Lovaza® label that allowed its manufacturer to engage in such marketing.

> Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease. One serving of [name of the food] provides [] gram of EPA and DHA omega-3 fatty acids. [See nutrition information for total fat, saturated fat, and cholesterol content.]

105. Supplement manufacturers who sell fish oil or other omega-3 fatty acid capsules with both EPA and DHA or with EPA only have included this health claim on their labels—as FDA permits. Norwegian Gold EPA 1000 Omega capsules contain fish oil and have EPA only. Those supplements contain the health claim directly on the container:


NORWEGIAN GOLD®
THE ADVANCED FISH OILS
What Makes Norwegian Gold Omega-3 Fish Oils So Advanced?
Each Norwegian Gold softgel provides all the benefits of expertly formulated, highly absorbable Omega-3 fish oils and so much more.
✓ Highest potency of Omega-3 EPA per softgel
✓ Burp-free enteric coating
✓ Enhanced digestion with lipase for better Omega-3 EPA absorption*
✓ Certified highest 5-star purity rating
✓ Fresh-Assure glass bottle to protect softgels from damaging light and moisture
✓ Fish gelatin softgels
No Fishy Aftertaste and Increased Omega-3 Absorption*
Enteric-coating helps each Norwegian Gold softgel bypass the stomach to release in the intestines for no fishy aftertaste and better absorption of the Omega-3s.*
Natural Lipase is added to further aid in Omega-3 absorption. Lipase is essential for oil digestion, yet other fish oils lack this powerful fat-splitting enzyme.*
*Supportive but not conclusive research shows that consumption of EPA & DHA Omega-3 fatty acids may reduce the risk of coronary heart disease.

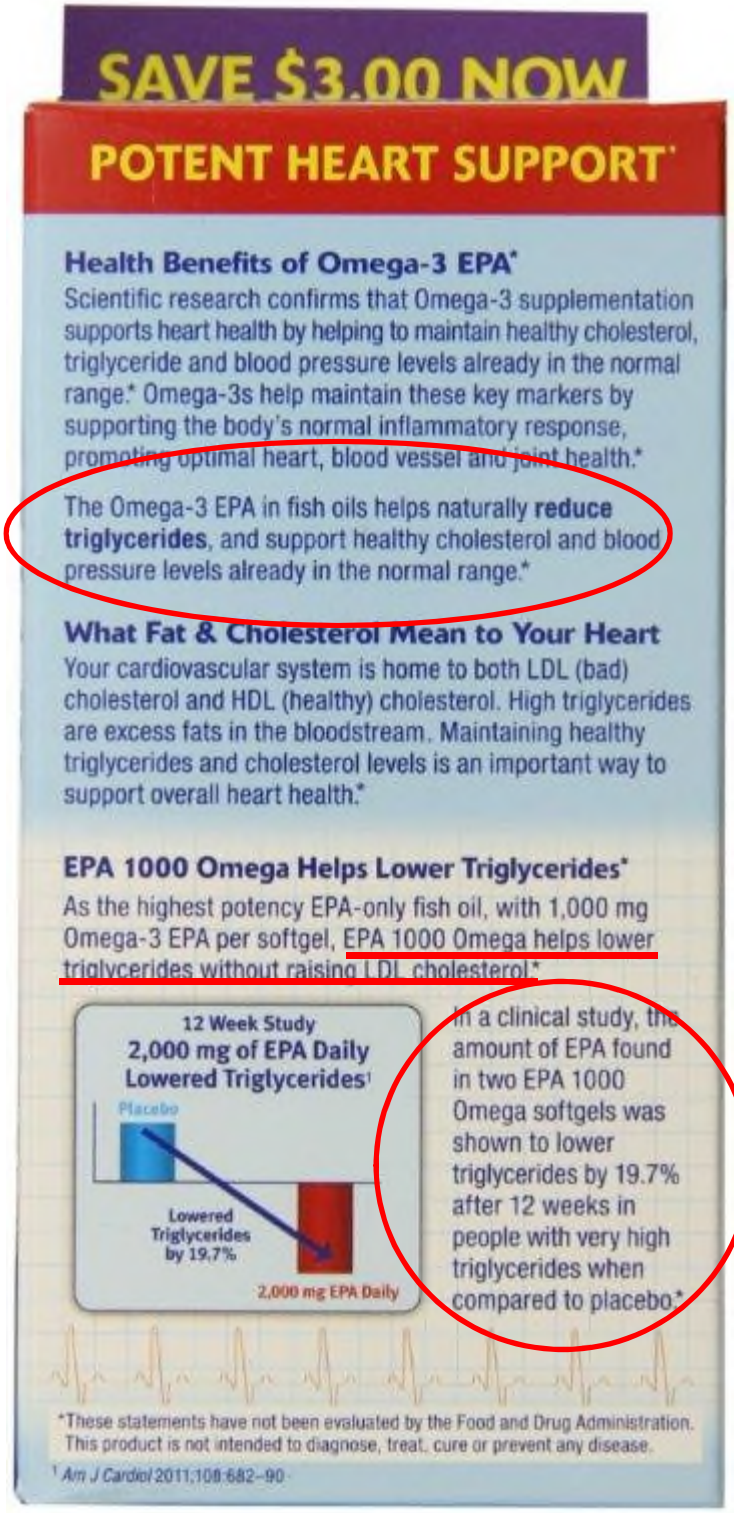
106. In some instances, the qualified health claim is even described on the package as an "FDA approved health statement." For instance, the label below comes from vegan omega-3 capsules made from algae oil that contains DHA and EPA:

107. FDA knows these supplements contain this qualified health claim on their labels and allows them to do so.

108. FDA also knows that certain dietary supplement manufacturers that market supplements that include EPA and/or DHA make prominent claims that their products reduce triglycerides, referencing Amarin's clinical studies of Vascepa® to support these statements. For example, the product details for Norwegian Gold EPA 1000 Omega states: (1) "In a clinical

study, the amount of EPA found in two EPA 1000 Omega softgels was shown to lower triglycerides by 19.7% after 12 weeks in people with very high triglycerides when compared to placebo"; (2) "EPA 1000 Omega helps lower triglycerides without raising LDL cholesterol"; and (3) "The Omega-3 EPA in fish oils helps naturally reduce triglycerides."[15] These statements are printed directly on the container:

[15] Product Details for Norwegian Gold EPA 1000, http://www.amazon.com/Renew-Life-1000-Omega-Count/dp/B00B7LFL0A (last visited May 3, 2015); *see also* Nordic Naturals website, http://www.nordicnaturals.com/en/Support_Labels_Pro/Targeted_Support/955 (claiming, in relation to a number of EPA supplements, "High EPA levels have been shown to reduce elevated triglyceride levels.") (last visited May 3, 2015).



109. Dietary supplement companies must notify FDA within 30 days of first marketing a dietary supplement that contains a statement that describes the effect of the dietary supplement

on the structure or function of the body. 21 U.S.C. § 343(r)(6); 21 C.F.R. §101.93(a)(1). The statements must be accompanied by an FDA disclaimer stating, "this statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease." 21 C.F.R. §101.93(c). FDA will review the notifications and issue "courtesy letters" when the agency considers the statement to be a "disease claim," which is prohibited on dietary supplements. *See* C.F.R. § 101.93(f) (deeming a dietary supplement subject to regulation as a drug if its label or labeling bears a disease claim). Disease claims are defined as including a statement that "has an effect on the characteristic signs or symptoms of the disease or class of diseases." If FDA views a claim such as "lowers triglycerides" as a disease claim due to the relationship between triglyceride levels and heart disease, the agency will issue a courtesy letter, but it will not issue such a letter if the agency considers the claim appropriate for use on dietary supplements.

110. In numerous instances, FDA has received 30-day notifications for omega-3 dietary supplements and has raised no objections to the use of a "triglyceride lowering" claim. *See, e.g.*, FDA Courtesy Letter to Pharma Defense, April 10, 2012; FDA Courtesy Letter to The JB Group, July 8, 2008; FDA Courtesy Letter to Market America, Inc., December 6, 2004. In each of these courtesy letters, FDA objected to other claims in the 30-day notification as disease claims but did not object to triglyceride-reduction claims. Upon information and belief, FDA is taking the view that a "triglyceride lowering" claim is appropriate for dietary supplements and does not imply disease prevention when the claim appears on dietary supplements but takes the view that the same claim cannot appear on drugs because it implies the product will reduce the risk of heart disease.

111. That FDA has taken this view is further supported by Amarin having notified FDA of the "lowers triglycerides" and other such unapproved health claims made directly to the

public by dietary omega-3 supplement manufacturers. But FDA has taken no action against these manufacturers, in some cases for more than two years after notice from Amarin.

112. Thus, FDA permits lay consumers to be told that research shows that consumption of EPA and DHA "may" reduce the risk of coronary heart disease, and that EPA "lowers triglycerides"—without regard to risk characteristics for a particular patient population—but forbids Amarin from telling sophisticated doctors that Vascepa®, which consists of EPA, effectively lowers triglycerides for patients with persistently high triglycerides—even if Amarin discloses that it has not yet been determined whether Vascepa® reduces the risk of cardiovascular disease. This gets things backwards. The First Amendment "directs us to be especially skeptical of regulations that seek to keep people in the dark for what the government perceives to be their own good," particularly applicable when the audience consists of prescribing physicians considered to be "sophisticated and experienced consumers." *Sorrell* v. *IMS Health, Inc.*, 131 S. Ct. 2653, 2671 (2011) (internal citations and quotation marks omitted). To allow lay consumers but not sophisticated doctors to receive qualified health claims about the potential cardiovascular benefits of omega-3 fatty acids defies common sense and violates the First Amendment.

113. In light of FDA's refusal to approve the supplemental new drug applications in the CRL, FDA regulations (discussed below) effectively prevent Amarin from engaging in a truthful and non-misleading dialogue about Vascepa® and prevent the doctors who prescribe Vascepa®, including the Doctor Plaintiffs, from obtaining truthful and non-misleading information from Amarin about Vascepa® and its effect on patients with high triglyceride levels.

114. This outcome not only violates Amarin's First Amendment right to provide such information, but also violates the Doctor Plaintiffs' First Amendment right to receive the information they need to properly evaluate and prescribe an FDA-approved product.

115. Dietary supplement manufacturers may promote their EPA products to lay consumers with the aid of the FDA-reviewed and authorized qualified health claim suggesting a po-

tential coronary heart disease benefit. But if Amarin made that same suggestion to healthcare professionals with respect to Vascepa®, Amarin would be subject to criminal prosecution and civil liability due to FDA's regulatory scheme. This *misleads* healthcare professionals because it permits speech about dietary supplements' potential effectiveness in reducing the risk of coronary heart disease but prohibits the same speech about Vascepa®, despite the fact that Vascepa® is a high-quality, pharmaceutical-grade product that, unlike dietary supplements, has been clinically proven to lower triglycerides and has a demonstrated safety profile comparable to placebo. As a result, doctors like the Doctor Plaintiffs, who are interested in treating patients to lower their persistently high triglyceride levels, are informed that dietary supplements may reduce the risk of disease but not similarly informed that Vascepa® might also do the same.

116. Upon information and belief, this dynamic has led certain doctors to advise their patients to take omega-3 dietary supplements instead of pharmaceuticals like Vascepa® and has contributed to significant growth in the omega-3 dietary supplement market. According to data from Euromonitor International, a market intelligence firm, sales of fish oil supplements in the United States rose from $425 million in 2007 to over $1 billion in 2012.

117. Unfortunately for patients, the dietary supplement industry is loosely regulated. Omega-3 dietary supplements are not recommended by FDA at doses of more than 2 grams per day (Vascepa® is approved at 4 grams per day) and are not recommended by FDA at any dose to treat or mitigate disease. Dietary supplements are not required to meet strict FDA drug standards for safety, efficacy, and manufacturing. Many omega-3 and fish oil dietary supplements are low in omega-3 content, may vary in content from lot to lot, need only contain 80% of labelled claims, can contain harmful contaminants, are prone to oxidation (spoilage) that mitigates antioxidant effects and can lead them to be pro-oxidants, and contain DHA, which is associated with increases in bad cholesterol in patients at high risk characterized by high and very high blood levels of triglycerides.

118. Moreover, public policy concerns compel at least a level playing field. Dietary supplement manufacturers making claims about reducing the risk of life-threatening diseases such as coronary heart disease present a serious public health risk because they divert patients from treatments administered under the care and supervision of a physician. FDA recognized this risk in the final rule for dietary supplement structure-function claims, again using the comparable example of disease claims regarding a product's ability to lower cholesterol levels:

> FDA agrees that prevention of heart disease is an extremely important public health goal. Lowering cholesterol with certain drugs has been conclusively shown to be effective in reducing mortality from coronary artery disease. Indeed, the evidence linking the lowering of elevated cholesterol with preventing heart disease is so strong that identifying and using effective therapies to lower cholesterol in patients with elevated cholesterol levels has become of compelling importance. With this in mind, use of possibly ineffective therapies in persons with elevated cholesterol, which can delay or prevent effective treatment, poses significant public health risks.

65 Fed. Reg. at 1019.

Amarin's Proposed Speech and the "Off-label" Prescription of Vascepa®

119. Many physicians, including the Doctor Plaintiffs, continue to treat triglyceride levels in at-risk patients, even though such treatment has not been proven to reduce the risk of cardiovascular disease, because in their clinical judgment with the support of numerous treatment guidelines, it is in their patients' best interests to do so. Many doctors consider Vascepa® to be a superior product among FDA-approved triglyceride-lowering drugs because of its effectiveness and limited side effects. It is perfectly legal for these doctors to prescribe Vascepa® for the "off-label use" of treating patients with high triglyceride levels. These doctors want and need, for patient benefit, detailed information about Vascepa® and its safety and effectiveness for this "off-label" use. FDA's regulatory response to Vascepa® renders impossible the type of complete and candid discussion of these issues to which these doctors are legally entitled.

120. Other doctors who continue to treat persistently high triglycerides with drug therapy may not know about all of their treatment options, given that FDA precluded Amarin from

marketing Vascepa® for treatment of persistently high triglycerides for years, while allowing manufacturers of other similarly, or even worse-situated drugs to do so. These doctors need truthful and accurate information about Vascepa® and its safety and effectiveness for treatment of persistently high triglycerides to make fully-informed decisions about what is best for their patients.

121. Amarin does not seek to engage in direct-to-consumer communications about the off-label use of Vascepa®. Nor does it seek to discuss with consumers the cardiovascular risk reduction effect still under evaluation in the REDUCE-IT trial.

122. Beyond FDA's narrow exceptions set forth in guidance, including for responses to unsolicited requests, Amarin seeks only to engage in truthful, non-misleading speech about Vascepa® directly with healthcare professionals such as doctors, pharmacists, and managed care professionals, including but not limited to the Doctor Plaintiffs.

123. Amarin may now promote Vascepa® for use in patients with very high ($\geq$ 500 mg/dL) triglycerides based on its FDA-approved labeling. That labeling includes data on Vascepa® safety (from both the MARINE and ANCHOR studies). That labeling also warns readers that the effect of Vascepa® on the risk for pancreatitis and cardiovascular mortality and morbidity in patients with very high triglyceride levels has not been determined.

124. Amarin seeks the freedom to disclose to doctors and other healthcare professionals, and the Doctor Plaintiffs want to receive information from Amarin that:

- Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease.
- The ANCHOR study demonstrates that Vascepa® lowers triglyceride levels in patients with high ($\geq$ 200 mg/dL and < 500 mg/dL) triglyceride levels not controlled by diet and statin therapy.

- In the ANCHOR study, Vascepa® 4g/day significantly reduced TG [triglycerides], non-HDL-C [non-high density lipoprotein cholesterol or non-"good cholesterol"], Apo B [Apolipoprotein B], VLDL-C [very-low-density lipoprotein cholesterol], TC [total cholesterol] and HDL-C [high density lipoprotein cholesterol or "good cholesterol"] levels from baseline relative to placebo in patients with high ($\geq$ 200 mg/dL and < 500 mg/dL) triglyceride levels not controlled by diet and statin therapy. The reduction in TG [triglycerides] observed with Vascepa® was not associated with elevations in LDL-C [low-density lipoprotein cholesterol or "bad cholesterol] relative to placebo.

Amarin also seeks to provide healthcare professionals with the following detailed and accurate information:

- peer-reviewed scientific publications relevant to the potential effect of EPA on the reduction of the risk of coronary heart disease, a representative sample of which is included as Exhibit A; and
- efficacy data from the ANCHOR study, including, but not limited to, the written statement attached to this Complaint as Exhibit B.

To ensure that these messages are not misleading, Amarin would also contemporaneously disclose to healthcare professionals that:

- FDA has not approved Vascepa® to reduce the risk of coronary heart disease;
- FDA has not approved Vascepa® for the treatment of statin-treated patients with mixed dyslipidemia and high ($\geq$ 200 mg/dL and < 500 mg/dL) triglyceride levels;
- The effect of Vascepa® on the risk of cardiovascular mortality and morbidity has not been determined;

- A cardiovascular outcomes study of Vascepa® designed to evaluate the efficacy of Vascepa® in reducing cardiovascular mortality and morbidity in a high risk patient population on statin therapy is currently underway; and
- Vascepa® may not be eligible for reimbursement under government healthcare programs, such as Medicare or Medicaid, to reduce the risk of coronary heart disease or for treatment of statin-treated patients with mixed dyslipidemia and high ($\geq$ 200 mg/dL and < 500 mg/dL) triglyceride levels. We encourage you to check that for yourself.

125. The information in the preceding paragraph is truthful and non-misleading and fully protected under the First Amendment. Amarin has a First Amendment right to engage in this speech, and the Doctor Plaintiffs and other healthcare professionals have a First Amendment right to receive it.

126. Amarin would communicate this information to doctors and other healthcare professionals through written materials and digital media about its product and by proactively engaging in a dialogue with doctors and other healthcare professionals about Vascepa®, peer-reviewed scientific articles, the ANCHOR study and its results. The message in the written materials, digital media, and dialogue would be guided by and consistent with the information outlined in paragraph 124 above. The information would be communicated in a manner that is truthful and non-misleading.

The Regulatory Regime

127. The Second Circuit recently explained that the FDCA cannot "criminaliz[e] the simple promotion of a drug's off-label use," because such a construction of the FDCA would "raise First Amendment concerns." *United States* v. *Caronia*, 703 F.3d 149, 160 (2d Cir. 2012). Yet, given FDA's interpretation of the FDCA and the complex regulatory regime built up around it, the threat of criminal prosecution for simple promotion of a drug's off-label use remains very

real. In addition, the Government's interpretation of the False Claims Act, 31 U.S.C. §§ 3729-3733, raises the specter of enormous civil liability for simple promotion of a drug's off-label use.

a. The FDCA and Accompanying Regulations

128. The threat of criminal prosecution under the FDCA is not a result of the plain language of the FDCA itself, but of FDA's interpretation of the FDCA and application of regulations that far exceed the scope of the FDCA. This is not a facial challenge to the FDCA or those regulations. But as applied in this case, FDA's regulations result in a construction of the FDCA that violates the First Amendment because it criminalizes the truthful and non-misleading information that Amarin wishes to convey and the Doctor Plaintiffs wish to receive.

129. Under the FDCA, a manufacturer like Amarin may not introduce or deliver for introduction into interstate commerce any "new drug" that FDA has not approved. 21 U.S.C. §§ 331(d), 355(a). The FDCA also prohibits the introduction or delivery for introduction into interstate commerce of a drug that is "misbranded," even if FDA has approved the drug. 21 U.S.C. §§ 331(a), 352.

130. A manufacturer seeking approval for a new drug must submit a detailed application to FDA to demonstrate the drug's safety and efficacy and propose labeling for the drug. 21 U.S.C. §§ 355(b). FDA evaluates whether the drug is safe and effective under the conditions "prescribed, recommended, or suggested" in the labeling, and it ensures that the labeling is not "false or misleading in any particular." 21 U.S.C. § 355(d).

131. FDA approval of a new drug application extends only to the uses prescribed, recommended, or suggested by the drug's FDA-approved "labeling." 21 U.S.C. § 321(p). Thus, if the manufacturer of an approved drug distributes "labeling" that prescribes, recommends, or suggests a new use not already generally recognized as safe and effective, the drug is considered a "new drug" under 21 U.S.C. § 321(p), and the manufacturer must obtain separate approval for the new use to avoid violating the FDCA.

132. The FDCA defines a "label" as "a display of written, printed, or graphic matter upon the immediate container of any article." 21 U.S.C. § 321(k). "Labeling" includes "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." 21 U.S.C. § 321(m). Materials are considered to "accompany" an article if they are sent from the same origin, to the same destination, as part of an "integrated . . . transactio[n]," and have a "textual relationship" to the article. *Kordel* v. *United States*, 335 U.S. 345, 349-50 (1948).

133. The FDCA regulates "labeling" content by prohibiting the introduction of "misbranded" drugs into interstate commerce. A drug is "misbranded" if, *inter alia*: (1) "its labeling is false or misleading in any particular"; or (2) the labeling does not bear "adequate directions for use." 21 U.S.C. § 352(a) and (f)(1).

134. Violations of the FDCA's "new drug" and "misbranding" requirements are criminal offenses subject to up to three years imprisonment and substantial fines and penalties. 21 U.S.C. § 333(a). Although introduction of an unapproved "new drug" or a "misbranded" drug into interstate commerce is generally a misdemeanor, the offenses are felonies if they are committed "with the intent to defraud or mislead" or after a prior conviction has become final. *Id.*

135. Besides potential imprisonment, conviction under the "new drug" and "misbranding" provisions of the FDCA may also carry significant collateral consequences. The Secretary of HHS may exclude from participation in any federal healthcare program an individual or entity convicted of a criminal offense "relating to fraud, theft, embezzlement, breach of fiduciary responsibility, or other financial misconduct" "in connection with the delivery of a health care item or service or with respect to any act or omission" in a government-operated healthcare program. 42 U.S.C. § 1320a-7(b)(1)(A)(i). If conviction is for a felony offense in connection with the delivery of a healthcare item or service, such exclusion is mandatory. 42 U.S.C. § 1320a-7(a)(3). To the extent a "new drug" or "misbranding" violation falls within § 1320a-7, conviction could

mean financially devastating exclusion from federal healthcare programs for manufacturers and individuals.

136. Although the FDCA broadly prohibits manufacturers from circulating "misbranded" drugs for non-approved use, 21 U.S.C. § 331, the FDCA does *not* limit or interfere with the authority of healthcare professionals to prescribe or administer legal drugs to treat any condition or disease in any manner.

137. FDA has acknowledged that "[o]nce a drug or medical device has been approved or cleared by the FDA, generally, healthcare professionals can lawfully use or prescribe that product for uses or treatment indications that are not included in the product's approved labeling." FDA, *Draft Guidance for Industry Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices*, 2011 WL 7029653 (Dec. 2011), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM285145.pdf ("Draft Guidance on Unsolicited Requests"); *see also* FDA, *Good Reprint Practices for Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices* (Jan. 2009), http://www.fda.gov/oc/op/goodreprint.html ("Good Reprint Practices"); *More Information for Better Patient Care: Hearing on S. 1477 Before the Senate Comm. on Labor and Human* Resources, 104th Cong. 81-82 (1996) ("Hearing on S.1477"); *accord* 59 Fed. Reg. 59820, 59820-22 (Nov. 18, 1994).

138. In discussing this compromise, FDA has conceded that "these off-label uses or treatment regimens may be important therapeutic options and may even constitute a medically recognized standard of care." Draft Guidance on Unsolicited Requests, at 2. *See also* Hearing on S.1477, at 81 ("[I]n certain circumstances, off label uses of approved products are appropriate, rational, and accepted medical practice").

139. FDA's written guidance for pharmaceutical industry treatment of off-label use information further recognizes that (i) healthcare professionals should receive comprehensive, up-to-date, accurate information about prescription drugs, and (ii) manufacturers are often in the best position to provide such information. As FDA states:

> [F]irms are capable of responding to requests about their own named products in a truthful, non-misleading, and accurate manner. Furthermore, as these firms are regulated by FDA and have robust and current information about their products, FDA recognizes that it can be in the best interest of public health for a firm to respond to unsolicited requests for information about off-label uses of the firm's products that are addressed to a public forum, as other participants in the forum who offer responses may not provide or have access to the most accurate and up-to-date information about the firm's products.

Draft Guidance on Unsolicited Requests, at 3.

140. But the guidance—which is not even binding on FDA—does not allow for full and frank communication because it suggests that manufacturers may only "respond to unsolicited requests for information about off-label uses of the firm's products." *Id.* It does not suggest that manufacturers may *initiate* exchanges of truthful and non-misleading speech about off-label uses. It also limits the information that a manufacturer may give in response to an unsolicited request. Finally, it prevents doctors, such as the Doctor Plaintiffs, from engaging in a full-blown dialogue with a manufacturer about off-label uses.[16]

141. Despite FDA's acknowledgement that it can be in the public interest for drug manufacturers to speak in certain instances about off-label uses of their products, FDA has constructed a web of regulations that, in conflict with the FDCA itself, criminalize virtually all manufacturer communication to healthcare professionals about the off-label use of prescription

[16] FDA's Revised Draft Guidance for Industry is substantially similar to the previous guidance on Good Reprint Practices. *Compare* Good Reprint Practices, *supra*, *with* FDA, Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices (Feb. 2014), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/ Guidances/UCM387652.pdf ("Revised Draft Guidance"). The revised guidance has not yet been approved. But even if it were approved, it would remain non-binding, and would not resolve the First Amendment problems with FDA's regulations as applied in this case.

drugs. In so doing, FDA's interpretation of the regulatory scheme, as-applied to Plaintiffs, would criminalize truthful and non-misleading commercial speech that is fully protected under the First Amendment. *See Caronia*, 703 F.3d at 160.

142. The primary purpose of commercial speech is to urge the recipient to buy or use a product or service. *See Va. State Bd. of Pharmacy* v. *Va. Citizens Consumer Council*, 425 U.S. 748, 762 (1976) (defining core commercial speech as speech that does "no more than propose a commercial transaction") (quoting *Pittsburgh Press Co.* v. *Hum. Rel. Comm'n*, 413 U.S. 376, 385 (1973)). In the context of off-label promotion, that means that the primary purpose of the speech is to promote the sale of the drug for an off-label use. Such speech is protected under *Caronia*, but FDA's regulations (as outlined below) still prohibit speech by drug manufacturers that proposes off-label use of their drug.

143. At the very least, FDA has been unclear about what is permitted and what is not post-*Caronia*. The resulting uncertainty, coupled with the very real threats of criminal prosecution or massive civil liability, has chilled drug manufacturer's speech about off-label uses.

144. FDA's vagueness in this area "raises special First Amendment concerns because of its obviously chilling effect" on otherwise permissible speech, *Reno* v. *ACLU*, 521 U.S. 844, 871-72 (1997), and creates uncertainty as to what speech will trigger criminal prosecution by FDA, which is unacceptable under the Due Process Clause of the Fifth Amendment, *FCC* v. *Fox Television Stations*, 132 S. Ct. 2307, 2317 (2012) (*Fox II*) (Due Process Clause of the Fifth Amendment requires "fair notice of what is prohibited.").

145. FDA's expansive interpretation of "labeling" and "prohibited advertisements" effectively captures all manufacturer speech concerning off-label uses of prescription drugs. As a result, all manufacturer speech about off-label uses, regardless of how truthful, non-misleading, and *beneficial* to the medical community the speech may be, is essentially banned.

146. First, FDA has expanded the category of materials that constitute "labeling" to make it virtually impossible for manufacturers to communicate with healthcare professionals independent of the FDA labeling regime. In contrast to the FDCA's relatively narrow definition of "labeling," which includes only "labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying any such article," 21 U.S.C. § 321(m), FDA's definition of "labeling" includes any:

> Brochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, sound recordings, exhibits, literature, and reprints and similar pieces of printed, audio, or visual matter descriptive of a drug and references published (for example, the "Physicians' Desk Reference") for use by medical practitioners, pharmacists, or nurses, containing drug information supplied by the manufacturer, packer, or distributor of the drug and which are disseminated by or on behalf of its manufacturer, packer, or distributor are hereby determined to be labeling as defined in [21 U.S.C.§ 321(m)].

21 C.F.R. § 202.1(*l*)(2). FDA's definition of "labeling" therefore encompasses any tangible materials distributed by the manufacturer that contain manufacturer-supplied drug information, whether or not those materials "accompan[y an] article" of a drug as contemplated by § 321(m).

147. As interpreted by FDA, this expanded definition precludes a manufacturer from disseminating any tangible materials to healthcare professionals that contain manufacturer-supplied drug information if those materials prescribe, recommend, or suggest an unapproved use of an approved prescription drug, because disseminating such information would render the manufacturer's drug an unapproved new drug.

148. Based on FDA's application of 21 C.F.R. § 202.1(*l*)(2), the FDCA's prohibition on statements in the "labeling" that are "false or misleading in any particular," 21 U.S.C. § 352(a), applies to any tangible materials containing manufacturer-supplied drug information that is distributed by the manufacturer. The Government has interpreted the phrase "false or misleading in any particular" to apply not only to actually or inherently false or misleading statements—which may be prohibited under the First Amendment—but also to any "scientific claims

about the safety, effectiveness, contraindications, side effects, and the like regarding prescription drugs" where FDA has not "had the opportunity to evaluate" those claims, despite the existence of bona fide scientific research supporting such claims. *Wash. Legal Found.* v. *Friedman*, 13 F. Supp. 2d 51, 67 (D.D.C. 1998), *vacated as moot on other grounds sub. nom. Wash. Legal Found.* v. *Henney*, 202 F.3d 331, 333 (D.C. Cir. 2000). The Government's interpretation of § 352(a) and redefinition of "labeling" thus effectively precludes any manufacturer-supplied drug information not directly focused on FDA-approved uses.

149. Second, even if certain information does not fall under FDA's interpretation of "labeling," FDA's interpretation of the FDCA and application of its regulations work to prohibit any discussion of off-label uses of prescription drugs. Consistent with First Amendment protections, the provisions of the FDCA governing prescription drug advertising do not by their terms prohibit advertisements for prescription drugs that contain information about off-label uses. 21 U.S.C. § 352(n). FDA, however, has proscribed through regulation any "advertisements" that "recommend or suggest any use that is not in the labeling accepted in [the drug's] approved new-drug application," 21 C.F.R. § 202.1(e)(4)(i)(a), effectively prohibiting any direct-to-physician advertisements suggesting off-label uses, regardless of the informational disclosures about the use. *Id.* Thus, it does not matter whether FDA considers manufacturer speech to be part of the drug's "labeling" or a separate "advertisement." The outcome is the same: no off-label promotion.

150. In addition, FDA has promulgated regulations concerning the FDCA's misbranding provisions that operate as additional restraints on manufacturer speech. As noted above, the FDCA deems a prescription drug "misbranded" if the drug's labeling lacks "adequate directions for use." 21 U.S.C. § 352(f)(1). FDA regulation provides that "adequate directions for use" means "directions under which the layman can use a drug safely and for *the purposes for which it is intended*." 21 C.F.R. § 201.5 (emphasis added). FDA has interpreted this to mean that a

drug's labeling must contain adequate directions for a consumer to engage in self-medication. However, by definition, a prescription drug can be used only under a physician's supervision, and therefore it is "impossible" under FDA's interpretation for prescription drugs to contain labeling with "adequate directions for use." *Becton, Dickinson & Co.* v. *Food & Drug Admin.*, 589 F.2d 1176, 1179 (2d Cir. 1978); *see also United States* v. *Articles of Drug*, 625 F.2d 665, 673 (5th Cir. 1980).

151. Because prescription drugs cannot satisfy the "adequate directions for use" requirement of the FDCA's misbranding provisions, as interpreted by FDA, FDA promulgated an exemption from the "adequate directions for use" requirement for prescription drugs. Under 21 C.F.R. § 201.100, a prescription drug will be exempt from the "adequate directions for use" requirement, and not misbranded, if, among other things, the "labeling on or within the package from which the drug is to be dispensed bears adequate information for its use." 21 C.F.R. § 201.100(c)(1). FDA defines "adequate information" broadly, to mean directions under which a medical professional "can use the drug safely and for *the purposes for which it is intended.*" *Id*. (emphasis added). The "intended" purpose or use is defined by FDA to include "all purposes for which [the drug] is intended, including all purposes for which [the drug] is advertised or represented," to be "intended" uses. 21 C.F.R. § 201.100(c)(1). As a result, for a prescription drug to avoid being misbranded, under FDA's interpretation of its regulations, its labeling must have sufficient directions for *all* such intended uses.

152. The misbranding and intended use regulations as interpreted by FDA thus operate to transform any off-label promotion, whether oral or in writing, and no matter how truthful and non-misleading, into criminal "misbranding." Under 21 C.F.R. § 201.100(c)(1), all representations made in any form by a manufacturer concerning its prescription drug that do not directly focus on the drug's on-label use may invoke additional "intended" uses for which the manufacturer must provide "adequate information," consisting of "indications, effects, dosages, routes,

methods, and frequency and duration of administration, and any relevant hazards, contraindications, side effects, and precautions." *See id*. Under FDA regulations, the required "adequate information" for all intended purposes of a drug must be provided through the FDA-approved labeling, which by definition does not include information about off-label uses. 21 C.F.R. § 201.100(c)(2). Thus, a prescription drug that is "advertised or represented" for an off-label use but cannot possibly contain off-label uses in its FDA-approved labeling violates the "adequate information" provision of FDA regulations and cannot, based on FDA interpretation, comply with the "adequate directions for use" requirement of § 352(f)(1). It is therefore automatically considered to be "misbranded" in criminal violation of § 352(f)(1). *See* 21 U.S.C. §§ 331(a), 333(a). FDA's regulations thus criminalize a manufacturer's truthful, non-misleading speech regarding lawful, off-label use of an approved prescription drug.

153. In addition to providing "adequate information" for all intended uses, a prescription drug manufacturer must ensure that all "labeling" is consistent with package inserts to be exempt from the "adequate directions" requirement of § 352(f)(1), which, under FDA interpretation, no prescription drug can satisfy. *See* 21 C.F.R. 201.100(d)(2); *Becton, Dickinson & Co.*, 589 F.2d at 1179. Thus, even if FDA's interpretation of "intended" uses was more limited, the distribution of information concerning a study would be prohibited by this requirement, which, taken together with FDA's expansive definition of "labeling," would require the package insert to contain study information as well. A failure to comply with this and other requirements to satisfy the prescription drug exemption created by FDA in § 201.100 results in an automatic violation of the FDCA's misbranding provisions as interpreted by FDA.

154. The "intended use" and other provisions of 21 C.F.R. § 201.100 apply to any affirmative manufacturer communication about off-label uses, regardless of how truthful and non-misleading the communication is, or how important the off-label use is to the public health.

b. FDA's Interpretation of the FDCA and Application of the Regulatory Regime To Plaintiffs Violate the First and Fifth Amendments and Conflict with the FDCA

155. Taken together, the "intended use" regulations and the "new drug" and "misbranding" provisions of the FDCA as interpreted and applied to Amarin by FDA, effectively prohibit any and all truthful and non-misleading off-label promotion. This outcome flies in the face of long-standing United States Supreme Court precedent holding that Government restrictions on truthful and non-misleading promotional speech are invalid *unless* such restrictions directly serve a substantial government interest and are no more extensive than necessary. *Cent. Hudson Gas & Electric Corp.* v. *Pub. Serv. Comm'n*, 447 U.S. 557, 566 (1980).[17]

156. Amarin's proposed speech and disclosures, taken together, are truthful and non-misleading. Accordingly, FDA's actions targeting lawful off-label promotion such as Amarin's are "presumptively invalid" and subject to "heightened" First Amendment scrutiny. *Caronia*, 703 F.3d at 163-65; *Sorrell* v. *IMS Health, Inc.*, 131 S. Ct. 2653, 2662-64 (2011). Although FDA certainly has a substantial and valid interest in safeguarding public health and safety, the restrictions resulting from FDA's interpretation of the FDCA and accompanying regulations do not materially advance those goals—in fact, they undermine them—and are far more extensive than necessary.

157. Amarin's proposed speech and disclosures strike a balance between satisfying the Government's interest in protecting public health and safety, while imposing only the necessary

[17] Plaintiffs believe that commercial speech restrictions should be governed by strict scrutiny. *See Milavetz, Gallop & Milavetz, P.A.* v. *United States*, 559 U.S. 229, 255-56 (2010) (Thomas, J., concurring in part and concurring in the judgment); *see also Sorrell* v. *IMS Health Inc.*, 131 S. Ct. 2653, 2664 (2011) ("The First Amendment requires heightened scrutiny whenever the government creates a regulation of speech because of disagreement with the message it conveys. . . . Commercial speech is no exception.") (internal citations omitted). Although Plaintiffs expressly preserve this issue for later review, this Complaint applies controlling precedent, under which FDA and the Government's interpretation of the statutes and regulations discussed herein is unconstitutional.

restrictions on Amarin's speech. Amarin's proposed speech allows Amarin to communicate—and healthcare professionals, such as the Doctor Plaintiffs, to receive—research on EPA, DHA, and coronary heart disease, the ANCHOR study, and the use of Vascepa® by patients with high triglycerides, while clarifying and putting doctors and other healthcare professionals on notice that (a) FDA has not approved Vascepa® to reduce the risk of coronary heart disease; (b) FDA has not approved Vascepa® for the treatment of statin-treated patients with mixed dyslipidemia and high (>200 mg/dL and <500 mg/dL) triglyceride levels; (c) the effect of Vascepa® on the risk of cardiovascular mortality and morbidity has not been determined; (d) a cardiovascular outcomes study of Vascepa® designed to evaluate the efficacy of Vascepa® in reducing cardiovascular mortality and morbidity in a high risk patient population on statin therapy is underway; (e) Vascepa® may not be eligible for reimbursement under government healthcare programs for such uses.

158. In contrast, FDA's effective all-out ban on any proactive discussion of the off-label use of Vascepa® by patients with high triglycerides restricts Amarin's speech with no connection to protecting public health and safety. With the ultimate goal to reduce cardiovascular risk, based on available scientific evidence, numerous national and international cardiovascular treatment guidelines and position statements continue to recommend using drug therapy to treat patients who have persistently high (200-499 mg/dL) triglyceride levels despite statin therapy and lifestyle changes to lower those patients' triglycerides and/or non-HDL cholesterol. This is the case, even though it is not known if triglycerides and/or non-HDL cholesterol lowering will achieve the ultimate intended clinical outcome, such as a lower risk of a heart attack or stroke. The practice of medicine itself must be informed by truthful and non-misleading information about drug effects on the human body to enable the medical profession to implement treatment consistent with medical guidelines in the best interest of patients. As the Supreme Court held in *Sorrell*, concerns about the free flow of commercial speech are perhaps most heightened "in the

fields of medicine and public health, where information can save lives." *Sorrell*, 131 S. Ct. at 2664.

159. Besides being unconstitutional under the First Amendment, FDA's application of the regulations resulting in the prohibition of any off-label promotion is wholly inconsistent with the FDCA and violates Amarin's right to due process under the Fifth Amendment. The Second Circuit has held that the FDCA must be construed not to "criminaliz[e] the simple promotion of a drug's off-label use by pharmaceutical manufacturers and their representatives because such a construction . . . would run afoul of the First Amendment." *Caronia* 703 F.3d at 162. But FDA has applied its regulations to do precisely that. This is not only at-odds with the constitutionally permissible interpretation of the FDCA, it also creates unacceptable uncertainty under the Due Process Clause of the Fifth Amendment as to what speech FDA will prosecute as violative of its regulations. *Fox II*, 132 S. Ct. at 2318; *Keyishian* v. *Bd. of Regents of the Univ. of New York*, 385 U.S. 589, 603-04 (1967). Such uncertainty is "particularly treacherous" in a case such as this, where criminal penalties "deter those who seek to exercise protected First Amendment rights." *Buckley* v. *Valeo*, 424 U.S. 1, 76-77 (1976); *see also Reno*, 521 U.S. at 872 ("The severity of criminal sanctions may well cause speakers to remain silent rather than communicate even arguably unlawful words, ideas, and images.").

160. FDA approval of "new drugs" costs millions of dollars and takes years to achieve. During the period in which an FDA decision is pending, the off-label use for a "new drug" may become standard practice in the medical community, effectively forcing the manufacturer to choose between changing the drug's labeling in violation of the FDCA's "new drug" rule or keeping incomplete labeling that fails to provide adequate "directions" or "information" for use in violation of the FDCA's "misbranding" rule. The manufacturer therefore cannot avoid violating at least one criminal provision, and could violate both provisions. If the manufacturer provides directions for an off-label use to comply with FDA regulations and the FDCA's misbrand-

ing provisions, but FDA deems the directions inadequate, the manufacturer violates the "new drug" rule and the misbranding rule. If the manufacturer does not add directions for off-label use but its "labeling" (i.e., virtually any materials it distributes to healthcare professionals) is read to "prescribe, recommend, or suggest" such off-label use, the manufacturer is deemed to know the drug is being used for certain off-label uses and once again violates both rules.

161. FDA has failed to promulgate any regulations, or alter its interpretation of existing regulations, to mitigate the significant chill on manufacturers' truthful, non-misleading speech to medical professionals. Instead, FDA has issued non-binding "guidance" documents concerning distributing medical or scientific publications regarding off-label uses for approved drugs, *see* Good Reprint Practices, *supra*, and permissible manufacturer responses to unsolicited requests for off-label information, Draft Guidance on Unsolicited Requests, *supra*. Even as these documents carve-out a narrow set of communications concerning off-label uses of FDA-approved drugs, they do not cure concerns about FDA's unconstitutional vagueness or infringement on protected speech because manufacturers continue to face the risk of prosecution with respect to this small subset of speech because "[g]uidance documents do not establish legally enforceable rights or responsibilities." 21 C.F.R. § 10.115(d)(1). The guidance documents themselves provide that they do not "establish legally enforceable rights or responsibilities," "confer any rights for or on any person [or] operate to bind FDA or the public," and that they "describe the [FDA's] current thinking on a topic and should be viewed only as recommendations." Good Reprint Practices, *supra*; Draft Guidance on Unsolicited Requests, *supra*; Revised Draft Guidance, *supra*.

162. As applied to Amarin and the Doctor Plaintiffs, the foregoing regulatory scheme prohibits the discussion of truthful, non-misleading information by Amarin, while allowing everyone else—e.g., academics, doctors, and insurance companies—to talk freely and openly about the off-label use of Vascepa®. Under *Sorrell* and *Caronia*, the regulations are subject to height-

ened scrutiny because they are content- and speaker-based restrictions on speech. *Sorrell*, 131 S. Ct. at 2664; *Caronia*, 703 F.3d at 163. The regulations cannot survive under this standard.

b. Amarin's Fear Of Criminal Prosecution Is Real

163. Recent FDA enforcement of the current regulatory regime confirms that even truthful, non-misleading speech to healthcare professionals about the results of the ANCHOR trial would expose Plaintiffs to a risk of criminal prosecution and severe civil penalties. The government has consistently and aggressively prosecuted pharmaceutical manufacturers for alleged "off-label promotion" based on its "new drug" and "misbranding" theories. *See* U.S. Accountability Office, GAO-08-835, Prescription Drugs: FDA's Oversight of the Promotion of Drugs for Off-Label Uses 26-27 (2008); *see also, e.g.*, *United States* v. *Eli Lilly & Co.*, No. 09-CR-020 (E.D. Pa., filed Jan. 5, 2009); *United States* v. *Caronia*, 576 F. Supp. 2d 385 (E.D.N.Y. 2008), *vacated and remanded*, 703 F.3d 149 (2d. Cir. 2012); *United States* v. *Warner-Lambert Co.*, No. 04-cr-10150 RGS (D. Mass. 2004). In addition to criminal liability, such enforcement actions can also involve civil remedies including disgorgement and civil restitution for alleged violations of the FDCA. *See* 21 U.S.C. § 332(a); Justice News, Johnson & Johnson to Pay More than $2.2 Billion to Resolve Criminal and Civil Investigations (Nov. 4, 2013) ("J&J Settlement Release") (summarizing settlement involving civil payments and criminal fines and forfeiture), http://www.justice.gov/opa/pr/johnson-johnson-pay-more-22-billion-resolve-criminal-and-civil-investigations.

164. The government has also repeatedly and unequivocally stated that it has "continued to pursue aggressively" alleged incidents of "off-label" promotion. *See, e.g.*, J&J Settlement Release; Justice News, Pharmaceutical Companies to Pay $214.5 Million to Resolve Allegations of Off-Label Promotion of Zonegran (Dec. 15, 2010), http://www.justice.gov/opa/pr/2010/December/10-civ-1444.html. This response, which extends to truthful, non-misleading speech, has resulted in numerous multi-billion dollar settlements by

drug manufacturers targeted for enforcement. *See, e.g.*, Justice News, GlaxoSmithKline to Plead Guilty and Pay $3 Billion to Resolve Fraud Allegations and Failure to Report Safety Data (July 2, 2012), http://www.justice.gov/opa/pr/2012/July/12-civ-842.html, (resolving claims for off-label promotion of prescription drugs); Justice News, Abbott Labs to Pay $1.5 Billion to Resolve Criminal & Civil Investigations of Off-label Promotion of Depakote (May 7, 2012), http://www.justice.gov/opa/pr/2012/May/12-civ-585.html; Justice News, Justice Department Announces Largest Health Care Fraud Settlement in Its History (Sept. 2, 2009) ("Pfizer Settlement"), http://www.justice.gov/opa/pr/2009/September/09-civ-900.html (announcing $2.3 billion settlement with Pfizer to settle claims of allegedly fraudulent marketing practices); FDA News, Eli Lilly & Company Agrees to Pay $1.415 Billion to Resolve Allegations of Off-label Promotion of Zyprexa (Jan. 15. 2009), http://www.justice.gov/archive/opa/pr/2009/January/09-civ-038.html.

165. FDA's enforcement tactics have not gone unnoticed in recent judicial review of FDA claims. As previously noted, in 2012, the Court of Appeals for the Second Circuit reversed the criminal conviction of a drug manufacturer representative for alleged off-label promotion and expressly held that the government had improperly prosecuted the representative solely on the basis of his truthful and non-misleading speech in violation of the First Amendment. *United States* v. *Caronia*, 703 F.3d 149, 168-69 (2d Cir. 2012). The Court noted in its decision that FDA's interpretation of the Food, Drug, and Cosmetic Act had "essentially legalize[d an] outcome—off-label use—but prohibit[ed] the free flow of information that would inform that outcome," 703 F.3d at 167, with the result that FDA regulations operated to impermissibly restrict truthful and protected promotional speech.

166. Moreover, as noted above, FDA warned Amarin in the CRL that that any effort by Amarin to market Vascepa® for treatment of adult patients with persistently high triglycerides could constitute "misbrand[ing] under the Federal Food, Drug, and Cosmetic Act."

167. In light of the government's stated commitment to continuing prosecution of alleged "off-label promotion" and its express warning that off-label promotion in this instance could result in criminal prosecution, Amarin and the Doctor Plaintiffs now seek a declaratory judgment to prospectively preclude the government from engaging in enforcement conduct that the Second Circuit has already deemed would violate the First Amendment, as applied to this case.

c. The False Claims Act

168. Like the Federal Food, Drug, and Cosmetic Act, the False Claims Act ("FCA"), does not, on its face, prohibit Amarin from exercising its First Amendment right to promote the off-label use of Vascepa®. Because of the Government's interpretation of the FCA, however, Amarin risks exposure to civil suit and millions of dollars in treble damages for engaging in constitutionally protected speech.

169. Under the FCA, any person who has knowingly "cause[d] to be presented a false or fraudulent claim for payment or approval" or who has knowingly made or caused to be made "a false record or statement material to a false or fraudulent claim" to the United States Government must pay a civil penalty of between five and ten thousand dollars, and "3 times the amount of damages which the Government sustains because of the act of that person." 31 U.S.C. § 3729(a)(1). False claims include requests for reimbursements of healthcare costs not covered or reimbursable by federal healthcare programs, such as Medicare or Medicaid. *See* 31 U.S.C. § 3729; *Strom ex rel. United States* v. *Scios, Inc.*, 676 F. Supp. 2d 884, 890 (N.D. Cal. 2009).

170. Federal healthcare programs generally cover medically-accepted indications of drugs, which include uses approved by FDA but also include certain off-label uses supported by citation in an approved drug compendium if certain other conditions are met. *See* 42 U.S.C. §1396r-8(k)(6) (Medicaid); *id.* § 1395x(t)(2)(B) (Medicare).

171. While Vascepa® does not currently have an approved indication from FDA for use to reduce persistently high triglycerides in adult patients, it is supported by a medical compendium listing for use by such patients. Although Vascepa® is likely reimbursable under federal healthcare programs when prescribed to such patients, there may be certain circumstances in which it does not meet additional State-specific requirements.

172. Amarin's proposed speech about Vascepa® does not violate the FCA because it could not cause the submission of a false claim. Amarin's proposed speech unambiguously states that (a) Vascepa® has not been approved by FDA to reduce coronary heart disease or for treatment of patients with triglyceride levels in the 200 – 499 mg/dL range and (b) Vascepa® may not be eligible for reimbursement under federal healthcare programs, such as Medicare and Medicaid, for such uses. It also expressly encourages doctors to "check for themselves" whether such reimbursement is appropriate under the law.

173. As applied to Amarin's proposed speech described herein, any claim brought under the FCA would not only be without merit, it would raise serious First Amendment concerns. *See New York Times* v. *Sullivan*, 376 U.S. 254, 277 (1964) ("What a State may not constitutionally bring about by means of a criminal statute is likewise beyond the reach of its civil law of libel. The fear of damage awards . . . may be markedly more inhibiting than the fear of prosecution under a criminal statute.").

174. Just as FDA's effective ban on off-label promotion is contrary to the FDCA and would fail First Amendment "heightened" scrutiny, any action by the Government under the FCA targeting Amarin's truthful and non-misleading speech would contravene the FCA itself, and would once again result in an overly-expansive prohibition on protected speech that could

not satisfy First Amendment scrutiny. *See Sorrell*, 131 S. Ct. at 2662-65; *Caronia*, 703 F.3d at 166-69.

d. Amarin's Fear of a Potential Action Under the False Claims Act Is Real

175. A submission by the Government in an FCA action in late 2013 demonstrates that Amarin risks exposure to civil suit and treble damages by engaging in its truthful and non-misleading proposed speech.

176. On November 7, 2013, the U.S. Attorney's Office for the Southern District of New York filed a statement of interest in an action against a pharmaceutical manufacturer for the alleged off-label promotion of two drugs, resulting in the submission of false claims for reimbursement of those drugs. *United States ex rel. Matthew Cestra* v. *Cephalon, Inc.*, 10 Civ. 6457 (SHS), Statement of Interest, ECF No. 83 (S.D.N.Y. Nov. 7, 2013).[18] In its statement of interest, the Government argues that claims brought under the FCA do not implicate the First Amendment at all, because the FCA does not prohibit speech, but instead "prohibits *conduct* that knowingly causes the submission of false claim." Statement of Interest, 5-6 (emphasis added). The Government further emphasizes that "as a statutory matter, it is irrelevant whether a party causes the submission of a false claim by words, by conduct, or by a combination of both." *Id.* at 6.

177. The Government's position is that the FCA does not implicate the First Amendment at all, even if the allegations are based solely on speech. Under the Government's view, even truthful speech might somehow arguably "cause the submission of a false claim"—e.g., truthful off-label promotion might induce a doctor to prescribe a drug for an off-label use and improperly submit it for reimbursement to Medicare or Medicaid—and subject the speaker to substantial liability under the FCA.

[18] This action was subsequently transferred to the Eastern District of Pennsylvania to be considered with a parallel action filed in January 2008. *United States ex rel. Matthew Cestra* v. *Cephalon*, Inc., 10 Civ. 6457 (SHS), 2014 WL 1087960 (S.D.N.Y. Mar. 19, 2014).

178. This interpretation plainly contradicts the Second Circuit's decision in *Caronia*, and shows that the Government will now potentially try to do through the FCA what it can no longer do under the FDCA. The Government is correct that, like the FDCA, the FCA does not on its face regulate speech. But, as with the FDCA and the accompanying regulations, the Government has interpreted the FCA to prohibit even truthful off-label promotion to the extent it arguably causes the submission of a false claim. Under the Government's reading of the FCA, Amarin could violate the FCA by distributing materials discussing off-label use of Vascepa®, despite including explicit language that such off-label use may not be reimbursable by federal healthcare programs, if healthcare professionals who received the materials wrote prescriptions for off-label use based on their review of Amarin's materials and those prescriptions resulted in the submission of claims to Medicare or Medicaid. Thus, under the Government's interpretation of the FCA, Amarin could still be liable simply for engaging in truthful and non-misleading speech.

179. Because of the Government's interpretation of the FCA, if Amarin engages in truthful and non-misleading off-label promotion, it still risks being sued under the FCA by either the Government or by private litigants who sue as *qui tam* plaintiffs. *See* 31 U.S.C. § 3730(b). The Government and private plaintiffs have brought numerous FCA actions based on off-label promotion. Because the FCA provides for treble damages, many pharmaceutical manufacturers have settled such suits, often for amounts in the hundreds of millions, or even billions, of dollars. *See, e.g.*, J&J Settlement Release (civil settlements with federal government and states for alleged off-label promotion totaling $1.72 billion); Pfizer Settlement, *supra* (Pfizer paid $1 billion to resolve FCA claims); Justice News, Pharmaceutical Companies to Pay $214.5 Million to Resolve Allegations of Off-label Promotion of Zonegran (Dec. 15, 2010), http://www.justice.gov/opa/pr/2010/December/10-civ-1444.html (over $100 million to resolve civil allegations under FCA); Justice News, Novartis Vaccines & Diagnostics to Pay More Than

$72 Million to Resolve False Claims Act Allegations Concerning TOBI (May 4, 2010), http://www.justice.gov/opa/pr/2010/May/10-civ-522.html.

180. Based on the Government's interpretation of the FCA, Amarin and the Doctor Plaintiffs now seek a declaratory judgment providing that any action brought against Amarin under the FCA for its proposed speech would violate the First Amendment, or, in the alternative, that Amarin's proposed speech does not violate the FCA.

V. CLAIMS FOR RELIEF

COUNT I

(FDA's Interpretation and Re-Definition of "Labeling" in 21 C.F.R. § 202.1(*l*)(2) is Unconstitutional or Invalid as Applied to the Truthful, Non-Misleading Speech of Amarin Regarding the Off-Label Use Presented)

181. Plaintiffs reallege and incorporate herein by reference paragraphs 1 through 180.

182. The First Amendment protects Amarin's truthful, non-misleading speech regarding the ANCHOR trial and the Doctor Plaintiffs' right to receive such speech.

183. FDA's definition of "labeling" to encompass all tangible materials distributed by the manufacturer that contain manufacturer-supplied drug information, regardless of whether or not such materials are distributed with the prescription drug, 21 C.F.R. § 202.1(*l*)(2), so broadens the category of expression deemed "labeling" that Amarin is left with virtually no speech regarding its product, including a neutral announcement of FDA-supervised clinical trial results, that is not considered part of Vascepa®'s "labeling."

184. By construing almost all speech by Amarin to healthcare professionals as "labeling," FDA's regulation prevents Amarin from communicating truthfully about Vascepa® without transforming Vascepa® from an approved drug into a "new drug" that may not be distributed absent FDA approval under 21 U.S.C. § 355(a). *See* 21 U.S.C. 321(p).

185. As-applied to prohibit Amarin's truthful, non-misleading speech regarding off-label use of Vascepa® and the ANCHOR trial, 21 C.F.R. § 202.1(*l*)(2) violates the First Amendment.

186. Plaintiffs have no adequate remedy at law.

187. Plaintiffs therefore seek entry of a judgment declaring that 21 C.F.R. § 202.1(*l*)(2) violates the First Amendment as applied to Amarin's truthful and non-misleading speech to healthcare professionals regarding what Defendants deem to be off-label use of an FDA-approved drug and enjoining Defendants from enforcing the regulation to prohibit Amarin's speech.

COUNT II

(21 U.S.C. § 352(a)'s Prohibition on Labeling that is "False or Misleading in Any Particular" is Unconstitutional as Applied to, or Does Not Encompass, Truthful and Non-Misleading Off-Label Promotion in this Case)

188. Plaintiffs reallege and incorporate herein by reference paragraphs 1 through 187.

189. Amarin's right to engage in, and the Doctor Plaintiffs' right to receive, truthful and non-misleading speech about the off-label use of Vascepa®, are both protected by the First Amendment.

190. The FDCA prohibits a manufacturer from introducing a drug into interstate commerce if its "labeling" is "false or misleading in any particular." 21 U.S.C. §§ 331(a), 352(a).

191. The Government has interpreted the phrase "false or misleading in any particular" to apply not only to actually or inherently false or misleading statements, but also to prosecute manufacturers for any speech that FDA has not approved.

192. The Government's interpretation of § 352(a) criminalizes a manufacturer's protected speech, and thereby violates the First Amendment.

193. The Government's interpretation of § 352(a) also conflicts with the plain text of the FDCA itself, which prohibits only statements in labeling that are *actually* "false or misleading in any particular," not any and all statements—including truthful and non-misleading statements—that FDA has not explicitly approved. At a minimum, the Government's interpretation of the statute is unreasonable, and should be rejected under the principle of constitutional avoidance.

194. Plaintiffs have no adequate remedy at law.

195. Plaintiffs seek the entry of a judgment declaring that the Government's interpretation and application of 21 U.S.C. § 352(a) is unconstitutional as applied to Amarin's truthful and non-misleading speech or that § 352(a) does not prohibit truthful and non-misleading off-label promotion. Plaintiffs also seek a judgment enjoining Defendants from enforcing the regulation to prohibit Amarin's speech.

COUNT III

(FDA's Effective Prohibition of any "Advertisement" for an Off-Label Use in 21 C.F.R. § 202.1(e)(4)(i)(a) is Unconstitutional or Invalid as Applied to the Truthful, Non-Misleading Speech of Amarin Regarding the Off-Label Use Presented)

196. Plaintiffs reallege and incorporate herein by reference paragraphs 1 through 195.

197. Amarin's truthful and non-misleading promotion of the off-label use of Vascepa® is protected by the First Amendment when made in a commercial advertisement. *See Thompson* v. *W. States Med. Ctr.*, 535 U.S. 357, 366 (2002).

198. The FDCA prohibits introducing "misbranded" drugs into interstate commerce. 21 U.S.C. § 331(a). A prescription drug is "misbranded" under the FDCA if, among other things, an "advertisement" issued by the manufacturer concerning the drug fails to disclose certain information, including the "established name" of the drug, and information such as "side effects, contraindications, and effectiveness." 21 U.S.C. § 352(n).

199. FDA regulations expand the misbranding provision from § 352(n) of the FDCA, providing that a prescription drug will be considered "misbranded" by FDA if a manufacturer advertisement "recommend[s] or suggest[s] any use that is not in the labeling accepted in [the drug's] approved new-drug application." 21 C.F.R. § 202.1(e)(4)(i)(a). Under FDA's application of this regulation, any direct-to-physician advertisement suggesting the off-label use of Vascepa®, regardless of the nature or quality of disclosures by Amarin to healthcare professionals, is *per se* unlawful. *See id.*

200. 21 C.F.R. § 202.1(e)(4)(i)(a) is unconstitutional as applied because it explicitly prohibits Amarin's protected expression through truthful and non-misleading advertisements.

201. 21 C.F.R. § 202.1(e)(4)(i)(a) is also contrary to and inconsistent with the FDCA itself, which does not prohibit advertisements of prescription drugs that contain information about off-label uses. At a minimum, the Government's interpretation of the 21 U.S.C. § 352(n) through 21 C.F.R. § 202.1(e)(4)(i)(a) is unreasonable, and should be rejected under the principle of constitutional avoidance.

202. Plaintiffs have no adequate remedy at law.

203. Plaintiffs seek the entry of a judgment declaring that 21 C.F.R. § 202.1(e)(4)(i)(a) is unconstitutional as applied to a Amarin's truthful and non-misleading "advertisement[s]" to physicians, or that it is an invalid interpretation of 21 U.S.C. § 352(n). Plaintiffs also seek a judgment enjoining Defendants from enforcing the regulation to prohibit Amarin's speech.

COUNT IV

(FDA's Interpretation of §352(f)(1) of the FDCA and Regulations 21 C.F.R. § 201.5, and 21 C.F.R. § 201.100 Are Unconstitutional or Invalid as Applied to the Truthful, Non-Misleading Speech of Amarin Regarding the Off-Label Use Presented)

204. Plaintiffs reallege and incorporate herein by reference paragraphs 1 through 203.

205. Though Amarin's truthful and non-misleading speech regarding Vascepa® and the outcome of the ANCHOR trial relates to an off-label use of its drug, the First Amendment nevertheless safeguards that speech.

206. Under FDA's interpretation of the FDCA's misbranding provisions and 21 C.F.R. § 201.5, it is impossible for a prescription drug manufacturer to satisfy the "adequate directions for use" requirement of §352(f)(1) of the FDCA. *See Becton, Dickinson & Co*, 589 F.2d at 1179; *Articles of Drug*, 625 F.2d at 673. FDA has promulgated an exemption to §352(f)(1) for prescription drugs that includes, among other things, a requirement that prescription drug labeling contains "adequate information for use" for any "intended" use of the drug. "Intended use" includes "all purposes for which [the drug] is advertised or represented." 21 C.F.R. § 201.100(c)(1).

207. FDA's interpretation of the FDCA and its "intended use" regulation effectively prohibits Amarin's truthful and non-misleading speech to medical professionals because such speech would render Vascepa® criminally "misbranded," since the drug's "labeling" does not, and could not, bear "adequate information," for the off-label use to treat high, but not very high, triglyceride levels in at-risk patients.

208. Such a criminal prohibition of speech would violate the First Amendment, as applied to Amarin's truthful and non-misleading speech to healthcare professionals regarding Vascepa®.

209. 21 C.F.R. §§ 201.5 and 201.100, as interpreted by FDA, are contrary to Plaintiffs' constitutional rights as applied to Amarin's truthful and non-misleading speech to healthcare professionals regarding Vascepa®.

210. Plaintiffs have no adequate remedy at law.

211. Plaintiffs therefore seek entry of a judgment declaring that 21 C.F.R. §§ 201.5 and 201.100 violate the First Amendment as interpreted by FDA and applied to Amarin's truthful and non-misleading speech to healthcare professionals regarding what Defendants deem off-label use of an FDA-approved drug, and enjoining Defendants from enforcing the regulations to prohibit Amarin's speech.

COUNT V

(FDA's Regulations as Applied in this Case Are Unconstitutional or Invalid Under the Fifth Amendment)

212. Plaintiffs reallege and incorporate herein by reference paragraphs 1 through 210.

213. Under FDA's interpretation of its regulations and the FDCA, a drug is criminally misbranded if it is "advertised or represented" for any use not approved by FDA. *See* 21 U.S.C. §§ 33l(a), 333(a); 21 C.F.R. § 201.100(c)(1); 21 C.F.R. § 202.1(e)(4)(i)(a). As-applied, FDA's regulations thus effectively prohibit any promotion—regardless of how truthful and non-misleading the promotion would be—of Vascepa® for any off-label use, including to reduce the risk of coronary heart disease or by patients with persistently high, but not very high, triglycerides. The Second Circuit has ruled, however, that the FDCA itself cannot "criminaliz[e] the simple promotion of a drug's off-label use" because such a construction of the FDCA would "raise First Amendment concerns." *Caronia*, 703 F.3d at 160.

214. FDA has failed to clarify what off-label promotion, if any, it believes is permitted after *Caronia*. This lack of clarity has had a chilling effect on drug manufacturers' speech.

215. The Due Process Clause of the Fifth Amendment requires agencies to establish clear rules that give "fair notice of what is prohibited". *Fox II*, 132 S. Ct. at 2318. "When speech is involved, rigorous adherence to [these] requirements is necessary to ensure that ambiguity does not chill protected speech." *Id.* at 2317. FDA's current regulatory regime fails to do that.

216. As-applied in light of *Caronia*, FDA's regulations create uncertainty and doubt about what FDA views as permissible versus impermissible speech and violate Amarin's right to due process under the Due Process Clause of the Fifth Amendment.

217. Amarin has no adequate remedy at law.

218. Amarin therefore seeks entry of a judgment declaring that FDA's "intended use" regulations violate Amarin's Fifth Amendment right to due process because they create uncertainty about the application of misbranding prohibitions to Amarin's truthful and non-misleading speech about the off-label use of Vascepa® and chill otherwise lawful speech, and enjoining Defendants from enforcing the regulations to prohibit Amarin's speech.

COUNT VI

(Amarin's Proposed Speech Does Not Violate the False Claims Act)

219. Plaintiffs reallege and incorporate herein by reference paragraphs 1 through 218.

220. The FCA prohibits, among other things, conduct that causes the submission of false claims, or forms the material basis of a false or fraudulent claim, to the Government for payment. 31 U.S.C. § 3729(a)(1). Conduct that "causes the submission of false claims," as interpreted by the Government, can include simple promotion for off-label uses of prescription drugs that are not reimbursable under federal healthcare programs, such as Medicare and Medicaid. *See* 31 U.S.C. § 3729.

221. Federal healthcare programs generally cover uses either approved by FDA, or supported by a citation in an approved drug compendium if certain other conditions are met. *See* 42 U.S.C. §§ 1396r-8(k)(6), 1395x(t)(2)(B).

222. Vascepa® does not currently have an indication from FDA for use by patients on statin therapy with persistently high triglyceride levels, but it is supported by a medical compendium listing for use by such patients.

223. Vascepa® does not currently have an indication from FDA for use to reduce the risk of coronary heart disease.

224. Amarin's proposed speech does not violate the FCA. Amarin's proposed speech includes the clear and unambiguous statement that "Vascepa® may not be eligible for reimbursement under federal healthcare programs such as Medicare or Medicaid for treatment of patients with triglyceride levels in the 200 – 499 mg/dL range. We encourage you to check that for yourself." Therefore, any false submission of a claim for the off-label use of Vascepa® could not reasonably be caused by Amarin's speech, which explicitly states that submission of the claim may not be proper and encourages others to check the law for themselves before making any submission for reimbursement.

225. In addition, an FCA claim brought against Amarin based solely on mere off-label promotion that is both truthful and non-misleading would chill protected speech and violate the First Amendment. *See, e.g.*, *Sorrell*, 131 S. Ct. at 2662-65; *Caronia*, 703 F. 3d at 166-69.

226. Plaintiffs have no adequate remedy at law.

227. Plaintiffs seek entry of a judgment declaring that an action brought by the Government against Amarin for its proposed speech under the FCA would violate the First Amendment, or, in the alternative, that Amarin's proposed speech is not false or misleading and does not violate the FCA.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request that the Court:

A. Enter a judgment declaring that FDA regulations, including but not limited to those enumerated in this Complaint, as applied to prevent Amarin or any of its directors, officers, employees, or agents from communicating truthful, non-misleading information about its FDA-approved product, Vascepa®, are an unconstitutional infringement on Plaintiffs' free speech

rights in violation of the First Amendment to the United States Constitution and, therefore, of no force;

B. Enter a judgment declaring that FDA regulations, including but not limited to those enumerated in this Complaint, as applied to prevent Amarin or any of its directors, officers, employees, or agents from communicating truthful, non-misleading information about its FDA-approved product, Vascepa®, are an unconstitutional infringement of Amarin's right to due process under the Due Process Clause of the Fifth Amendment to the United States Constitution, and, therefore, of no force;

C. Enter a judgment declaring that any action brought under the FCA against Amarin, or any of its directors, officers, employees, or agents for Amarin's proposed off-label promotion of Vascepa®, as described herein, is either invalid or unconstitutional under the First Amendment;

D. Enter a preliminary injunction, pending final resolution of this action, enjoining Defendants from taking any action under the FDCA, FDA regulations, or the FCA against Amarin or any of its directors, officers, employees, or agents for Amarin's proposed off-label promotion of Vascepa®, as described herein;

E. Enter a permanent injunction, enjoining Defendants from taking any action under the FDCA, FDA regulations, or the FCA against Amarin or any of its directors, officers, employees, or agents for Amarin's proposed off-label promotion of Vascepa®, as described herein; and

F. Grant Plaintiffs such additional or different relief as it may deem just and proper, including an award of reasonable attorneys' fees and the costs of this action.

Dated: New York, New York
May 7, 2015

Respectfully submitted,

CAHILL GORDON & REINDEL LLP

By: /s/ Joel Kurtzberg

Floyd Abrams
Joel Kurtzberg
Michael B. Weiss
80 Pine Street
New York, New York 10005
Telephone: (212) 701-3000
Facsimile: (212) 269-5420

Attorneys for Plaintiffs

EXHIBIT A

Representative Sample of Peer Reviewed Scientific Publications Relevant to the Potential Effect of EPA on the Reduction of the Risk of Coronary Heart Disease

Bays H, Ballantyne C, Braeckman R, et al. Icosapent ethyl, a pure ethyl ester of eicosapentaenoic acid: effects on circulating markers of inflammation from the MARINE and ANCHOR studies. *Am J Cardiovasc Drugs*. 2013;13:37-46.

Doi M, Nosaka K, Miyoshi T, et al. Early eicosapentaenoic acid treatment after percutaneous coronary intervention reduces acute inflammatory responses and ventricular arrhythmias in patients with acute myocardial infarction: a randomized, controlled study. *Int J Cardiol.* 2014:176(3):577-582.

Harris W. Are n-3 fatty acids still cardioprotective? *Curr Opin Clin Nutr Metab Care*. 2013;16(2):141-149.

Matsuzaki M, Yokoyama M, Saito Y, et al. Incremental effects of eicosapentaenoic acid on cardiovascular events in statin-treated patients with coronary artery disease. *Circ J.* 2009;73:1283-1290.

Mozaffarian D, Lemaitre RN, King IB, et al. Plasma phospholipid long-chain omega-3 fatty acids and total and cause-specific mortality in older adults: the cardiovascular health study. *Ann Intern Med*. 2013;158(7):515-525.

Mozaffarian D, Wu JHY. Omega-3 Fatty Acids and Cardiovascular Disease. *J Am Coll Cardiol.* 2011;58(20):2047-2067.

Saito Y, Yokoyama M, Origasa H, et al. Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: sub-analysis of primary prevention cases from the Japan EPA Lipid Intervention Study (JELIS). *Atherosclerosis*. 2008;200:135-140.

Takaki A, Umemoto S, Ono K, et al. Add-on therapy of EPA reduces oxidative stress and inhibits the progression of aortic stiffness in patients with coronary artery disease and statin therapy: a randomized controlled study. *J Atheroscler Thromb.* 2011;18:857-866.

Thies F, Garry JMC, Yaqoob P, et al. Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: a randomized controlled trial. *Lancet*. 2003;361:477-485.

Ueeda M, Doumei T, Takaya Y, et al. Serum n-3 polyunsaturated fatty acid levels correlate with the extent of coronary plaques and calcifications in patients with acute myocardial infarction. *Circ J.* 2008;72:1836-1843.

Vecka M, Dusejovska M, Stankova B, et al. N-3 polyunsaturated fatty acids in the treatment of atherogenic dyslipidemia. *Neuroendocrinol Lett.* 2012;33(Suppl. 2):87-92.

Wu JHY, Mozaffarian D. Omega-3 fatty acids, atherosclerosis progression and cardiovascular outcomes in recent trials: new pieces in a complex puzzle. *Heart.* 2014;100(7):530-533.

Yokoyama M, Origasa H, Matsuzaki M, et al. Effects of eicosapentaenoic on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet.* 2007;369:1090-1098.

EXHIBIT B

Co-administration Therapy with Statins for Additional Lipid Management in Mixed Dyslipidemia

The effects of VASCEPA as add-on therapy to treatment with statins were evaluated in a randomized, placebo-controlled, double-blind, parallel-group study of 453 adult patients (226 on VASCEPA and 227 on placebo) with persistent high triglyceride levels (≥200 mg/dL and <500 mg/dL) despite statin therapy. All patients were receiving statin therapy (atorvastatin, rosuvastatin, or simvastatin) and were treated to LDL-C goal prior to randomization. Patients were randomized to either VASCEPA or placebo and treated for 12 weeks with statin co-therapy. The same statin at the same dose was continued throughout the study. The median baseline TG and LDL-C levels in these patients were 259 mg/dL and 83 mg/dL, respectively. The randomized population in this study was mostly Caucasian (96%) and male (61%). The mean age was 61 years and the mean body mass index was 35 kg/m^2. Seventy-three percent (73%) of patients had diabetes at baseline.

The changes in the major lipoprotein lipid parameters for the groups receiving VASCEPA plus statin or placebo plus statin are shown in the following table:

Response to the Addition of VASCEPA to Ongoing Statin Therapy in Patients with High Triglyceride Levels (≥200 mg/dL and <500 mg/dL)

Parameter	Vascepa 4 g/day + Statin N=226		Placebo + Statin N=227		Difference (95% Confidence Interval)	p-value
	Baseline	% Change	Baseline	% Change		
TG (mg/dL)	265	-18	259	6	-22 (-27, -16)	<0.0001
LDL-C (mg/dL)	82	2	84	9	-6 (-11, -2)	<0.01
Non-HDL-C (mg/dL)	128	-5	128	10	-14 (-17, -10)	<0.0001
Apo B (mg/dL)	93	-2	91	7	-9 (-12, -6)	<0.0001
VLDL-C (mg/dL)	44	-12	42	15	-24 (-32, -17)	<0.0001
TC (mg/dL)	167	-3	168	9	-12 (-15, -9)	<0.0001
HDL-C (mg/dL)	37	-1	39	5	-5 (-7, -2)	<0.01

% Change= Median Percent Change from Baseline
Difference= Median of [VASCEPA % Change – Placebo % Change] (Hodges-Lehmann Estimate)
p-values from Wilcoxon rank-sum test

VASCEPA significantly reduced TG, non-HDL-C, Apo B, VLDL-C, TC and HDL-C levels from baseline relative to placebo. The reduction in TG observed with VASCEPA was not associated with elevations in LDL-C relative to placebo.

The effect of VASCEPA on cardiovascular mortality and morbidity in patients with mixed dyslipidemia has not been determined.