UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

AMARIN PHARMA, INC., DR. JONATHAN HERBST, DR. ERIC RISHE, DR. PETER GOTTESFELD, and DR. RALPH YOUNG, Plaintiffs, v. UNITED STATES FOOD & DRUG ADMINISTRATION, UNITED STATES OF AMERICA, STEPHEN OSTROFF, M.D., in his official capacity as Acting Commissioner of Food and Drugs, and SYLVIA MATHEWS BURWELL, in her official capacity as Secretary of the Department of Health & Human Services, Defendants.	15 Civ. 3588 (PAE) ECF Case

DECLARATION OF CURTIS ROSEBRAUGH

I, Curtis Rosebraugh, M.D., M.P.H., hereby declare under penalty of perjury, pursuant to 28 U.S.C. § 1746, that the following is true and correct to the best of my knowledge, information, and belief:

1. I am the Director of the Office of Drug Evaluation II, Office of New Drugs, Center for Drug Evaluation and Research (CDER), United States Food and Drug Administration (FDA or the Agency). I am a board-certified Internist, and I have been with the Agency for approximately fifteen years. For the last ten years, I have served as Deputy Director, Acting Director, and Director of the Office of Drug Evaluation II, in which the Division of Metabolism and Endocrinology Products resides. That Division is responsible for reviewing and approving, among other things, new drug applications for drugs intended for the prevention and treatment of conditions relating to hyperlipidemia, which refers to elevated levels of lipids in the blood.

Drugs that fall into this class include Trilipix, Niaspan, Lovaza, and Vascepa. I have also held the positions of Deputy Director of Over-the-Counter Drug Products and Senior Medical Reviewer in the Division of Pulmonary and Allergy Drug Products in FDA's CDER. I received my medical degree from the University of Kansas School of Medicine, my master's degree in public health from The Johns Hopkins School of Public Health, and my undergraduate degree in pharmacy from the University of Kansas School of Pharmacy. I have held teaching appointments at University of Texas Medical Branch and University of Kansas Medical Center.

2. In these capacities, I am familiar with the steps FDA has taken to ensure that the labeling for triglyceride-lowering drug products reflects the most accurate and up-to-date scientific information regarding the relationship between drug-induced lowering of triglyceride levels and reducing the risk of cardiovascular events in patients on statin therapy. More specifically, I am familiar with FDA's decisions to remove indications related to statin co-administration from the labeling of Trilipix (fenofibric acid) and Niaspan (niacin extended-release) and to remove data and information about a triglyceride-lowering trial in statin-treated patients from the Clinical Studies section of the labeling for Lovaza (omega-3 acid ethyl esters). I am also familiar with the regulatory history for Vascepa (omega-3 acid eicosapentaenoic acid), which is accurately set forth in the June 5 letter from FDA to Amarin Pharma, Inc. ("Amarin").

3. In this declaration, I describe the approvals for Trilipix, Niaspan, Lovaza, and Vascepa, certain cardiovascular outcomes trials that are relevant to the labeling and approvals for these products, and steps FDA has taken and continues to take to ensure that healthcare professionals have information reflecting the best and most current scientific data about the lack of evidence to support the conclusion that decreasing triglyceride levels with a drug further reduces the risk of cardiovascular events among patients on statin therapy.

Approvals for Trilipix, Niaspan, Lovaza, and Vascepa

4. Trilipix is a fenofibrate-based drug. FDA first approved Trilipix on December 15, 2008, for several indications, including the following indication for co-administration with a statin: "Trilipix is indicated as an adjunct to diet in combination with a statin to reduce TG [triglycerides] and increase HDL-C [high-density lipoprotein cholesterol] in patients with mixed dyslipidemia and CHD [coronary heart disease] or a CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C [low-density lipoprotein cholesterol] goal." 2013 Trilipix Labeling, attached hereto as Exhibit 1.

5. Niaspan is an extended-release formulation of niacin. FDA initially approved Niaspan on July 28, 1997, for five indications. In 2003, FDA approved a supplemental new drug application ("sNDA"), adding an indication for the use of Niaspan in combination with lovastatin for the treatment of primary hypercholesterolemia and mixed dyslipidemia. *See* 2003 Niaspan Letter, attached hereto as Exhibit 2. In 2009, FDA approved an sNDA revising the indication related to statin co-administration to include mention of simvastatin as well. As of March 2015, this indication read as follows: "NIASPAN in combination with simvastatin or lovastatin is indicated for the treatment of primary hyperlipidemia and mixed dyslipidemia when treatment with NIASPAN, simvastatin, or lovastatin monotherapy is considered inadequate." 2013 Niaspan Labeling, attached hereto as Exhibit 3.

6. Lovaza is composed of omega-3-acid ethyl esters, and contains mostly the ethyl esters of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). In 2004, FDA approved Lovaza (originally known as Omacor) as an adjunct to diet to reduce very high (≥ 500 mg/dL) triglyceride levels in adult patients. Subsequently, Lovaza's sponsor conducted a trial in simvastatin-treated patients with triglyceride levels between 200 and 499 mg/dL, and well-controlled low-density lipoprotein cholesterol ("LDL-C") levels, to investigate the effect of

Lovaza on lipid measurements such as non-HDL-cholesterol and triglycerides, after 8 weeks of Lovaza treatment. FDA determined that the data on reductions in triglyceride levels from the trial were not sufficient to support the approval of an indication for the reduction of non-HDL-cholesterol, triglycerides, and other lipid parameters in this population, but FDA approved labeling that summarized data and information about the trial in the Clinical Studies section. *See* 2007 Lovaza Letter (approving Lovaza's proposed labeling), attached hereto as Exhibit 4.

7. Vascepa is a purified ester of EPA derived from fish oil. *See* June 5 Letter and citations therein. FDA approved Vascepa in July 2012 as a drug to be used as an adjunct to diet to reduce triglyceride levels in adult patients with severe hypertriglyceridemia, defined as trigylceride levels ≥500 mg/dL ("very high trigylceride levels"). The primary rationale for treating individuals with very high trigylceride levels is to reduce the risk of pancreatitis. Pursuant to a Special Protocol Assessment ("SPA") agreement with FDA, Amarin also conducted the "ANCHOR trial" to assess the effect of Vascepa on trigylceride levels in statin-treated patients with well-controlled LDL-C levels whose trigylceride levels remained high. In this context, changes in trigylceride levels were being used as a surrogate to predict lowering the risk of cardiovascular events. In February 2013, Amarin then sought FDA approval to market Vascepa for another use, namely to treat patients with trigylceride levels between 200 mg/dL and 499 mg/dL ("high trigylceride levels") who are already being treated with statins to lower cholesterol. The primary rationale for treating statin-treated patients with this range of trigylceride levels with a second drug is to further reduce the risk of cardiovascular events, such as cardiovascular morbidity or mortality, resulting from atherosclerotic cardiovascular disease.

ACCORD-Lipid Trial

8. In March 2010, the results from the ACCORD-Lipid trial were published online in the *New England Journal of Medicine*, attached hereto as Exhibit 5. The ACCORD-Lipid trial evaluated the effectiveness of fenofibrate. Specifically, the ACCORD-Lipid trial was designed to answer the following question: In the context of good glycemic control, does a therapeutic strategy that uses a fibrate to increase HDL-C and lower triglyceride levels together with a statin to lower LDL-C reduce the rate of cardiovascular disease events compared with a strategy that uses a statin and a placebo?

9. Although there were favorable changes in lipids, including reductions in triglyceride levels, the ACCORD-Lipid trial failed to demonstrate a statistically significant reduction in major adverse cardiovascular events among individuals treated with fenofibrate and simvastatin compared with those treated with simvastatin alone. The active ingredient in Trilipix is the active metabolite of fenofibrate.

Trilipix and ACCORD-Lipid Advisory Committee

10. FDA convened an advisory committee on May 19, 2011, to discuss the results of the ACCORD-Lipid trial and their implications regarding the Trilipix labeling. The committee considered whether FDA should allow continued marketing of Trilipix's indication for co-administration with a statin without revision of the labeling, withdraw approval of the indication, or allow continued marketing of the indication with revision of the labeling to incorporate the principal findings from the ACCORD-Lipid trial. Three members voted to allow continued marketing of the indication without revision to the labeling; four members voted to withdraw approval of the indication for co-administration with a statin; and six members voted to allow continued marketing with a statin, but to revise the labeling to incorporate the principal findings

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