

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought NDA 22-224 Trilipix® (fenofibric acid) to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: 25 April 2011

FROM: Eric Colman, MD
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TO: Members and Consultants,
Endocrinologic & Metabolic Drugs Advisory Committee

SUBJECT: 19 May 2011, Advisory Committee meeting for choline
fenofibrate/fenofibric acid (Trilipix®) and the ACCORD-Lipid trial

Background

Thank you for agreeing to participate in the May 19, 2011 advisory committee meeting. This meeting is being held to discuss the results of the ACCORD-Lipid trial and how they relate to the approved indication for fenofibric acid (Trilipix®) for coadministration with a statin.

Fenofibric acid is the active ingredient of fenofibrate. Fenofibrate is a PPAR- α agonist that was approved for the treatment of hypertriglyceridemia in 1993. Fenofibrate was approved to reduce elevated LDL-C, TC, TG, and Apo B, and to increase HDL-C in patients with primary hypercholesterolemia or mixed dyslipidemia in 1999.

New Drug Application (NDA) for Fenofibric Acid (Trilipix®)

Abbott Laboratories submitted an NDA for fenofibric acid in 2007. The company sought approval of the following indications:

- When coadministered with an HMG-CoA reductase inhibitor to reduce elevated levels of TG, LDL-C, non-HDL-C, VLDL-C, Apo B and TC, and to increase HDL-C in adult patients with mixed/atherogenic dyslipidemia (Fredrickson Type IIb)
- To reduce elevated LDL-C, TC, TG, and Apo B, and to increase HDL-C in patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb)
- To treat patients with hypertriglyceridemia (Fredrickson Types IV and V)

The assessments of the clinical efficacy and safety of fenofibric acid were based in large part on data from 3 randomized, double-blind, active-controlled trials of 12-weeks duration followed by an open-label extension. Approximately 2700 patients with mixed dyslipidemia were enrolled into the three studies combined. Each study included a different statin as an active comparator: rosuvastatin, simvastatin, or atorvastatin. There were low-, moderate-, and high-dose statin and fenofibric acid monotherapy arms as well as fenofibric acid plus low- or moderate-dose statin arms in the three studies. Primary efficacy analyses were conducted for HDL-C, TG, and LDL-C.

For HDL-C, the principal comparisons were fenofibric acid in combination with each low- and moderate-dose of statin vs. statin monotherapy at the corresponding dose. For TG, the principal comparisons were fenofibric acid in combination with each low- and moderate-dose of statin vs. statin monotherapy at the corresponding dose. For LDL-C, the principal comparisons were fenofibric acid in combination with each low- and moderate-dose of statin vs. fenofibric acid monotherapy.

Treatment with fenofibric acid plus low- or moderate-dose statin led to statistically significant improvements in HDL-C and TG levels compared with low- or moderate-dose statin monotherapy. Statistically significant improvements in LDL-C levels were noted for fenofibric acid plus low- or moderate-dose statin compared with fenofibric acid monotherapy.

The major safety concern with fenofibrate is rhabdomyolysis, particular when coadministered with a statin. Events of lesser concern include hepatobiliary adverse reactions, elevations in serum creatinine and aminotransferases, and possible risks for pancreatitis and venous thromboembolic events (VTE).

There were no cases of rhabdomyolysis reported in the 3 pivotal fenofibric acid clinical studies. By design, none of the patients were treated with fenofibric acid in combination with the highest marketed doses of atorvastatin, rosuvastatin, or simvastatin.

The incidence of transaminitis in subjects treated with fenofibric acid monotherapy or coadministration with a statin was higher than that observed in subjects treated with statin monotherapy. However, there were no reports of severe liver injury. Serum creatinine levels did increase minimally to modestly in some subjects treated with choline fenofibrate/fenofibric acid. However, there were no reports of severe renal injury. Two subjects exposed to fenofibric acid versus no subject exposed to statin developed a VTE during the 12-week controlled phase of the trials. One subject exposed to fenofibric acid versus no subject exposed to statin developed pancreatitis during the 12-week controlled phase of the trials.

Taking into account the National Cholesterol Education Program Adult Treatment Panel's recommendation for fenofibrate as add-on therapy to a statin in high-risk patients with mixed dyslipidemia, the Division approved the following indication for Trilipix:

- In combination with a statin to reduce TG and increase HDL-C in patients with mixed dyslipidemia and CHD or a CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal.

Trilipix was also approved:

- As monotherapy to reduce TG in patients with severe hypertriglyceridemia
- As monotherapy to reduce elevated LDL-C, Total-C, TG and Apo B, and to increase HDL-C in patients with primary hyperlipidemia or mixed dyslipidemia.

The ACCORD-Lipid Trial

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid study was designed to answer the following question: In middle-aged or older people with type 2 diabetes who are at high risk for having a cardiovascular disease (CVD) event, does a therapeutic strategy that uses a fibrate to raise HDL-C/lower TG levels and uses a statin for treatment of LDL-C reduce the rate of CVD events compared to a strategy that only uses a statin for treatment of LDL-C? The primary efficacy outcome was major adverse cardiovascular events (MACE): nonfatal MI, nonfatal stroke, and CHD death.

A total of 2765 diabetics were randomized to simvastatin plus fenofibrate and 2753 diabetics were randomized to simvastatin plus placebo. All study participants received open-label simvastatin treatment for 4 weeks prior to initiation of blinded therapy with fenofibrate or placebo. The treatment groups were well-matched for baseline demographic characteristics. The mean age was 62 years, roughly 70% of the subjects were male and Caucasian, and approximately 37% had a history of a previous CVD event. The study subjects were obese, with an average baseline BMI of 32 kg/m². The mean baseline HbA1c was 8.3%. Nearly 65% of the subjects were taking a lipid-altering drug at entry into the study. The mean baseline LDL-C was 101 mg/dl; mean HDL-C was 38 mg/dl, and median TG was 162 mg/dl. It is important to note that the baseline lipid levels reflect measurements taken prior to the start of open-label simvastatin. Lipid levels following open-label simvastatin and immediately prior to starting blinded treatment with fenofibrate or placebo were not measured.

After an average follow-up of 4.7 years, the incidence rates of MACE in the simvastatin plus placebo group and the simvastatin plus fenofibrate group were 11.3% and 10.5%, respectively [HR 0.92; (0.79, 1.08); p=0.32].

In prespecified subgroup analyses of the primary efficacy outcome, gender was associated with a nominally significant interaction p-value (0.01), with a HR in the direction of harm for women from the fenofibrate group. Although not of nominal statistical significance (interaction p=0.06), the subgroup of subjects with baseline (i.e., pre-open-label simvastatin) TG levels ≥ 204 mg/dl and HDL-C ≤ 34 mg/dl had more favorable risk reduction for MACE with fenofibrate therapy compared with baseline TG and HDL-C levels classified as “all others”.

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study examined the effects of fenofibrate versus placebo on coronary events defined as non-fatal MI and CHD death in men and women with type 2 diabetes for an average of approximately 5 years. In this trial, the only other cardiovascular outcomes study of fenofibrate, 5.9% of subjects randomized to placebo and 5.2% of subjects randomized to fenofibrate had a coronary event [HR 0.89; (0.75, 1.05); p=0.16]. In prespecified subgroup analyses of total cardiovascular events, there was no evidence of significantly different treatment effects by gender or baseline TG/HDL-C levels (interaction p-values of 0.3 and 0.6, respectively).

FDA Briefing Document

In addition to an overview of ACCORD-Lipid, the Trilipix efficacy and safety data, and primary results from major fibrate monotherapy cardiovascular outcomes trials by Dr. Iffat N. Chowdhury from the Division of Metabolism and Endocrinology Products, FDA's briefing document includes a summary review of pharmacoepidemiological statin-fibrate safety data by Dr. Christian Hampp from the Office of Surveillance and Epidemiology and a consultative review of fenofibrate's renal effects by Dr. Nancy Xu from the Division of Cardiovascular and Renal Products.

Under separate cover, you will receive copies of published manuscripts for ACCORD-Lipid and FIELD, as well as three additional fibrate cardiovascular outcomes trials. You will also receive a copy of a published meta-analysis of fibrate trials and a recently-issued scientific statement by the AHA on TG and CVD.

As you read FDA and Abbott Laboratories' briefing documents and the supplementary publications, please keep in mind the following draft discussion points, as you will be asked to address them during the May 19th meeting.

Draft Discussion Points

In ACCORD-Lipid, over a mean duration of 4.7 years, the incidence of MACE in patients randomized to simvastatin plus placebo was 11.3% compared with 10.5% in patients randomized to simvastatin plus fenofibrate (HR 0.92; 95% CI 0.79, 1.08; p=0.32).

Trilipix is FDA approved for use in combination with a statin to reduce TG and increase HDL-C in patients with mixed dyslipidemia and CHD or a CHD equivalent who are on optimal statin therapy to achieve their LDL-C goal.

1. Discuss your interpretation of the primary efficacy results from ACCORD-Lipid, specifically as they relate to Trilipix's indication for coadministration with a statin.

2. In the subgroup of women from ACCORD-Lipid, the incidence of MACE in patients randomized to simvastatin plus placebo was 6.6% compared to 9.1% in patients randomized to simvastatin plus fenofibrate (interaction p-value 0.01 vs. men).

Discuss your interpretation of this subgroup finding, specifically as it relates to Trilipix's indication for coadministration with a statin.

3. In the subgroup of patients from ACCORD-Lipid with baseline levels of TG \geq 204 mg/dl and HDL-C \leq 34 mg/dl, the incidence of MACE in patients randomized to simvastatin plus placebo was 17.3% compared to 12.4% in patients randomized to simvastatin plus fenofibrate (interaction p-value 0.06 vs. all others).

Discuss your interpretation of this subgroup finding, specifically as it relates to Trilipix's indication for coadministration with a statin.

4. Discuss the safety profile of fenofibrate/fenofibric acid, specifically as it relates to Trilipix's indication for coadministration with a statin.

5. Discuss the benefit-risk profile of Trilipix when used in combination with a statin to reduce TG and increase HDL-C in patients with mixed dyslipidemia and CHD or a CHD equivalent who are on optimal statin therapy to achieve their LDL-C goal.

6. Taking into account all relevant data and levels of evidence, which action or actions do you recommend FDA take regarding Trilipix's indication for coadministration with a statin? **Please note that you may recommend more than one action.**

A. Allow continued marketing of Trilipix's indication for coadministration with a statin without revision of the labeling.

B. Withdraw approval of Trilipix's indication for coadministration with a statin.

C. Allow continued marketing of Trilipix's indication for coadministration with a statin with revision of the labeling to incorporate the principal findings from ACCORD-Lipid.

D. Require the conduct of a clinical trial designed to test the hypothesis that, in high-risk men and women at LDL-C goal on a statin with residually high TG and low HDL-C, add-on therapy with Trilipix versus placebo significantly lowers the risk for MACE.

E. Other

References

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3. Frick MH, et al. Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *NEJM* 1987; 317: 1237-45.
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5. The BIP Study Group. Secondary prevention by raising HDL-C and reducing TG in patients with coronary artery disease: the Bezafibrate Infarction Prevention (BIP) Study. *Circulation* 2000; 102:21-27.
6. Jun M, et al. Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. *Lancet* 2010; 375:1875-84.
7. Miller M, et al. Triglycerides and cardiovascular disease: A scientific statement from the American Heart Association. *Circulation*. Published online Apr 18 2011 at <http://circ.ahajournals.org>.

Clinical briefing document, EMDAC
NDA 22-224
Trilipix[®] (fenofibric acid)

Clinical Briefing Document
Endocrinologic and Metabolic Drugs Advisory Committee Meeting
May 19, 2011

New Drug Application 22-224: Trilipix[®] (fenofibric acid)
Sponsor: Abbott Laboratories
Clinical Reviewer: Iffat Nasrin Chowdhury, MD

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List of Abbreviations and Definitions

ACE-inhibitor	angiotensin-converting enzyme
AERS	adverse event reports
Apo B	apolipoprotein B
ARB	angiotensin-receptor blocker
ATP III	Adult Treatment Panel III
BMI	body mass index
CAD	coronary artery disease
CHD	coronary heart disease
CHF	congestive heart failure
CI	confidence interval
CPK	creatin phosphokinase
CVD	cardiovascular disease
	Diabetes Atherosclerosis Intervention Study
DBP	diastolic blood pressure
	drug-drug interaction
DMEP	Division of Metabolism and Endocrinology Products
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
HDL-C	high-density lipoprotein cholesterol
HHS (study)	Helsinki Heart Study
HPS (study)	Heart Protection Study
IDL	intermediate density lipoprotein
INN	International Non-Proprietary Name
LDL-C	low-density lipoprotein cholesterol
MACE	major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
NCEP	National Cholesterol Education Program

NHLBI	National Heart, Lung and Blood Institute
	peroxisome proliferator-activated receptors
PPRE	peroxisome proliferator response element
PT	preferred term
PTY	patient treatment year(s)
RCT	reverse cholesterol transport
SAE	serious adverse event
	systolic blood pressure
SOC	system organ class
TG	triglycerides
TNT (study)	Treatment to New Targets
Total-C	total cholesterol
	upper limit of normal
USAN	United States Adopted Name

Executive Summary

For the past forty years fibrates have been on the market, their popularity has waxed and waned with the results of clinical outcome trials and the emergence of competing lipid-lowering agents. Safety concerns from trials such as WHO-clofibrate and the impressive results of the statins in clinical trials resulted in diminishing use of the fibrates. In the 1980s fibrate use resurged with the introduction of gemfibrozil. Gemfibrozil use was supported by the Helsinki Heart Study (HHS) which showed significant relative risk reduction in coronary heart disease (CHD) events in a population of men without previous cardiovascular disease. In the late 1990s the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) demonstrated impressive results in reducing cardiovascular events this time in men with a history of previous cardiovascular events. Other fibrate outcome trials conducted with bezafibrate (BIP) and fenofibrate (FIELD) showed no significant overall cardiovascular benefit compared to placebo.

By the early 21st century, based on numerous outcome trials, treatment guidelines recommended the use of statins as first line therapy to target low density lipoprotein cholesterol (LDL-C). Treatment guidelines also recommended the use of niacin or fibrate to treat the residual risk of CVD in statin-treated patients with high triglycerides (TG), although the level evidence in support of this recommendation was not based on data from large outcome clinical trials.

The Action to Control Cardiovascular Risk in Diabetes – Lipid (ACCORD-Lipid) trial investigated the concomitant use of fenofibrate and a statin against statin monotherapy in a population with moderately elevated TG. Although there was no significant additional cardiovascular benefit with the use of statin plus fenofibrate as compared to statin monotherapy, a subgroup analysis raised the possibility that patients with TG greater than 204 mg/dL and high density lipoprotein cholesterol (HDL-C) below 34 mg/dL might benefit from the addition of fenofibrate to a statin. There was also a suggestion of cardiovascular harm in women from the gender subgroup analysis of the ACCORD-Lipid trial.

Fibrates have been investigated in at least five major clinical trials and have produced mixed results. Although outcome trials with gemfibrozil have shown cardiovascular benefit over placebo, fenofibrate has not. The answer to the question of why fenofibrate produced unimpressive cardiovascular outcome results relative to gemfibrozil is not known. The inconsistent findings may be a result of pharmacodynamic differences between individual fibrates and diverse study populations or both.

One way to obtain a more definitive answer to the question of fenofibrate's cardiovascular benefit when added to a statin is to conduct a clinical trial specifically designed to test the hypothesis that, in high-risk men and women at LDL-C goal on a statin with residually high TG and low HDL-C, treatment with fenofibrate versus placebo significantly reduces the risk for major adverse cardiovascular events (MACE). Such a trial would also provide additional information regarding the cardiovascular effects of fenofibrate plus statin versus statin monotherapy in women versus men.

Introduction

Regulatory Background

On 14 March 2010, the National Heart, Lung and Blood Institute (NHLBI) released the results of the Action to Control Cardiovascular Risk in Diabetes – Lipid (ACCORD-Lipid). The ACCORD-Lipid trial was the first major cardiovascular outcome trial to evaluate the practice of combining fenofibrate with a statin in a diabetic population and compare it to statin monotherapy.

After an average follow-up of 4.7 years, there were 291 (10.5%) major fatal or nonfatal cardiovascular events in the fenofibrate-simvastatin therapy study arm and 310 (11.3%) events in the simvastatin monotherapy study arm. The difference in events was not statistically significant. Among the secondary end points, there was also no statistically significant difference between the two treatments.

On 15 March 2010, the FDA issued a statement informing healthcare professionals that it was aware of the principal ACCORD-Lipid findings and planned to review the data when available. The statement noted that Trilipix[®] (fenofibric acid) was approved for co-administration with a statin and that this indication would be re-evaluated following complete review of the ACCORD-Lipid data.

Product Information

Trilipix[®] (fenofibric acid) belongs to the class of fenofibrate products; the non-proprietary name is choline fenofibrate. Trilipix[®] and other fenofibrates are “prodrugs” and therefore are pharmacologically inactive. However, fenofibrates are hydrolyzed to an active metabolite, fenofibric acid.

The first fenofibrate was approved in 1993 for the treatment of severe hypertriglyceridemia. In 1999, a fenofibrate product was also approved for the reduction of LDL-C, TG, total cholesterol (TC), and apolipoprotein B (apo B) and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia. These approved indications were based on favorable lipid profile changes.

Trilipix[®] (fenofibric acid) was approved in the United States on December 15, 2008, with similar indications given to previous fenofibrate products:

- As monotherapy to reduce TG in patients with severe hypertriglyceridemia
- As monotherapy to reduce elevated LDL-C, Total-C, TG, and Apo B, and to increase HDL-C in patients with primary hyperlipidemia or mixed dyslipidemia

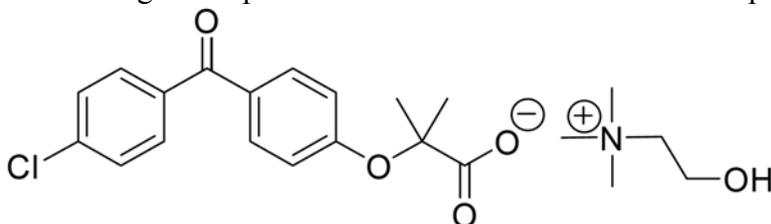
However, Trilipix was and remains the only fenofibrate product to receive the following indication:

- In combination with a statin to reduce TG and increase HDL-C in patients with mixed dyslipidemia and CHD or a CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal

The approval of Trilipix® was supported by the findings from three 12-Week randomized, controlled clinical trials, comparing the effect of therapy with fenofibric acid and a statin versus fenofibric acid monotherapy or statin monotherapy on key lipid parameters. The primary endpoints in these trials were TG and HDL-C changes with the combination of a statin and fenofibric acid as compared to fenofibric acid monotherapy. Change in LDL-C with the combination of fenofibric acid and statin was compared with statin monotherapy. The development program also included two long-term open-label extension studies, which followed patients on combination therapy for up to 116 weeks of treatment.

Trilipix® is available as oral delayed-release capsules at doses equivalent to 45 mg and 135 mg of fenofibric acid. The recommended dosage for patients with mixed dyslipidemia and primary hypercholesterolemia is 135 mg once daily; for patients with hypertriglyceridemia it is 45 to 135 mg once daily; and in renally impaired patients it is 45 mg once daily.

The following is a depiction of the structural formula of Trilipix®.



The chemical name is 2-[4-(4-chlorobenzoyl) phenoxy]-2-methylpropanoic acid choline salt. The molecular formula is C₂₂H₂₈ClNO₅; the non-proprietary name is choline fenofibrate.

Differences between fibrates

Fibrates mediate their effect through activation of the peroxisome proliferator-activated receptors selective for the alpha subtype (PPAR α). Fibrate-activated PPAR α regulates gene expression after heterodimerization with the retinoid X receptor (RXR) to modulate the expression of a number of target genes critical for lipid and lipoprotein metabolism.¹

Among the fibrates, gemfibrozil is structurally different. It is a non-halogenated fibrate, which chemically differentiates it from other fibrates.² In addition, several studies have shown qualitative and quantitative differences between gemfibrozil and the other fibrates. For example, although both fenofibrate and gemfibrozil increase HDL-C, fenofibrate increases apolipoprotein (apo) A-1 concentrations, whereas gemfibrozil seems to have little or no effect on apo A-1

¹ Rotllan N, et al. Differential effects of gemfibrozil and fenofibrate on reverse cholesterol transport from macrophages in vivo. *Biochimica et Biophysica Acta* 2011; 1811:104-110.

² Murphy M, et al. "Dyslipidemias." *Pharmacology and Therapeutics: Principles to Practice*. Saunders Elsevier Publisher. Editors: S.A. Waldman and A. Terzic 2009 Chapter 23, pg. 314.

levels.³ This lack of effect on apo A-1 is due to gemfibrozil's differential co-activator recruitment to the PPAR/RXR complex depending on the geometry of the PPAR response element (PPRE).⁴

In a study that compared the effects of gemfibrozil with bezafibrate in patients with type IIb hyperlipoproteinemia, gemfibrozil significantly decreased intermediate density lipoprotein (IDL) and the TG content of IDL and LDL-C more than bezafibrate. The authors conclude that the effects of both drugs may be qualitatively and quantitatively different in primary type IIb and IV hyperlipoproteinemia.⁵

Other studies highlight differential action of fenofibrate on HDL-C as compared to gemfibrozil. Rotllan and colleagues demonstrated the ability of fenofibrate to increase the macrophage-specific reverse cholesterol transport (RCT) pathway in vivo in female hApoA-ITg mice, a mouse model that elicits a humanized response to fibrates. In contrast, gemfibrozil did not change the rate of macrophage-specific RCT in the same animal model.⁶

A key difference between gemfibrozil and fenofibrates is the potential for drug-drug interactions (DDI). Pharmacokinetic studies indicate gemfibrozil significantly increases peak plasma concentration and mean area under the concentration-time curve of all statins except fluvastatin. This interaction occurs secondary to gemfibrozil inhibiting metabolism through glucuronidation of the statin which results in higher overall statin concentrations and suggests a greater potential for muscle toxicity.⁷ Gemfibrozil has no effect on the cytochrome P450 (CYP) 3A4 isoenzyme, but does inhibit CYP2C9 and CYP2C8 and OATP transporter.

Conversely, fenofibrate does not significantly inhibit the major CYP isoenzymes and utilizes different isoforms of the hepatic glucuronidation enzymes from those used by statins and gemfibrozil. However, fenofibrates are thought to have the potential to increase the incidence of myopathy with co-administration with a statin through pharmacodynamic interactions, as both agents can cause myopathy.⁸

Currently Available Treatment for Lipid-Altering Indications

Clofibrate, the first fibrate, was approved in the late 1960s and was followed in 1981 by gemfibrozil. Although fenofibrate had been used in Europe since the 1970s the first fenofibrate product was approved in the US in 1993. Bezafibrate and ciprofibrate are available in other countries. Other lipid-lowering agents available in the US are listed by indication below.

³ Duez H. et al. Regulation of Human Apo A-I by Gemfibrozil and Fenofibrates Through Selective Peroxisome Proliferator-Activated Receptor alpha Modulation. *Arterioscler Thromb Vasc Biol.* 2005;25:585-591.

⁴ Ibid.

⁵ Durrington P, et al. Effects of two different fibric acid derivatives on lipoproteins, cholesterol ester transfer, fibrinogen, plasminogen activator inhibitor and paraoxonase activity in type IIb hyperlipoproteinemia. *Atherosclerosis* 1988;138:217-225.

⁶ Rotllan N, et al. Differential effects of gemfibrozil and fenofibrate on reverse cholesterol transport from macrophages in vivo. *Biochimica et Biophysica Acta* 2011; 1811:104-110.

⁷ Kyrklund C, et al. Plasma concentrations of active lovastatin acid are markedly increased by gemfibrozil but not bezafibrate. *Clin Pharmacol Ther* 2001;69:340-5.

⁸ Davidson M. Statin/fibrate combination in patients with metabolic syndrome or diabetes: evaluating the risks of pharmacokinetic drug interactions. *Expert Opin Drug Saf* 2006;5:145-56.

Indication 1: Co-administration therapy with statins for the treatment of mixed/atherogenic dyslipidemia

- Niacin extended-release (Niaspan®, Advicor®, Simcor®)
- Ezetimibe (as a component of Vytorin® only)

Indication 2: Treatment of primary hypercholesterolemia or mixed dyslipidemia

- Statins (lovastatin, rosuvastatin, fluvastatin, atorvastatin, pravastatin, simvastatin, pitavastatin)
- Ezetimibe (Zetia®, Vytorin®)
- Bile acid sequestrants (cholestyramine, colestevlam, colestipol)
- Niacin

Indication 3: Treatment of severe hypertriglyceridemia

- Niacin
- Omega-3-acid ethyl esters

Brief Disease Background

Heart disease and stroke are the first and third leading cause of death in the United States and have maintained this ranking since 1921 and 1938, respectively. In 2006, cardiovascular disease was responsible for 32% of all deaths: 26% from heart disease and 6% from stroke.⁹

Elevated levels of TC, LDL-C, and apo B and decreased levels of HDL-C are risk factors for atherosclerosis. Epidemiologic studies have established that cardiovascular morbidity and mortality vary directly with the levels of TC, LDL-C, and TG and inversely with the level of HDL-C. The independent effect of raising HDL-C or lowering TG on the risk of cardiovascular morbidity and mortality has not been determined.

However, substantial evidence from randomized controlled trials identify LDL-C as a primary target of lipid-lowering therapy and the use of statins to lower LDL-C has significantly reduced the risk of coronary heart disease, stroke, and mortality. Despite significant reductions in cardiovascular events, substantial risk for future events remain in statin-treated patients with pre-existing CVD.¹⁰

This residual risk of CVD has been associated with “atherogenic dyslipidemia”, a term used to describe the phenotype of high TG, low levels of HDL-C, and a predominance of small, dense LDL particles. Atherogenic dyslipidemia can be further characterized by low levels of

⁹ Keenan N et al. Coronary heart disease and stroke deaths in US 2006. *Morbidity and Mortality Weekly Report* 2011; 60 (01):62-66.

¹⁰ Cholesterol Treatment Trialists (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomized trials of statins. *Lancet*. 2005;366:12367-78.

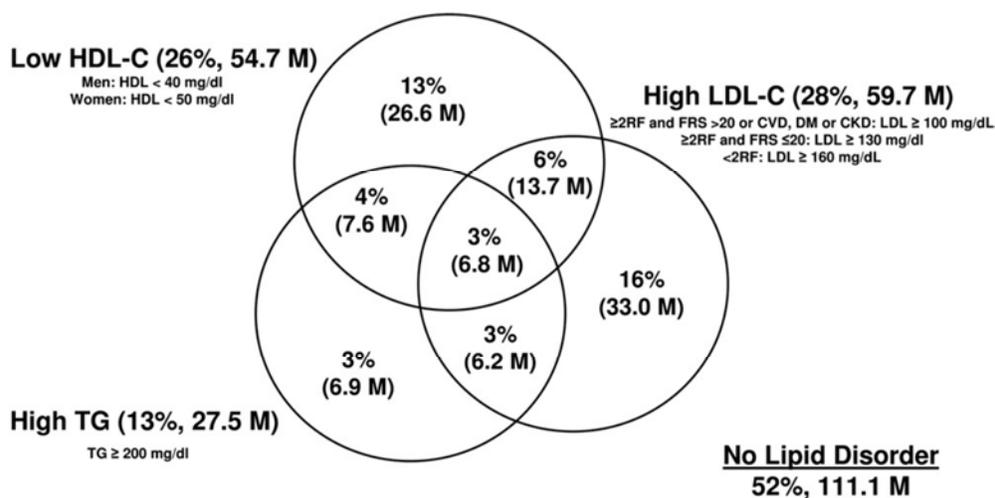
apolipoprotein (apo) A-1, increased apo B and very low density lipoprotein (VLDL) remnant particles.¹¹

The term diabetic dyslipidemia essentially refers to atherogenic dyslipidemia occurring in persons with type 2 diabetes mellitus (T2DM). It is characterized by elevated triglyceride remnant lipoproteins, small LDL particles, and low HDL-C concentrations.

Figure 1 shows the proportion of and estimated number of subjects with individual or combined lipid abnormalities projected to the 2007 US adult population. The data was analyzed from 2,883 individuals (weighted to a US population of 128.5 million) in the National Health and Nutrition Examination Survey (NHANES) 2003-2004.¹² The NHANES is a stratified probability sampling of non-institutionalized civilians and derives data from personal interview, physical examination, and laboratory testing.

Overall, 7% of subjects had low HDL-C (< 40 /50 mg/dL) and elevated TG (defined as ≥200 mg/dL), 9% with low HDL-C combined with elevated LDL-C, and 6% had elevated LDL-C along with elevated TG. LDL-C was defined as high if not meeting the current NCEP-ATPIII lipid guidelines. Approximately 30% of projected 2007 US adult population had a single lipid disorder, whereas 16% had at least two abnormalities. Only 3% of all persons had all three lipid abnormalities.¹³

Figure 1 Projected (2007) US Population With and Without Lipid Disorders



Source: NHANES IV 2003-2004 data, US population projected to 2007

Source: Ghandehari et al. *Am Heart J*, 2008; 156:112-9.

¹¹ Superko HR, et al. Lipid management to reduce cardiovascular risk: a new strategy is required. *Circulation*. 2008;117;560-568.

¹² Ghandehari et al. Prevalence and extent of dyslipidemia and recommended lipid levels in US adults with and without cardiovascular co morbidities: The National Health and Nutrition Examination Survey 2003-2004. *Am Heart J*, 2008; 156:112-9

¹³ Ibid.

A different study evaluated data from the NHANES for trends in major lipid fractions in United States adults 20 to 74 years of age from 1976 to 2006.¹⁴

Table 1 Proportion of adults with lipid fractions according to NCEP-ATP III Classification - NHANES 1976-2006

	NHANES II (1976-1980) N=5792	NHANES III (1988-1994) N=7012	NHANES 1999-2006 (1999-2006) N=8,174
LDL-C mg/dL			
≥ 160	20%	16%	12%
100-< 160	44%	55%	56%
<100	17%	23%	31%
Not available	18%	5%	2%
TG mg/dL			
> 200	16%	14%	18%
150-< 200	14%	13%	15%
<150	67%	68%	67%
Not available	3%	5%	1%
HDL-C mg/dL			
< 40	21%	23%	19%
40 -< 60	43%	51%	52%
> 60	18%	22%	28%
Not available	18%	5%	1%

Source: Cohen et al. *Am J Cardiol* 2010;106:969-975.

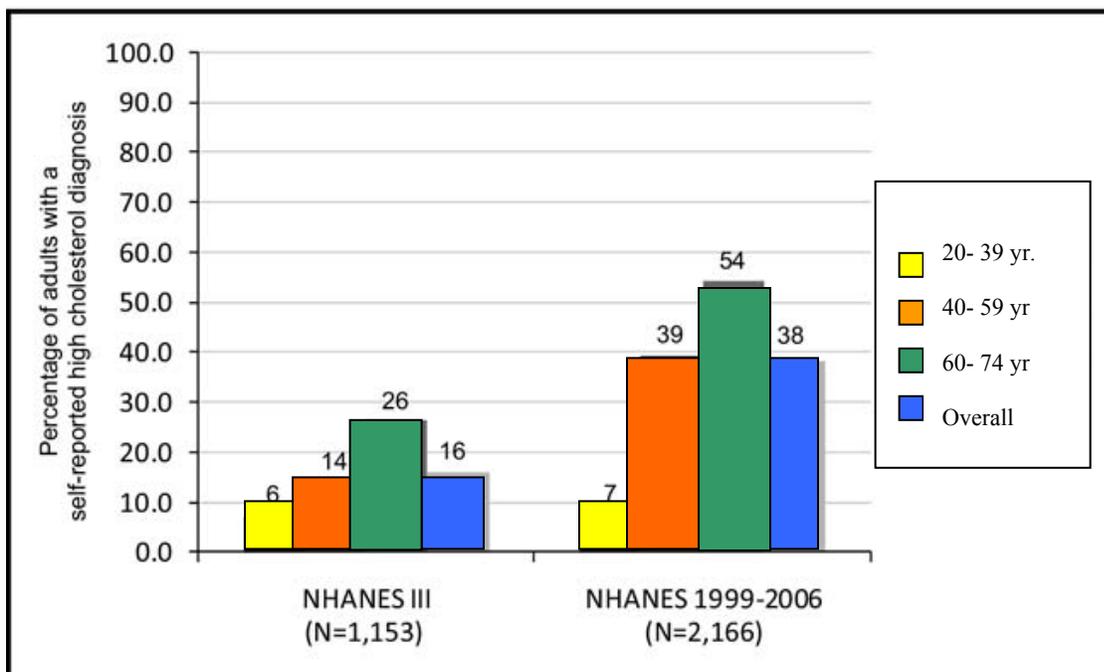
Based on the NHANES surveys, the proportion of adults with LDL-C < 100 mg/dL increased from 17% to 31% from 1976 to 2006. Both men and women had similar decreases in LDL-C from NHANES II to NHANES 1999-2006. Trends in TG shifted slightly higher from 1976 to 2006, from a mean TG of 137 mg/dL to 146 mg/dL. HDL-C levels increased slightly from 50 mg/dL to 53 mg/dL.¹⁵

According to Cohen et al, prevalence of self-reported high cholesterol increased over the recent survey periods, suggesting more awareness of cholesterol/lipid levels. In addition, lipid-lowering medication use in respondents with self-reported high cholesterol more than doubled from NHANES III to NHANES 1999 to 2006 (16% to 38%) (Figure 2), and this has likely contributed to the downward trend of LDL-C levels.

¹⁴ Cohen et al. 30-Year Trends in serum lipids among United States Adults: results from the National Health and Nutrition Examination Surveys II, III, and 199-2006. *Am J Cardiol* 2010;106:969-975.

¹⁵ Cohen et al. 30-Year Trends in serum lipids among United States Adults: results from the National Health and Nutrition Examination Surveys II, III, and 199-2006. *Am J Cardiol* 2010;106:969-975.

Figure 2: Percent lipid medication use NHANES 1976- 2006



Source: Cohen et al. *Am J Cardiol* 2010;106:969-975.

In 2002, the NCEP ATP III treatment guidelines introduced a secondary target of therapy, non-HDL-C, in patients with elevated TG (≥ 200 mg/dL). Non-HDL-C equates to VLDL + LDL-C and is a surrogate of apo B levels. Non-HDL-C was added as a secondary target of therapy to take into account the atherogenic potential associated with remnant lipoproteins in patients with hypertriglyceridemia.¹⁶

The NCEP ATP III guidelines further recommended that in high-risk patients with high TG or low HDL-C, consideration may be given to combining a fibrate or nicotinic acid to an LDL-C lowering drug. According to the report, although the evidence base to support fibrate therapy at that time was not as strong as that for statins, fibrates may have an adjunctive role in the treatment of patients with high TG/low HDL-C, especially in combination with statins.¹⁷

The 2006 update to the American Heart Association/American College of Cardiology (AHA/ACC) guidelines for secondary prevention for patients with coronary vascular disease also advocated the targeting of non-HDL-C in patients with elevated TG. The AHA/ACC listed the following as therapeutic options to reduce non-HDL-C:

- More intense LDL-C lowering therapy
- Niacin (after LDL-C lowering therapy)
- Fibrate (after LDL-C lowering therapy)

¹⁶ Grundy S, et al. Implications of recent clinical trials on the National Cholesterol Education Program, Adult Treatment Panel III. *Circulation* 2004;110:227-239.

¹⁷ Ibid.

Both the addition of niacin or fibrate is Class IIa Recommendation; that is, the weight of evidence/opinion is in favor of usefulness/efficacy.¹⁸

NCEP ATP III Treatment Guidelines

NCEP ATP III adopts lower cutpoints for TG abnormalities relative to ATP II because of the growing evidence for TG as an independent risk factor for cardiovascular disease.

Table 2: Triglyceride Categories as defined by NCEP-ATP III

Category	Serum Triglyceride Levels (mg/dL)
Normal triglycerides	Less than 150
Borderline high triglycerides	150 to 199
High triglycerides	200 to 499
Very high triglycerides	Greater than 500

The NCEP ATP III therapeutic guidelines for borderline high TG and high TG are described below.

Therapeutic considerations for persons with borderline high TG (150- 199 mg/dL)

Serum TG in the range of 150–199 mg/dL often indicates adverse life habits. Borderline high TG should alert the physician to the possible presence of the metabolic syndrome and should signal the need for changes in life habits. When TG are borderline high, LDL-C remains the primary target of treatment and it is not necessary to evoke non-HDL-C as a secondary target of therapy. Drug therapy to specifically reduce VLDL remnants is rarely needed for TG in this range, although statins concomitantly lower LDL and VLDL remnants. Thus the general approach to management of elevated LD-C need not be modified when TG are borderline high.

High TG (200-499 mg/dL)

In persons with high serum TG, LDL-C remains the primary target of therapy. In addition, non-HDL-C becomes a secondary target. Changes in life habits represent first-line therapy, but it is also important to determine whether a patient is taking drugs known to exacerbate hypertriglyceridemia, and, if so, these should be modified. Among hypolipidemic agents, the statins are the most effective for lowering non-HDL-C. Not only do statins reduce LDL-C, but they also lower VLDL-TG and VLDL-C.

When LDL-C levels are not significantly elevated, the goal for non-HDL-C with a TG lowering drug alone usually is within reach. If fibrates are employed it is usually necessary to combine them with a statin to attain the non-HDL-C goal.

Table 3: NCEP ATP III Treatment Considerations for Elevated Serum Triglycerides

Serum Triglyceride Category	Special Treatment Considerations
	<ul style="list-style-type: none"> • Primary goal: achieve LDL-C goal • Life-habit changes: first-line therapy for

¹⁸ Smith SC, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update. *J Am Coll Cardiol.* 2006; 47: 2130-2139.

Serum Triglyceride Category	Special Treatment Considerations
<p>Borderline High Triglycerides (150-199 mg/dL)</p>	<p>borderline high triglycerides</p> <ul style="list-style-type: none"> ○ Body weight control ○ Regular physical activity ○ Restriction of alcohol use (when consumed in excess) ○ Avoid high carbohydrate intakes (> 60% of calories) <ul style="list-style-type: none"> ● Drug Therapy <ul style="list-style-type: none"> ○ Triglycerides in this range not a direct target of drug therapy
<p>High Triglycerides (200-499 mg/dL)</p>	<ul style="list-style-type: none"> ● Primary goal: achieve LDL-C goal ● Secondary goal: achieve non-HDL-C goal: 30 mg/dL higher than LDL-C goal ● First-line therapy for high triglycerides: TLC-emphasize weight reduction and increased physical activity ● Second line therapy: drugs to achieve non-HDL-C goal <ul style="list-style-type: none"> ○ Statins: lowers both LDL-C and VLDL-C ○ Fibrates: lowers VLDL-triglycerides and VLDL-C ○ Nicotinic acid: lowers VLDL-triglycerides and VLDL-C ● Alternative approaches to drug therapy for lowering non-HDL-C <ul style="list-style-type: none"> ○ High doses of statins (lowers both LDL-C and VLDL-C) ○ Moderate doses of statins and triglyceride-lowering drugs (fibrate or nicotinic acid) <p>Caution: Increased frequency if myopathy with statins and fibrates</p>
<p>Very High Triglycerides (≥ 500 mg/dL)</p>	<ul style="list-style-type: none"> ● Goals of therapy <ul style="list-style-type: none"> ○ Triglyceride lowering to prevent acute pancreatitis (first priority) ○ Prevention of CHD (second priority) ● Triglyceride lowering to prevent pancreatitis <ul style="list-style-type: none"> ○ Very low-fat diet ○ Medium chain TG replacement ○ Institute weight reduction ○ Fish oils ○ Triglyceride lowering drugs ○ Statins: not first line agent for very high triglycerides ○ Bile acid sequestrants: contraindicated ● Triglyceride lowering to prevent CHD: <ul style="list-style-type: none"> ○ Efficacy of drug therapy to prevent CHD in persons with very high triglycerides not demonstrated by clinical trials

Therapeutic considerations for persons with diabetic dyslipidemia

According to the NCEP ATP III guidelines, since diabetes falls into the category of CHD risk equivalent, the goal for LDL-C in persons with diabetes, particularly T2DM, is <100 mg/dL. For LDL-C lowering, statins are usually the drugs of choice in persons with diabetic dyslipidemia. They are highly efficacious for LDL-C reduction, and they are well tolerated by persons with diabetes. When baseline LDL-C is <100 mg/dL and TG is 200 to 500 mg/dL, non-HDL-C should be estimated to determine whether it is still a target for cholesterol-lowering therapy. If the TG level is ≥200 mg/dL, use of a fibrate or a low dose of nicotinic acid (<3 g/day) may assist in achieving the non-HDL-C goal of <130 mg/dL (or + 30 mg/dl compared with the LDL-C level) in persons with diabetic dyslipidemia.

Table 4: NCEP ATP III Treatment Considerations for Diabetic Dyslipidemia

Serum LDL-Cholesterol Level	Special Therapeutic Considerations
<p>LDL ≥ 130 mg/dL</p>	<ul style="list-style-type: none"> • Initiate TLC in all persons • Many persons with type 1 or type 2 diabetes, will require LDL-lowering drugs (statins usually first choice) • LDL goal: <100 mg/dL • If triglycerides ≥200 mg/dL, non-HDL-C goal: <130 mg/dL • If LDL ≥130 mg/dL, LDL-lowering drug usually indicated along with TLC • Type 1 diabetes: clinical judgment required for how intensively to employ LDL-lowering therapy to reach an LDL of <100 mg/dL (however, consider LDL-lowering drug if LDL ≥130 mg/dL) • Type 2 diabetes: generally delay management of atherogenic dyslipidemia until LDL goal has been achieved • If triglycerides ≥200 mg/dL, consider treatment with fibrate or nicotinic acid (either as alternative to or in combination with LDL-lowering drug) to achieve goal for non-HDL-C • Intensively treat nonlipid risk factors (hypertension, cigarette smoking, hyperglycemia) • If nicotinic acid is employed, use relatively low doses (<3 g/day)

Serum LDL-Cholesterol Level	Special Therapeutic Considerations
<p align="center">Baseline LDL 100-129 mg/dL</p>	<p>Initiate TLC in all persons</p> <ul style="list-style-type: none"> • Intensively treat nonlipid risk factors • Consider therapeutic options: intensive TLC; LDL-lowering drug; drug to lower triglycerides or raise HDL; control of nonlipid risk factors • If triglycerides ≥ 200 mg/dL, non-HDL-C goal: < 130 mg/dL • If triglycerides ≥ 200 mg/dL, consider treatment with fibrate or nicotinic acid (either as alternative to or in combination with LDL-lowering drug) to achieve goal for non-HDL-C • If nicotinic acid is employed, use relatively low doses (< 3 g/day)
<p align="center">On- Treatment LDL 100-129 mg/dL</p>	<ul style="list-style-type: none"> • Intensify TLC in all persons • Intensively treat nonlipid risk factors • If triglycerides < 200 mg/dL, consider intensifying LDL-lowering therapy (e.g., higher dose of statin or combining a statin with a bile acid sequestrant) • If triglycerides ≥ 200 mg/dL, consider adding fibrate or nicotinic acid to statin therapy to achieve non-HDL-C goal < 130 mg/dL* • If nicotinic acid is employed, use relatively low doses (< 3 g/day)
<p align="center">Baseline LDL < 100 mg/dL</p>	<ul style="list-style-type: none"> • Initiate TLC in all persons to reduce overall risk • Intensively treat nonlipid risk factors • If triglycerides ≥ 200 mg/dL, consider using a fibrate or low-dose nicotinic acid to achieve non-HDL-C goal < 130 mg/dL. • If nicotinic acid is employed, use relatively low doses (< 3 g/day)

Source: NCEP-ATPIII 2002 Table VII.4-2. pg. 3341.

Action to Control Cardiovascular Risk in Diabetes (ACCORD) - Lipid

Rationale for the ACCORD Lipid

The central rationale for the design of ACCORD-Lipid was that CVD is increased in patients with T2DM. Although the use of statins in diabetic patients is efficacious, CVD event rates of statin-treated diabetic patients remain elevated. ACCORD-Lipid investigated if more aggressive control of diabetic dyslipidemia, specifically raising HDL-C and lowering TG (with a fenofibrate) in the context of desirable levels of LDL-C (with a statin), would provide greater benefit compared with only having desirable levels of LDL-C.

Study Objectives

Sponsored by NHLBI, the ACCORD-Lipid was a component of the larger ACCORD trial that evaluated whether intensive versus standard management of blood pressure, lipids, and glycemia in diabetic patients could reduce cardiovascular event rates.

Specifically, ACCORD-Lipid evaluated whether the combination of fenofibrate and simvastatin reduced MACE compared to simvastatin monotherapy in patients with T2DM.

The primary outcome in ACCORD-Lipid was a composite of

- 1) nonfatal myocardial infarction,
- 2) nonfatal stroke, or
- 3) death from cardiovascular causes

Cardiovascular causes of death included fatal MI, congestive heart failure, documented arrhythmia, death after invasive cardiovascular interventions, death after non-cardiovascular surgery, fatal stroke, unexpected death presumed to be due to ischemic CVD occurring <24 hours after the onset of symptoms, and death due to other vascular diseases (e.g., pulmonary emboli, abdominal aortic aneurysm rupture).

The diagnosis of MI was based on the occurrence of a compatible clinical syndrome associated with diagnostic elevation of cardiac enzymes (i.e., an increase in troponin T or troponin I to a level indicating myonecrosis and/or an increase in creatine kinase–myocardial band to a level more than twice the upper limit of normal). Q-wave MI was defined as the development of new significant Q waves. Silent MI was diagnosed when new (compared with the previous 12-lead electrocardiogram) significant Q waves were detected by surveillance electrocardiography performed every 2 years and at study end in all participants.

Stroke was diagnosed by a focal neurologic deficit that lasted >24 hours, associated with evidence of brain infarction or hemorrhage by computed tomography, MRI, or autopsy¹⁹

Secondary outcomes in the ACCORD-Lipid included the following:

- 1) Expanded macrovascular outcome: defined as the combination of the primary end point plus any revascularization and hospitalization for congestive heart failure
- 2) Major coronary artery disease events: fatal events, nonfatal MI, and unstable angina
- 3) Nonfatal Myocardial Infarction
- 4) Total stroke: combined fatal and nonfatal stroke
- 5) Nonfatal Stroke
- 6) Total mortality
- 7) Cardiovascular mortality
- 8) Congestive heart failure: death or hospitalization for heart failure (with documented clinical and radiologic evidence)²⁰

Pre-specified subgroups in the ACCORD-Lipid included:

¹⁹ Supplemental Appendix to ACCORD-Lipid Study. *NEJM* 2010;362:1563-74.

²⁰ Ibid.

- Gender
- Age (< 65, > 65 yrs)
- Race (Nonwhite, White)
- Presence of clinical CVD (primary, secondary prevention)
- Glycemia Trial treatment assignment (Intensive, Standard)
- LDL-C (tertiles)
- HDL-C (tertiles)
- TG (tertiles)
- High TG + Low HDL-C' (upper tertile TG + lower tertile HDL-C) versus 'all Others'
- Hba1c (< median, > median)

Study Design

The larger ACCORD trial was a randomized, double 2 X 2 factorial design of 10,251 participants with T2DM. All participants were in the glycemia trial. In addition, one 2 X 2 trial addressed the blood pressure question in 4,733 of the recruited participants, while the other 2 X 2 trial addressed the lipid question in 5,518 of the participants. Therefore, each participant was in a 2 X 2 trial testing two treatment strategies of two interventions, one of which was glycemic control and the other was either lipid or blood pressure control. The lipid component was the only blinded portion of the ACCORD trial. The following table shows the distribution of the participants in the trial.

Table 5: ACCORD- Distribution of Participants

Glycemia Trial	Blood Pressure Trial		Lipid Trial		Total
	SBP < 120 mmHg	SBP < 140 mmHg	Placebo	Fenofibrate	
HbA1C < 6.0%	1,178	1,193	1,383	1,374	5,128
HbA1C 7.0-7.9%	1,184	1,178	1,370	1,391	5,123
	2,362	2,371	2,753	2,765	
Total	4,733		5,518		10, 251

Base; Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial: Design and Methods. *Am J of Cardiol* 2007; 99: 21i-33i

The ACCORD-Lipid trial was a parallel treatment arm study design. All eligible subjects were treated with open-label simvastatin for 4 weeks, then received the masked study drug, either fenofibrate or placebo. However, the masked study drug was administered without the benefit of a lipid profile after the 4 weeks of open-label simvastatin. .

An adaptive study design would have allowed for a statin monotherapy treatment interval, then based on a lipid profile randomized those patients at LDL-C goal and TG \geq 200 mg/dL to treatment with statin plus masked medication (either a fenofibrate or placebo).

According to the ACCORD-Lipid Study Group, during the first five years of the trial the results of several major clinical trials, including HPS, PROVE-IT-TIMI 22, and TNT, and expert lipid panelists' recommendations (NCEP ATP III) led to significant modifications in the ACCORD lipid trial study design. Amendments to the ACCORD Lipid protocol are summarized in the table below.

Table 6: Amendments to ACCORD Lipid Protocol over time

	Vanguard Phase		Main Trial		
	10/16/00 Protocol	9/13/01 Protocol	11/14/02 Protocol	8/31/04 Protocol	05/11/05 Protocol
LDL-C Eligibility Criterion	≤ 170 mg/dl	Same	85-170 mg/dl	60-180 mg/dl	Same
HDL-C eligibility Criterion	< 50 mg/dl	Same	Same	< 55 mg/dl, Women or Black; < 50 mg/dl all others	Same
Starting Dose Of Statin	0 if LDL-C < 116 mg/dl 5 mg/day if LDL-C 116-150 mg/dl 10 mg/day if LDL-C 151-170 mg/dl	Same	All 20 mg/day No titration	All 20 mg/day to start except ppts with CVD = 40 mg/day	Same
LDL-C Level for Statin Up-titration	Initial 120 mg/dl Subsequent 130 mg/dl	120 mg/dl for all	No titration	Uptitrate to 40 mg/day if LDL > 100 mg/dl X 2	Same, with addition to uptitrate to 40 mg/day if ppt has CVD event
LDL-C alert-D/C Study Meds	If 130 mg/dl X 2 & on max statin D/C study lipid meds/transfer	Same	Same	if > 120 mg/dl X 2 & on 40 statin, D/C blinded meds/transfer	Same
Triglyceride Alert	if > 750 mg/dl X 2, D/C blinded meds/transfer	Same	Same	Same	Same
Downtitrate Statin	< 50 mg/dl	Same	if < 40 mg/dl X 2, D/C statin	Same	Same
Fibrate Dose	160 mg/day	Same	Same	54 or 160 mg/day (or bioequivalent doses), based upon eGFR	Same

CVD = cardiovascular disease; D/C = discontinue; fibrate = fenofibrate; GFR = glomerular filtration rate estimated by the Modified Diet in Renal Disease equation (see text for details); HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; ppt = participant; statin = simvastatin (a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor); transfer = transferring this aspect of patient care back to participant's private physician.

* For HDL-C and LDL-C, 1 mg/dL = 0.02586 mmol/L. † For triglyceride, 1 mg/dL = 0.01129 mmol/L.

Source: Ginsberg, et al. Evolution of the lipid trial protocol of the Action to Control Cardiovascular Risks in Diabetes (ACCORD) Trial. *Am J Cardiol* 2007;99[suppl]:56i-67i.

There were two important developments relating specifically to the use of fenofibrate in the trial. Starting in 2004, the dose of fenofibrate changed from 160 mg/day to one in which subjects' baseline eGFR determined the fenofibrate dose. Subjects with a baseline eGFR ≥ 50 mL/min/1.73m² received 160 mg/day of fenofibrate or placebo and subjects with a baseline eGFR between 30 and <50 ml/min/1.73² received 54 mg/day fenofibrate or placebo. Those in whom the eGFR fell below 30 mL/min/1.73m² fenofibrate or placebo were permanently discontinued. Serum creatinine level monitoring every four months to estimate the GFR was also written into the protocol.

In ACCORD-Lipid, approximately 440 (16%) of patients in the Fenofibrate treatment arm and 194 (7.1%) in the Placebo treatment arm were on a reduced dose of masked medicine, presumably due to decreases in eGFR or elevated creatinine. Sixty-six (2%) patients in the Fenofibrate treatment arm vs. 30 (1%) patients in the Placebo treatment arm were discontinued

from the masked medicine for “Low GFR/Elevated creatinine”.²¹ Altogether 18% of patients in the Fenofibrate treatment arm as compared to 8% in the Placebo treatment arm were either on a reduced dose of masked medicine or had to be discontinued from the masked medication because of low eGFR or elevated creatinine.

During the course of the ACCORD-Lipid trial, the dose of simvastatin was modified in response to changing guidelines. The final protocol-specified starting dose for simvastatin was 20 mg or 40 mg for patients without or with a history of clinical CVD, respectively. For patients who could not tolerate simvastatin, the ACCORD-Lipid physician could substitute a dose-equivalent non-study LDL-C lowering agent. If a patient’s personal physician prescribed another statin at a dose that was equivalent to >40 mg/day of simvastatin, care of lipid levels was transferred to the personal physician and all study medications were stopped. All such patients continued to be followed for events and continued to be treated in the glycemia trial.²²

Study escape criteria for elevated LDL-C and TG were also incorporated into the ACCORD-Lipid protocol. Approximately 12 patients in the Fenofibrate treatment arm and 7 patients in the Placebo arm were discontinued from a masked medicine due to elevated LDL-C. Two patients in the Fenofibrate arm and 17 patients in the Placebo arm were discontinued from a masked medicine due to elevated TG.²³

Study methods

ACCORD- Lipid investigated an “add-on fenofibrate to a statin” approach to the treatment of dyslipidemia. However, as noted above, randomization to the add-on masked medication in ACCORD-Lipid was not based on reaching goal LDL-C levels and then randomizing to masked add-on therapy because of residually elevated TG/ non-HDL-C levels..

Lipid levels were checked at screening and were termed “Baseline” values. A fasting plasma lipid profile was also measured at 4, 8, and 12 months after randomization, annually thereafter, and at the end of the study (see schedule of laboratory procedures in Appendix).

Safety profiles, including liver tests and measurements of creatine phosphokinase (CPK) levels, were determined at 1, 4, 8, and 12 months after randomization and annually thereafter. If symptoms or signs suggestive of drug-induced toxic effects developed, liver tests including measurement of alanine aminotransferase (ALT), CPK, or both were obtained. If the liver test values were elevated, lipid medications were temporarily discontinued; if CPK values were elevated, lipid medications were permanently discontinued. Seven patients in the fenofibrate treatment arm versus none in the placebo arm were discontinued from the masked medicine due to elevated CPK.²⁴

²¹ Supplemental Appendix to ACCORD-Lipid Study. *NEJM* 2010;362:1563-74.

²² Supplementary Appendix to ACCORD-Lipid.

²³ Ibid.

²⁴ Ibid.

Procedures for endpoint adjudication

ACCORD utilized a centralized adjudication process for all deaths, and hospitalizations for myocardial infarction and strokes. Two blinded reviewers on the Morbidity and Mortality committee completed their adjudication independently. Stroke cases were also independently reviewed by an experienced stroke adjudicator in addition to the two primary reviewers. Cases in which the original reviewers agreed on the primary outcome (MI, stroke, or cause of death) were considered closed. If there was disagreement between the two (or three in the case of stroke) primary reviewers, the case was presented to the entire Morbidity and Mortality committee and consensus obtained on the outcome.²⁵

Statistical analysis plan

Primary comparisons of intervention groups were performed according to the intention-to-treat (ITT) principle. All randomized participants in these analyses were grouped according to their intervention assignment at randomization, regardless of adherence.

The study was designed to recruit 5800 patients, with a power of 87% to detect a 20% reduction in the rate of the primary outcome for patients in the fenofibrate group, as compared with placebo, assuming a two-sided alpha level of 0.05, a primary outcome rate of 2.4% per year in the placebo group, and an average follow-up of approximately 5.6 years for patients who did not have an event.

Inclusion and Exclusion Criteria

To be eligible for the ACCORD-Lipid trial, patients had to fulfill the overarching glycemia trial entry criteria as well as the lipid trial criteria.

All patients had T2DM and a glycated hemoglobin level of 7.5% or more. If patients had evidence of clinical CVD, the age range was limited to 40 to 79 years; if they had evidence of subclinical CVD or at least two additional cardiovascular risk factors, the age range was compressed to 55 to 79 years. Thus, both primary and secondary prevention populations were enrolled into the ACCORD-Lipid trial.

Key exclusion criteria for the overarching glycemia trial included frequent or recent serious hypoglycemic events, unwillingness to do home glucose monitoring or inject insulin, a body-mass index (the weight in kilograms divided by the square of the height in meters) of more than 45 kg/m², a serum creatinine level of more than 1.5 mg/dL or other serious illness.

Participants were also eligible for ACCORD-Lipid if they met the following additional entry criteria using lipid measurements obtained within the previous year:

- (1) the observed (or estimated if currently on a lipid-altering medication) LDL-C was between 60 and 180 mg/dL, inclusive;
- (2) HDL-C was less than 55 mg/dL for women and Blacks, or less than 50 mg/dL for all other groups; and
- (3) TG was less than 750 mg/dL if not on a lipid medication or less than 400 mg/dL if on a lipid medication.

²⁵ Supplemental Appendix to ACCORD-Lipid Study. *NEJM* 2010;362:1563-74.

ACCORD- Lipid exclusion criteria included the use of a medication known to interact with statins or fibrate; history of pancreatitis, myositis/myopathy, or gallbladder disease; or refusal to discontinue any current lipid-altering treatment.²⁶

Disposition

A total of 5518 patients were enrolled in the ACCORD-Lipid study, with 2765 assigned to receive fenofibrate plus simvastatin and 2753 assigned to receive placebo plus simvastatin. Approximately 88 (3%) subjects in the fenofibrate group were either lost to follow-up or discontinued the study as compared to 78 (3%) in the placebo group (Figure 4).

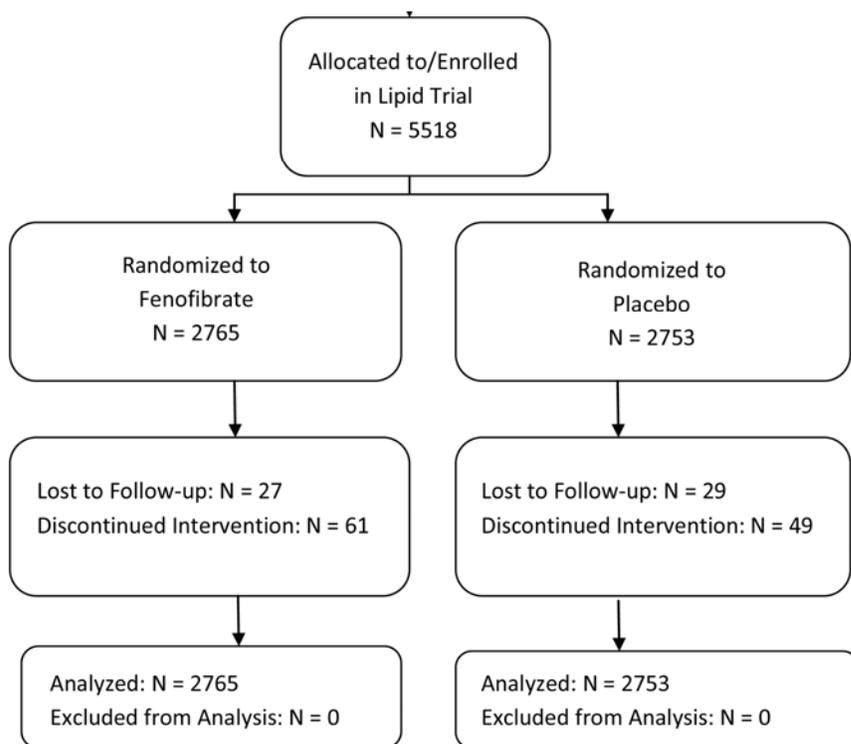


Figure 3: Disposition of Subjects in ACCORD-Lipid

Source: Supplemental Appendix to ACCORD-Lipid Study. *NEJM* 2010;362:1563-74.

Demographics and other subject characteristics

Baseline characteristics were similar between the 2765 patients assigned to received fenofibrate plus simvastatin and the 2753 patients assigned to receive placebo plus simvastatin. The mean age was 62 years, 31% of subjects were women, and 37% had a previous history of a cardiovascular event. The duration of diabetes, glycated hemoglobin at study entry, and eGFR were also similar between the two treatment groups. In each of the treatment groups, approximately 60% of patients had been taking a statin prior to study entry. Baseline LDL-C, TC, HDL-C and TG were at similar levels in the treatment groups.

²⁶ Supplemental Appendix to: The ACCORD-Lipid Study. *NEJM* 2010;362:1563-74.

Note: Baseline lipid values reflect the effects of the lipid-lowering agent patients were taking at study entry and not following 4 weeks of open-label simvastatin and immediately prior to receiving masked fenofibrate or placebo.

Table 7: ACCORD-Lipid Demographics and Baseline Characteristics (Prior to Open-Label Simvastatin)

	Fenofibrate (N=2765)	Placebo (N=2753)	All Patients (N=5518)
Sex, n (%)			
Men	1914 (69.2)	1910 (69.4)	3824 (69.3)
Women	851(30.8)	843(30.6)	1694 (30.7)
Age, years			
Mean	62.2 (±6.7)	62.3(±6.9)	62.3(±6.8)
Race, n (%)			
White	1909 (69)	1865 (67.7)	3774 (68.4)
Black	392 (14.2)	442 (16.1)	834 (15.1)
Hispanic	213 (7.7)	194 (7.0)	407 (7.4)
Body mass index, kg/m²			
Mean	32.2 (±5.4)	32.4 (±5.4)	32.3 (±5.4)
Prior statin use, n (%)	1641 (59.3)	1658 (60.2)	3299 (59.8)
Any lipid-lowering agent, n (%)	1773 (64.1)	1785 (64.8)	3558 (64.5)
Total Cholesterol, mg/dL			
Mean	174.7(±36.8)	175.7 (±37.9)	175.2 (±37.3)
LDL-C, mg/dL			
Mean	100.0 (±30.3)	101.1 (±31.0)	100.6 (±30.7)
HDL-C, mg/dL			
Mean	38.0 (±7.8)	38.2 (±7.8)	38.1 (±7.8)
Triglyceride, mg/dL			
Median	164	160	162
Interquartile range	114-232	112-227	113-229
Systolic BP, mmHg			
Mean	133.8 (±17.7)	134.0 (±17.9)	133.9 (±17.8)
Diastolic BP, mmHg			
Mean	73.9 (±10.7)	74.0 (±10.9)	74.0 (±10.8)
Current smoking, n (%)	410 (14.8)	393(14.3)	803 (14.6)
Previous cardiovascular event, n (%)	1008 (36.5)	1008 (36.6)	2016 (36.5)

	Fenofibrate (N=2765)	Placebo (N=2753)	All Patients (N=5518)
Duration of diabetes, years Median	10	9	9
Glycated hemoglobin, percent Mean	8.3 (±1.0)	8.3 (±1.0)	8.3 (±1.0)
Serum creatinine, mg/dL	0.9 (±0.2)	0.9 ± (0.2)	0.9 (±0.2)
Fasting plasma glucose, mg/dL	176.5 (±54.5)	175.1 (±55.3)	175.8 (±54.9)
Estimated GFR, n (%) 30-49 ml/min/1.73 m²	71 (2.6)	70 (2.5)	141 (2.6)
> 50 ml/min./1.73 m²	2668 (97.4)	2679 (97.5)	5347 (97.4)
<p>* Plus-minus values are means ±SD. Percentages may not total 100 because of rounding. To convert the values for glucose to millimoles per liter, multiply by 0.055551. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for creatinine to micromoles per liter, multiply by 88.4. † Race or ethnic group was self-reported, and patients could check multiple categories. ‡ The body-mass index is the weight in kilograms divided by the square of the height in meters. Data from the ACCORD Study Group; <i>NEJM</i> 2010;362:1563-74.</p>			

ACCORD-Lipid Efficacy Results

Primary Efficacy Outcome

For patients in ACCORD- Lipid, the primary outcome was the first occurrence of a major cardiovascular event, defined as:

- nonfatal myocardial infarction (MI),
- nonfatal stroke, or
- CVD death

The annual rate of the primary outcome was 2.2% in the Fenofibrate group, as compared with 2.4% in the Placebo group (Table 8). The rates of the primary outcome did not differ significantly between the Fenofibrate group and the Placebo group during 4.7 years of treatment and follow-up. (HR = 0.92; 95% CI: 0.79, 1.08; p = 0.32)

Table 8: Primary Efficacy Outcome Results

Primary Outcome	Fenofibrate, N= 2765		Placebo, N=2753		Hazard Ratio	P value
	No. of Events	Rate/Year	No. of Events	Rate/Year		
<ul style="list-style-type: none"> • Nonfatal MI • Nonfatal Stroke • CVD Death 	291	2.2%	310	2.4%	0.92 (0.79-1.08)	0.32

Secondary Efficacy Outcomes

Secondary outcomes included the following:

- combination of the primary outcome plus revascularization or hospitalization for congestive heart failure (expanded macrovascular outcome)
- a combination of a fatal coronary event, nonfatal MI, or unstable angina (major coronary disease events)
- nonfatal MI
- fatal or nonfatal stroke
- nonfatal stroke
- death from any cause
- death from cardiovascular causes
- hospitalization or death due to heart failure

Table 9: Secondary Efficacy Outcomes Results

Secondary Outcomes	Fenofibrate, N= 2765		Placebo, N=2753		Hazard Ratio (95% CI)	P value
	No. of Events	Rate/Year	No. of Events	Rate/Year		
Expanded Macrovascular Outcome	641	5.4%	667	5.6%	0.94 (0.85-1.05)	0.30
Major Coronary Disease	332	2.6%	353	2.8%	0.92 (0.79-1.07)	0.26
Nonfatal MI	173	1.3%	186	1.4%	0.91 (0.74-1.12)	0.39
Stroke- Any	51	0.4%	48	0.4%	1.05 (0.71-1.56)	0.80
Stroke- Nonfatal	47	0.4%	40	0.3%	1.17 (0.76-1.78)	0.48
Death-Any Cause	203	1.5%	221	1.6%	0.91 (0.75-1.10)	0.33
Death – CVD Cause	99	0.7%	114	0.8%	0.86 (0.66-1.12)	0.26
Fatal or nonfatal CHF	120	0.9%	143	1.1%	0.82 (0.65-1.05)	0.10

Source: ACCORD-Lipid Study; *NEJM* 2010;362:1563-74

None of the secondary outcomes reached nominal statistical significance.

Lipoprotein Values

The effect of the 4-week open-label simvastatin therapy is unknown, as lipid values were not obtained at the end of that time period.

The following table summarizes the Baseline, Month 4 and Final Visit lipid values.

Table 10: Lipid values at Baseline, Month 4 and Final Visit

	Baseline (Prior to Simvastatin)		Month 4 (On Simvastatin and Blinded Study Drug)		Final Visit	
	Fenofibrate N=2747	Placebo N=2735	Fenofibrate N=2636	Placebo N=2633	Fenofibrate N=2271	Placebo N=2287
LDL-C (mg/dL) Mean	100.0	101.1	90.3	91.5	81.1	80.0
HDL-C (mg/dL) Mean	38.0	38.2	41.0	39.2	41.2	40.5
TG (mg/dL) Median	164	160	120	152	122	144
TC (mg/dL) Mean	174.7	175.7	159.7	166.6	151.1	153.7

Source: Supplemental Appendix to ACCORD-Lipid Study; *NEJM* 2010;362:1563-74

Subgroup Analyses

Gender Differences

A statistically significant treatment-by-gender interaction for the primary outcome was observed in ACCORD-Lipid ($P = 0.01$) (Table 11). The hazard ratio for men was 0.82, whereas the hazard ratio for women was 1.38.

Table 11: Hazard Ratio for Primary Outcome by Gender

	Fenofibrate + Simvastatin	Simvastatin Monotherapy	Hazard Ratio	95% CI	Nominal p value
Men	214/1914 (11.2%)	254/1910 (13.3%)	0.824	(0.687, 0.989)	0.037
Women	77/851 (9.0%)	56/843 (6.6%)	1.378	(0.976, 1.945)	0.069

Source: Abbott submission to NDA 22-224 May 2010, pg. 55.

In another cardiovascular outcomes trial of fenofibrate in subjects with T2DM, the FIELD study, there was no significant treatment-by-gender interaction for the primary outcome.

TG/HDL-C Differences

There was a non-significant suggestion of heterogeneity in the subgroup of patients with the highest tertile of TG (≥ 204 mg/dL) and the lowest tertile of HDL-C (≤ 34 mg/dL) when compared with all other patients ($P=0.057$ for interaction)(Table 12). Some subgroup analyses from other fibrate cardiovascular outcomes trials also raise the possibility of cardiovascular benefit in patients with elevated TG (\pm low HDL-C) levels at baseline.

The ACCORD-Lipid subgroup analyses based on baseline HDL-C levels (≤ 34 mg/dL, 35-40 mg/dL or ≥ 41 mg/dL), independent of TG levels, did not suggest heterogeneity of treatment effect (P=0.24 for interaction).

Likewise, baseline TG levels (≤ 128 mg/dL, 129-203 mg/dL, or ≥ 204 mg/dL), independent of HDL-C levels, did not suggest heterogeneity (P=0.64 for interaction).

Table 12: Primary Outcome by TG/HDL Combinations

	Fenofibrate + Simvastatin	Simvastatin Monotherapy	Hazard Ratio	95% CI	P value for Interaction
TG ≥ 204 mg/dL/ HDL-C ≤ 34 mg/dL	60/485 (12.4%)	79/456 (17.3%)	0.692	(0.494, 0.969)	0.057
All other patients	226/2264 (10.1%)	228/2284 (10.1%)	0.992	(0.826, 1.192)	0.935

Source: Abbott Submission to NDA 22-224, May 2010.

Other ACCORD Outcomes

Microvascular outcomes were listed as a secondary endpoint in the ACCORD Protocol, but complete results have not yet been released by the investigators. The ACCORD Eye Substudy formed the main microvascular outcome investigation. In addition, fatal or non-fatal renal failure as defined by renal transplantation, or initiation of dialysis, or a rise in serum creatinine > 3.3 mg/dL in the absence of reversible cause was also defined as a secondary outcome to be examined in the entire ACCORD cohort.

Additionally the development of nephropathy was defined as

- Doubling of serum creatinine or a $20 \text{ ml/min}/1.73\text{m}^2$ decrease in eGFR as estimated by the MDRD equation
- Development of macroalbuminuria (albumin/creatinine ratio > 300 mg albumin per gram creatinine in random urine sample)
- Development of microalbuminuria (albumin/creatinine ratio > 30 mg albumin per gram creatinine in a random urine sample)

There are several limitations to the study that hamper the analyses of renal outcomes.

1. The ACCORD-Lipid trial (as well as the entire ACCORD cohort) excluded patients with a Baseline serum creatinine > 1.5 mg/dL.
2. Measurement of Baseline albuminuria was not collected in the ACCORD-Lipid patients.
3. Gold standard for measurement of GFR is inulin clearance and for measurement of renal blood flow is para-aminohippuric acid (PAH), neither of which were used in the ACCORD-Lipid trial.

In the course of the 4.7 years of the ACCORD-Lipid study, with a study population that excluded patients with serum creatinine > 1.5 mg/dL (mean serum creatinine at baseline = 0.9 mg/dL) and

with well-preserved kidney function (97% > 50 mL/min/1.73m² at baseline), the expected rate of “renal transplantation or initiation of dialysis or a rise in serum creatinine > 3.3 mg/dL in the absence of reversible cause” would be small, as was the case. .

ACCORD-Lipid Efficacy Conclusions:

Within the parameters of the ACCORD-Lipid trial, raising HDL-C and lowering TG with a fenofibrate plus a statin did not provide greater cardiovascular benefits as compared with treating LDL-C with a statin alone.

The combination of fenofibrate and simvastatin did not reduce the rate of the primary endpoint (fatal cardiovascular events, non-fatal MI, or nonfatal stroke) as compared with simvastatin monotherapy. The secondary endpoints were also not statistically significantly different in the two treatment groups. Therefore, the results of the ACCORD-Lipid trial suggest that adding fenofibrate to statin-treated diabetics with mildly elevated TG does not significantly reduce the risk for MACE.

Subgroup analysis suggested heterogeneity in treatment effect between men and women, with possible harm for women (P=0.01 for interaction). However, there was no evidence of harm in women treated with fenofibrate in the FIELD trial.

There was also a possible interaction according to lipid subgroup, with possible benefit for patients with baseline TG >204 mg/dL and HDL-C <34 mg/dL (P=0.057 for interaction). This is consistent with some subgroup findings from some fibrate monotherapy outcome trials.

Conclusions regarding renal protection afforded by fenofibrate in the ACCORD-Lipid trial are limited because of study design issues. The question of fenofibrate’s effect on the development of end stage renal disease in patients with diabetes remains unanswered. (Please see Dr. Nancy Xu’s consultative review.)

ACCORD-Lipid SAFETY REVIEW

The overall ACCORD trial was conducted in the manner of a ‘large-simple’ trial. Therefore, the collection of laboratory data was limited to known adverse events of the study drugs: ALT, CPK, and serum creatinine to monitor for muscle, hepatic, and renal toxicity.

Muscle Toxicity

Both statins and fibrates, as monotherapy, have been reported to cause myopathy. Therefore, an enhanced risk of myopathy with the combined use of a statin and a fibrate might be expected. Although the medical literature contains numerous reports of gemfibrozil/statin-associated rhabdomyolysis, cases of fenofibrate-associated myopathy/rhabdomyolysis, either as monotherapy or in combination, appear to be less common.²⁷

Rhabdomyolysis is a potentially life-threatening syndrome resulting from the breakdown of skeletal muscle fibers that leads to the excretion of excessive myoglobin, an iron-containing pigment, into the blood stream. Subsequently, the massive amounts of myoglobin are filtered

²⁷ Davidson M. Statin/fibrate combination in patients with metabolic syndrome or diabetes: evaluating the risks of pharmacokinetic interactions. *Expert Opin. Drug Saf.* (2006)5 (1):145-156.

by the glomerulus, leading to tubular obstruction and renal failure. Rhabdomyolysis contributes to 10% to 15% of all acute renal failure cases in the U.S. Approximately 26,000 cases of rhabdomyolysis occur each year in the U.S.²⁸ Many diverse causes and risk factors need to be ruled out prior to establishing drug-induced rhabdomyolysis. The most common causes are crush injury, overexertion, ischemic limb injury, and alcohol abuse followed by infectious, inflammatory, metabolic, and endocrinologic causes.²⁹

The Agency’s case definition is as follows:

One of the following criteria satisfies the inclusion criteria for rhabdomyolysis:

1. Clinical diagnosis of rhabdomyolysis
OR
2. Myoglobinuria (increased urinary excretion of myoglobin) alone can be used interchangeably with rhabdomyolysis³⁰
OR
3. All of the following:
 - a) Signs and symptoms (myopathy, myalgia, gait disturbance)
 - b) CPK levels five times higher than normal (total normal CPK serum levels: 40-150 U/L for females and 60-400 U/L for males)³¹
 - c) Myoglobinuria: >250 mcg/ml (normal- < 5ng/ml) or tea-colored urine

If case report has no mention of clinical diagnosis of rhabdomyolysis but has only the two of the three criteria (a,b), then the case is evaluated as a “myopathy.”

In ACCORD-Lipid, elevations of CPK above the upper limit of normal were similar in both the Fenofibrate and the Placebo treatment arm (Table 13). Modest elevations of CPK ($\geq 3XULN$ to $<5XULN$) occurred at 6.5 % in the Fenofibrate arm as compared to 6.0 % in the Placebo arm. More severe elevations of CPK ($\geq 10XULN$ to $< 20 XULN$ and $\geq 20XULN$) occurred at 0.3 % and 0.07% in the Fenofibrate arm as compared to 0.2% and 0.04% in the Placebo arm.

Table 13: Number (%) of Patients by Treatment Arm with Elevated CPK

CPK values	Fenofibrate N=2765 (%)	Placebo N=2753 (%)
$\geq 3XULN$ to $< 5XULN$	180 (6.5)	165 (6.0)
Men	152	141
Women	28	24
$\geq 5X ULN$ to $<10XULN$	47 (1.7)	54 (2.0)
Men	40	43
Women	7	11
$\geq 10X ULN$ to $<20XULN$	9 (0.3)	8 (0.2)
Men	8	6

²⁸ Graves EJ, Gillum BS. Detailed diagnoses and procedures, National Hospital Discharge Survey, 1995. Vital Health Stat 1997; 13 (130): 1-146.

²⁹ Warren J, Blumbergs, Thompson P. Rhabdomyolysis: A review. Muscle & Nerve 2002;25: 332- 347.

³⁰ Warren J, Blumbergs, Thompson P. Rhabdomyolysis: A review. Muscle & Nerve 25: 332- 347, 2002

³¹ Kratz A, Lewandrowski K. Normal reference laboratory values. NEJM, 339 (15), 1063- 1072, 1998

CPK values	Fenofibrate N=2765 (%)	Placebo N=2753 (%)
Women	1	2
≥ 20XULN	2 (0.07)	1 (0.04)
Men	1	1
Women	1	0

Source: ACCORD-Lipid Study Group Datasets.

In total, there were 19 patients (ten patients in the Fenofibrate group and nine patients in the Placebo group) with CPK \geq 10XULN. One patient in the fenofibrate group (# 13601) had two separate episodes of CPK elevations---once > 10XULN but <20XULN and the second time >20 XULN (Table 14).

Of the three patients with CPK \geq 20XULN, a case narrative was only available for one (Patient #12908). Patient #12908 (randomized to the Fenofibrate treatment arm) had three instances of CPK \geq 20XULN; she was also flagged for ‘myopathy’ by the investigators. Her case narrative is summarized below as submitted to the Agency.

Patient #12908 was a 66-year-old Hispanic female with medical history of type 2 diabetes, hypertension, and hyperlipidemia. Concomitant medications included: aspirin, docusate sodium, fluvastatin, lisinopril, metformin, metoprolol, prazosin, vitamin E. The participant presented to a walk-in clinic with complaints of bilateral upper and lower extremity fatigue and weakness. She was afebrile. Labs revealed CPK 5619 [U/L], AST 158 [U/L], and ALT 180 [U/L]. Fluvastatin and fenofibrate/placebo were discontinued and patient scheduled for follow-up with her primary care physician.

Based on the narrative above and the available data, Patient #12908 would meet the criteria for myopathy which is defined as having signs and symptoms (myopathy, myalgia, gait disturbance) plus CPK levels five times higher than normal.

The following table is a summary of patients with their concurrent CPK and serum creatinine value when their CPK \geq 10XULN regardless of muscle aches. Table 14 is summarized from the datasets provided to the Agency by the ACCORD-Lipid investigators and not necessarily from case narratives.

Table 14: CPK and Concurrent Serum Creatinine when CPK \geq 10XULN Regardless of Muscle Aches

	Subject ID	Gender	Treatment arm	Clinic Visit	CPK at Visit U/L	Serum Creatinine at Visit mg/dL	Disposition
	CPK \geq 20XULN						
1	11630	Male	Placebo	M1	7743	N/A	Completed Study
2	13601*	Male	Fenofibrate	Unscheduled	8066	1.3	Completed Study

	Subject ID	Gender	Treatment arm	Clinic Visit	CPK at Visit U/L	Serum Creatinine at Visit mg/dL	Disposition
3	12908	Female	Fenofibrate	M24	4260	0.53	Withdrew Consent
				M28	8015	0.62	
				Unscheduled	4085	0.56	
	CPK ≥10XULN < 20XULN						
4	10238	Female	Fenofibrate	M1	1803	0.9	Completed Study
5	10531	Female	Placebo	Unscheduled	3094	N/A	Completed Study
6	14230	Female	Placebo	M24	1805	1.1	Completed Study
7	10179	Male	Placebo	M36	2405	1.4	Completed Study
8	13604	Male	Placebo	M12	2134	1.3	Deceased (CVD death)
9	14098	Male	Placebo	M12	2545	0.9	Completed Study
10	10999	Male	Placebo	M28	2230	0.8	Completed Study
11	12166	Male	Placebo	M12	3762	1.0	Completed Study
12	12839	Male	Placebo	Exit	2283	1.5	Completed Study
13	14303	Male	Fenofibrate	M4	3507	0.8	Completed Study
14	10614	Male	Fenofibrate	Unscheduled	2025	N/A	Completed Study
				Unscheduled	2691	N/A	
15	10847	Male	Fenofibrate	M12	2742	1.3	Completed Study
16	11010	Male	Fenofibrate	Exit	1984	1.3	Completed Study
17	12011	Male	Fenofibrate	M8	2346	1.9	Completed Study
18	12084	Male	Fenofibrate	M24	2233	1.4	Completed Study
19	13135	Male	Fenofibrate	M8	2854	1.8	Completed Study
	13601*	Male	Fenofibrate	Unscheduled	2195	1.2	Completed Study

Source: ACCORD-Lipid Study Group Datasets. *Patient also reported in CPK ≥20XULN.

Table 15 is a summary of patients who reported muscle aches plus CPK ≥ 5XULN by gender and treatment arm. The percent of patients with muscle aches and CPK ≥ 5XULN to <10XULN

was slightly higher in the Placebo group (0.65% in Fenofibrate treatment arm vs. 0.87% in Placebo treatment arm). However, muscle aches and CPK > 10XULN occurred more frequently in the Fenofibrate group than in the Placebo group (0.25% vs. 0.07%).

Table 15: Number (%) of Patients by Treatment Arm and Gender with Elevated CPK and with Muscle Aches

CPK values + Muscle Aches	Fenofibrate N=2765 (%)	Placebo N=2753 (%)
≥ 5X ULN to <10XULN + Muscle Aches	18 (0.65)	24 (0.87)
Men	14	16
Women	4	8
CPK ≥ 10X ULN + Muscle Aches	7 (0.25)	2 (0.07)
Men	5	1
Women	2	1

Source: ACCORD-Lipid Study Datasets

Seven patients were reported with a SAE of myopathy/rhabdomyolysis (Table 16). Four out of these seven patients were in the Fenofibrate treatment group. The following table summarizes some information on these seven patients.

Table 16: Patients flagged with Myopathy/Rhabdomyolysis by Study Investigators

Subject ID	Treatment Arm	Text description SAE	Randomization and Onset Dates	CPK value	Outcome
#10303 77 yo Caucasian man	Fenofibrate	Rhabdomyolysis	Randomized 3/25/2003; Onset date 9/7/2006	CPK=1112 U/L myoglobin = 6253 Cr=2 mg/dL	Completed Study
#12728 60 yo Caucasian man	Fenofibrate	Suspected rhabdomyolysis	Randomized 12/18/2003; Onset date 7/8/2006	CPK=6504 U/L, Creatinine=2.6 mg/dL, ALT=101 U/L AST=233 U/L TSH=121 IU/mL	Admitted to hospital, IVF under treatment for sequelae; Completed Study
#12098* 66 yo Hispanic woman	Fenofibrate	Myositis/ myopathy	Randomized 10/26/2005; Onset date 4/9/2007	CPK=8015 AST=158 ALT=180	Withdrew consent
#13043 56 yo Asian woman	Fenofibrate	Myositis/ myopathy	Randomized 3/8/2005; Onset date 2/4/2006	CPK=6872 U/L	SLE & RA ruled out; symptomatic treatment recovered; Completed

Subject ID	Treatment Arm	Text description SAE	Randomization and Onset Dates	CPK value	Outcome
					Study
#10917 81 yo Caucasian man	Placebo	Myositis/ myopathy	Randomized 9/16/2004; Onset date 11/28/2008	Not reported in narrative	IVF in ED; recovered; Completed Study
#14379 85 yo AA man	Placebo	Myositis/ myopathy	Randomized 5/19/2003; Onset date 5/21/2007	CPK=3735 U/L	Completed Study
#14386 56 yo Caucasian woman	Placebo flagged twice	Myositis/ myopathy	Randomized 12/29/2003; Onset date 4/16/2004	CPK=4080 U/L myoglobin >2200	Admitted to hospital, sodium bicarbonate and fluids given; recovered; Completed Study

Source: ACCORD-Lipid Study Group Narratives submitted 4/13/2011.

Details of three of the patient narratives are also summarized: two of the rhabdomyolysis cases (#10303 and #12728), and the third patient (#14386) who was hospitalized and given sodium bicarbonate.

Patient #10303 is a 77-year-old non-Hispanic White male with significant medical history of type 2 diabetes, CAD, post CABG, CA of tongue, prostate cancer, moderate severe mitral regurgitation, and hyperlipidemia. The participant came to the ER via ambulance after he was unable to stand due to severe bilateral hip pain. Temperature was 100°F, RR 14, pulse 107, BP 146/68. Oral thrush seen in mouth and he was slightly dehydrated. The participant was admitted to hospital with rhabdomyolysis, which precipitated acute renal failure and chronic renal insufficiency. His ACE inhibitor was held and he was hydrated with IV fluids. The rhabdomyolysis resolved and renal function improved. The hospitalization was noted to be uneventful. An EMG for lower extremity weakness showed sensory, motor, and axonal polyneuropathy, which was consistent with diabetes or chemotherapy and there was no evidence of myopathy. Simvastatin was discontinued and the participant was discharged to the rehabilitation department for physical therapy on (b) (6).

LABORATORY/DIAGNOSTIC RESULTS

Date Time	Test Name	Results	Normal Range
9/7/2006	BUN	60 mg/dL	8 - 22
9/7/2006	CK	1112 U/L	15 - 200
9/7/2006	creatinine	2 mg/dL	0.7 - 1.5
9/7/2006	myoglobin	6253 ng/ml	0 - 90
9/7/2006	potassium	5.6 mmol/L	3.5 - 5.5
9/7/2006	sodium	129 mmol/L	135 -145
9/7/2006	troponin	0.09 ng/ml	0.00 - 0.04

Patient #10303 met the Agency's definition of rhabdomyolysis, but the etiology is unclear. Case details to rule out diverse causes of rhabdomyolysis are not available. Therefore, drug-induced rhabdomyolysis cannot be established.

Patient narrative #12728 is summarized below as submitted to the Agency:

Patient #12728 is a 60-year-old NHW male with medical history significant for hypothyroidism, hyperlipidemia, CAD, acute MI x 3 in '98, CABG x5 in '98, LLE popliteal stent in '02, diabetes type 2, sleep apnea, and GERD, with no tobacco use since '98, and no ETOH use x 1 yr. Participant admitted after 3-4 days of muscle tightness, cramping beginning in calves, extending up through thighs, back, neck, and shoulders. According to the ppt, he developed generalized swelling all over his body gradually, starting first in upper extremities. He sought medical attention and found to have elevated CPK (6,000). Creatinine which had recently increased from 1.3 to 1.8 between April 06 and June 21 06 (ACCORD lab) increased to 2.5 mg/dl. Patient denies fever, dark colored urine, recent surgery, or dehydration. Agree with housestaff assessment that combination lipid therapy along with recent increase in creatinine and worsened hypothyroidism converged to result in muscle syndrome. With vigorous IV hydration and discontinuation of simvastatin and fenofibrate/placebo, creatinine started trending back to baseline. During the hospital course, it was noted that with continuous IV fluids, his CPK, AST, ALT, and creatinine starting trending toward normal and he showed clinical improvement with decreased swelling, edema, and lessened stiffness.

LABORATORY/DIAGNOSTIC RESULTS

Date	Time	Test Name	Results	Normal Range
7/11/2006	13:08	urine myoglobin	<1 ng/mL	0 - 2
7/12/2006	23:19	urine myoglobin	negative	
7/17/2006	04:00	ALT	135 U/L	20 - 65
7/17/2006	04:00	AST	232 U/L	10 - 45
7/17/2006	04:00	CPK, total	3767 U/L	20 - 320
7/17/2006	04:00	creatinine	1.5 mg/dL	
7/8/2006	18:04	ALT	101 U/L	20 - 65
7/8/2006		AST	233 U/L	10 - 45
7/8/2006		CPK, total	6504 U/L	20 - 320
7/8/2006		creatinine	2.6 mg/dL	0.8 - 1.8
7/9/2006	14:37	Free T4 Cent	0.26 ng/dL	0.9 - 1.8
7/9/2006		TSH Cent	121.632 IU/ML	0.35 - 6.0

According to the Agency's case definition for rhabdomyolysis, this case most likely represents myopathy. Drug-induced myopathy cannot be established as there are confounding factors such as uncontrolled hypothyroidism.

Patient narrative #14386 is summarized below as submitted to the Agency:

56-year-old NHW female reports hospitalization. Medical history of diabetes type 2, hypertension, left ventricular systolic dysfunction, dyslipidemia, CAD, CHF, and GERD. Participant presented to ED with SOB and cough X 4 days. Patient experienced chest pain in ED that was relieved by NTG. Patient's myoglobin was found to be greater than 2200 and CK was elevated at 4080. Cardiac enzymes were negative and BNP was 27. Cardiology stopped simvastatin and ACE inhibitor. Patient's CK and myoglobin started dropping with low dose fluids and sodium bicarbonate. Per hospital consult, myositis may represent underlying collagen vascular disorder-polymyositis, simvastatin associated myositis, or polymyalgia rheumatica-giant cell arteritis. On 5/6/04, she was seen in the ACCORD clinic and CPK had returned to her baseline of 502. No laboratory results reported.

This case would meet the Agency's definition of myopathy. Prior to establishing drug-induced myopathy, other underlying causes need to be ruled out.

Liver Enzyme Elevations

Transaminase monitoring is recommended in the current Trilipix® label. In ACCORD-Lipid, mild-to-moderate increases in ALT were similar between the Fenofibrate and Placebo groups (Table 17). However, there was a nominally statistically significant difference between the two groups with the incidence of ALT \geq 5XULN (p=0.03).

Table 17: Number (%) of Patients by Treatment Arm with Elevated Alanine Aminotransferase

ALT values	Fenofibrate N=2765 n (%)	Placebo N=2753 n (%)	P-value
\geq 3XULN to <5XULN	52 (1.9)	40 (1.5)	0.22
\geq 5X ULN to <8XULN	13 (0.5)	4 (0.15)	0.03*
\geq 8X ULN	4	2	N/A

Source: ACCORD-Lipid Study Group Datasets. * **p-value refers to ALT Ever >5XULN**

There were 23 patients (seventeen patients in the Fenofibrate group and six patients in the Placebo group) with ALT \geq 5XULN. The ALT level, clinic visit and disposition of the patient are summarized in Table 18 below.

Two patients (#10220 and #14762) had multiple episodes of increased ALT \geq 5XULN and <8 XULN. Only one patient out of the 23 with ALT \geq 5XULN were also reported by the investigators with "hepatitis".

Table 18: Alanine Aminotransferase Values and Disposition by Treatment Arm and Gender of Patients with at Least ALT \geq 5XULN

	Subject ID	Gender	Treatment arm	Clinic Visit	ALT at Visit	Flagged for hepatitis/Disposition
	ALT > 8XULN					
1	10689	Male	Fenofibrate	M1	394	No; Completed Study
2	11342	Male	Fenofibrate	M4	347	No; Completed Study
3	14662	Male	Placebo	M56	638	No; Completed Study
4	10996	Male	Placebo	M36	1415	No; Deceased (Cancer death)
5	13419	Female	Fenofibrate	Unscheduled	671	No; Completed Study
6	15383	Female	Fenofibrate	M1	407	No; Deceased (Non-CVD, Non-Cancer)
	ALT ≥ 5X ULN to <8XULN					
7	10220*	Female	Fenofibrate	M4	209	No; Completed Study
				M24	256	No
8	10230	Male	Fenofibrate	M24	205	No; Completed Study
9	10875	Male	Fenofibrate	Unscheduled	239	No; Completed Study
10	11342	Male	Fenofibrate	Unscheduled	265	No; Completed Study
11	12502	Female	Fenofibrate	M8	232	No; Completed Study
12	12833	Female	Placebo	Exit	267	No; Completed Study
13	12908	Female	Fenofibrate	Unscheduled	262	No; Withdrew Consent
14	12996	Female	Fenofibrate	Unscheduled	316	No; Completed Study
15	13333	Male	Fenofibrate	Exit	281	No; Completed Study
16	13564	Male	Fenofibrate	M4	236	No; Completed Study
17	13782	Male	Fenofibrate	M36	273	No; Completed Study
18	13868	Male	Placebo	M4	217	No; Completed Study
19	14062	Male	Fenofibrate	M1	275	No; Completed Study
20	14604	Female	Fenofibrate	Exit	243	No; Completed Study
21	14740	Male	Placebo	M36	302	No; Completed Study
22	14762*	Male	Fenofibrate	M4	250	Yes; Completed Study
				M8	231	
23	15393	Male	Placebo	M8	256	No; Deceased (Cancer death)

Source: ACCORD-Lipid Study Group Datasets.*Patients with multiple episodes.

It is not known if any of these patients met the criteria for Hy's law, as bilirubin and alkaline phosphatase levels were not obtained during the trial. Hy's law is defined as an ALT or AST >3XULN accompanied by a bilirubin >2XULN with a normal alkaline phosphatase level. This constellation of laboratory findings signals potential for severe drug-induced hepatotoxicity.

The study investigators reported three subjects all with a SAE for hepatitis (Table 19). The narratives requested by the Agency were not adequate to determine drug causality. Of the three, one patient completed the study, one was lost to follow-up, and one patient died.

Table 19: Patients Flagged for "Hepatitis" by Study Investigators

Subject ID	Treatment Arm	Text description SAE	Randomization and Onset Dates	ALT values U/L	Outcome
#10352 59 yo American Indian woman	Fenofibrate	Hepatitis	Randomized 3/15/2005; Onset date 7/5/2005,	ALT=152 U/L	Resolved with discontinuation of simvastatin and fenofibrate Lost to follow-up
#14408 67 yo Caucasian man	Fenofibrate	Hepatitis	Randomized 4/25/2001; Onset date 8/21/2003	No report of ALT in narrative; ALT= 66 in dataset	Deceased (Non-CVD/ non-Cancer death)
#14762 55 yo Caucasian man	Fenofibrate	Hepatitis	Randomized 4/29/2004; Onset date 8/19/2004	ALT=204 U/L;	Positive re-challenge to fenofibrate; recovered; Completed Study

Source: ACCORD-Lipid Study Group Narratives submitted 4/13/2011.

Patient narrative #10352 is summarized below as submitted to the Agency:

Patient #10352 (randomized to Fenofibrate arm) is a 59-year-old American Indian female with history of type 2 diabetes, hypertension, dyslipidemia, history of viral hepatitis A, and no history of alcohol abuse. Participant's routine labs included ALT 152 on 7/5/05. Patient complained of mild anorexia, no nausea, no vomiting, no jaundice, and no discolored urine. Patient denied OTC or herbal meds. Patient states history of viral hepatitis 30 years ago. Concomitant medications: Avandia, Metformin, Zocor and Fenofibrate or placebo discontinued pending further work-up by primary physician.

LABORATORY/DIAGNOSTIC RESULTS

Date	Test Name	Results	Normal
07/05/2005	ALT	152 U/L	6-41 U/L

Patient narrative #14762 is summarized below as submitted to the Agency:

Patient #14762 (randomized to Fenofibrate arm) is a 55-year-old non-Hispanic White male with increased ALT values. Past medical history includes type 2 diabetes, hypercholesterolemia and hypothyroidism. Participant reports no history of hepatic dysfunction, no known drug allergies, and is a non-smoker. Participant started blinded lipid medication on May 27, 2004. On 08/19/04, participant's ALT was 250 u/L; simvastatin and blinded medications were stopped at that time. Simvastatin was restarted on 09/14/04 with ALT remaining normal on 10/05/04. Blinded lipid medication restarted at that time. Next lab on 12/15/04 showed increased ALT. Blinded lipid medication permanently discontinued with ALT subsequently returning to normal.

LABORATORY/DIAGNOSTIC RESULTS

Date	Test Name	Results	Normal Range
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04/13/2005 ---	ALT	25 U/L	
04/29/2004 ---	ALT	29 U/L	
05/27/2004 ---	ALT	33 U/L	
08/19/2004 ---	ALT	250 U/L	6-41 U/L
12/15/2004 ---	ALT	231 U/L	6-41 U/L

Patient #14762's history is consistent for drug-induced hepatitis with a positive re-challenge to fenofibrate in combination with simvastatin. Patient had no identifiable risk factors, according to the narrative. The increase in ALT to 250 U/L occurred after the start of simvastatin and fenofibrate. After discontinuation of both medications, simvastatin was re-started with ALT remaining normal (ALT value not provided). When fenofibrate was also re-started, ALT increased to 231 U/L. Discontinuation of fenofibrate resulted in ALT returning once more to normal.

In a study investigating the comparative rates of adverse events reports (AERs) associated with gemfibrozil and fenofibrate (excluding reports with concomitant cerivastatin use) submitted to the Food and Drug Administration, the authors found that reporting rates of liver AERs were lower for gemfibrozil compared to fenofibrate. Rhabdomyolysis AERs and muscle-related AERs with no rhabdomyolysis were higher for gemfibrozil compared to fenofibrate. Thus, this analysis shows that, after excluding concomitant cerivastatin use, there were important agent-specific differences in the reporting rates of AERs between gemfibrozil and fenofibrate.³²

Table 20: Reporting Rates of Adverse Events Reports (AERs) Associated with Gemfibrozil and Fenofibrate (Excluding Concomitant Cerivastatin Use) Submitted to Food and Drug Administration January 2000 to December 2004

	Rates per Million Prescriptions		Odds Ratio Gem vs. Feno	95% CI	p Value
	Gemfibrozil	Fenofibrate			
All AERs	31.0	40.0	0.76	0.69-0.83	<0.001
Serious AERs	20.0	27.9	0.72	0.65-0.81	<0.001
Rhabdomyolysis AERs	9.7	3.6	2.67	2.11-3.39	<0.001
Muscle-related AERs with no rhabdomyolysis	8.1	5.8	1.36	1.12-1.71	0.002
Liver AERs	2.6	6.9	0.37	0.28-0.50	<0.001

Source: Holoshitz N. et al. Am J Cardiol 2008;101:95-97.

Serum Creatinine Elevations

There is a well-described serum creatinine increase with fenofibrate use, of which the clinical implications for renal safety remain unclear. The increase in serum creatinine with fenofibrates has been observed in patients with normal renal function, in patients with renal failure, and in kidney transplant patients. The majority of studies have shown a return to baseline creatinine

³² Holoshitz N. et al, Relative Safety of Gemfibrozil and Fenofibrate in the Absence of Concomitant Cerivastatin Use. Am J Cardiol 2008;101:95-97.

after discontinuation of the fibrate. The exact mechanism of how fenofibrates increase serum creatinine is unclear. It is also unknown whether there are any long-term renal implications to this phenomenon.³³

Table 21 summarizes some of the indicators of risk for chronic kidney disease at baseline in the ACCORD-Lipid trial. Approximately 97% of patients had an eGFR > 50 mL/min/1.73 m². The mean serum creatinine was 0.9 mg/dL. Approximately 68% were either on an angiotensin-converting enzyme inhibitor (ACE-inhibitor) or angiotensin-receptor blocker (ARB). Subjects with a serum creatinine ≥ 1.5 mg/dL were excluded from the ACCORD-Lipid trial.

Table 21: Indicators of Chronic Kidney Disease Risk at Baseline

	Fenofibrate N=2765	Placebo N=2753
eGFR (baseline)		
30-49 mL/min/1.73 m ²	70 (2.5%)	71 (2.6%)
>50 mL/min/1.73 m ²	2679 (96.9%)	2668 (96.9%)
Missing	16 (0.6%)	14 (0.5%)
Creatinine (baseline), mean, mg/dL, (SD)	0.9 (0.2)	0.9 (0.2)
Missing	16 (0.6%)	14 (0.5%)
On ACE-Inhibitor (baseline)		
Yes	1473 (53.3%)	1494 (54.3%)
No	1292 (46.7%)	1259 (45.7%)
On ARB (baseline)		
Yes	405 (14.6%)	433 (15.7%)
No	2360 (85.4%)	2320 (84.3%)
Duration of diabetes, years Mean (SD)	10.7 (7.5)	10.7 (7.6)
Missing	16 (0.5%)	14 (0.5%)
Glycated hemoglobin, percent Mean (SD)	8.3 (1.0)	8.3 (1.0)
Missing	7 (%)	3 (%)
Systolic BP, mmHg Mean (SD)	133.8 (17.7)	134.0 (17.9)
Missing	21	23
Diastolic BP, mmHg Mean (SD)	73.9 (10.7)	74.0 (10.8)
Missing	21	23

Source: Abbott Submission to NDA 22-224, May 2010.

Table 22 shows the increase in serum creatinine between the two treatment groups. Mean serum creatinine levels increased from 0.91 to 1.10 mg/dL in the Fenofibrate group within the first year. In comparison, mean serum creatinine levels increased from 0.92 to 0.94 mg/dL in the Placebo

³³ Sica D. Fibrate therapy and renal function. *Current Atherosclerosis Reports* 2009,11:338-342.

group in the first year of the study. The mean percent change from Baseline to Closeout in the Fenofibrate group for serum creatinine was 29%. In comparison, the mean percent change from Baseline to Closeout in the Fenofibrate group for serum creatinine was 11%.

The study drug was discontinued by 66 patients (2.4%) in the Fenofibrate group and 30 (1.1%) in the Placebo group because of a decrease in the eGFR. Approximately 16% or 440 patients in the Fenofibrate group compared to 7% or 194 patients in the Placebo group had their dose of masked study drug reduced for a decrease in eGFR.

Table 22: Creatinine level by visit and by treatment arm

Treatment Arm	Baseline	4 Months	1 Year	2 Years	3 Years
Fenofibrate + Simvastatin	N=2625	N=2625	N=2576	N=2487	N=2404
Mean	0.92 mg/dL	1.09 mg/dL	1.10 mg/dL	1.13 mg/dL	1.13 mg/dL
Simvastatin Monotherapy	N=2620	N=2620	N=2576	N=2465	N=2363
Mean	0.92 mg/dL	0.92 mg/dL	0.94 mg/dL	0.98 mg/dL	0.99 mg/dL

Treatment Arm	4 Years	5 Years	6 Years	7 Years	Closeout
Fenofibrate + Simvastatin	N=2346	N=1466	N=791	N=248	N=2253
Mean	1.13 mg/dL	1.14 mg/dL	1.17 mg/dL	1.19 mg/dL	1.13 mg/dL
Simvastatin Monotherapy	N=2349	N=1469	N=796	N=240	N=2269
Mean	1.01 mg/dL	1.03 mg/dL	1.03 mg/dL	1.03 mg/dL	1.02 mg/dL

Source: Abbott, *Analysis of Creatinine, eGFR and albuminuria in the ACCORD-Lipid and FIELD studies*, Table 5, pg.13.

Deaths

There were 203 deaths in the Fenofibrate treatment arm and 221 deaths in the Placebo arm. Of the 203 deaths in the Fenofibrate group, 99 (49%) died from a CVD event compared to 114 (52%) in the Placebo group. The majority of the CVD deaths occurred in those who had a history of a previous CVD event at baseline (60/99, or 61%, in the Fenofibrate group versus 77/114, or 68%, in the Placebo group). Cancer deaths were similar in both treatment groups. The following table summarizes the causes of death during the trial.

Table 23: Number and Cause of Death by Treatment Arm

Cause of Death	Fenofibrate N=2765	Placebo N=2753
Total Mortality	203	221
Unexpected/Presumed Cardiovascular Disease	69	77
Fatal Myocardial Infarction	12	14
Fatal Congestive Heart Failure	15	21

Cause of Death	Fenofibrate N=2765	Placebo N=2753
Fatal Cardiovascular Disease Procedure	6	8
Fatal Arrhythmia	9	10
Fatal Non-Cardiovascular Disease Procedure	1	1
Fatal Stroke	7	12
Other Cardiovascular Disease	8	6
Cancer Death	57	58
Indeterminate	10	6
Not Cancer or Cardiovascular Disease	37	43

Supplementary Appendix to: The ACCORD-Lipid Study. *NEJM* 2010;362:1563-74

Serious Adverse Events

A serious adverse event (SAE) in ACCORD-Lipid was defined as any adverse experience that was significantly life threatening and/or resulted in death, permanent disability, hospitalization or prolongation of hospitalization, myositis/myopathy, or hepatitis and were considered by the investigators to be possibly, probably, or definitely related to lipid-lowering medications.³⁴ This is at odds with the regulatory definition of a SAE which does not take into account the investigator's attribution.

Events that were part of the primary and secondary ACCORD-Lipid outcomes (examples: Death, MI, stroke, unstable angina) were NOT considered SAEs unless the investigator believed that an ACCORD-Lipid study drug or device caused the event or contributed to the immediate cause of the event.³⁵

SAE datasets from the ACCORD-Lipid investigators were not tabulated according to the medical dictionary, MedDRA 13.1. Thus, the Division compiled and mapped the reported terms resulting in ninety-seven subjects with 106 non-fatal SAEs (Table 24).

Table 24: Summary of All Non-fatal Serious Adverse Events

System Organ Class	Reported Term	Preferred Term	Fenofibrate N= 2765	Placebo N= 2753
Patient reporting any Serious Adverse Event		Any	54	43
Blood and lymphatic system disorders		Any	1	1

³⁴ Supplementary Appendix to: The ACCORD-Lipid Study. *NEJM* 2010;362:1563-74.

³⁵ Ibid.

System Organ Class	Reported Term	Preferred Term	Fenofibrate N= 2765	Placebo N= 2753
	Anemia	Anemia	0	1
	Pancytopenia	Pancytopenia	1	0
Cardiac Disorders		Any	26	16
	Acute coronary syndrome	Acute coronary syndrome	1	0
	Acute MI	Acute myocardial infarction	1	0
	CHF; congestive heart failure	Cardiac failure congestive	18	13
	Fluid overload	Fluid Overload	1	2
	MI; myocardial infarction	Myocardial infarction	3	1
	Bilateral lower extremity edema	Oedema peripheral	1	0
	Non-ST elevation myocardial infarction	Silent myocardial infarction	1	0
Endocrine Disorders		Any	1	1
	Hyperosmolar non-ketotic syndrome	Hyperglycaemic hyperosmolar non-ketotic syndrome	1	0
		Hypoglycemia	0	1
Eye Disorders		Any	0	1
	Visual disturbance	Visual impairment	0	1
Gastrointestinal Disorders		Any	6	4
	Acute pancreatitis	Acute pancreatitis	1	0
	GI bleed	Gastrointestinal hemorrhage	1	0
	Pancreatitis	Pancreatitis	4	4
General Disorders and Administration Site Conditions		Any	0	2
	Chest pain	Chest pain	0	2
Hepatobiliary Disorders		Any	6	8
	Acute cholecystitis	Acute cholecystitis	0	2
	Cholecystitis	Cholecystitis	1	2
	Gallstones; Cholelithiasis	Cholelithiasis	2	4
	Hepatitis	Hepatitis	3	0
Injury, Poisoning, and Procedural Complications		Any	1	2

System Organ Class	Reported Term	Preferred Term	Fenofibrate N= 2765	Placebo N= 2753
		Fracture	1	2
	MVA	Road traffic accident	0	1
Investigations		Any	3	1
	Elevated creatinine	Blood elevated creatinine	2	0
	Increased INR	International normalized ratio increased	1	0
	Elevated AST/ALT	Liver function test abnormal	0	1
Musculoskeletal and Connective Tissue Disorders		Any	4	4
	Myositis/myopathy	Myopathy	2	4
	Rhabdomyolysis	Rhabdomyolysis	2	0
Nervous System Disorders		Any	0	2
	Toxic metabolic encephalopathy	Metabolic encephalopathy	0	1
	Syncope	Syncope	0	1
Renal and Urinary Disorders		Any	3	0
	Acute renal failure	Acute renal failure	2	0
	Chronic renal failure	Renal failure chronic	1	0
Respiratory, Thoracic and Mediastinal Disorders		Any	1	5
	Asthma exacerbation	Asthmatic crisis	0	1
		Chest pain	0	1
	Shortness of breath	Dyspnea	1	2
		Pulmonary edema	0	1
Surgical and Medical Procedures		Any	5	2
	Cholecystectomy	Cholecystectomy	4	0
	Hospitalization	Hospitalization	1	2

Source: Datasets from ACCORD-Lipid Study, tabulated by DMEP.

Cardiac disorders were the most common SAEs reported in the ACCORD-Lipid trial. This is not unexpected since diabetics are at a higher risk for CVD. Numerically there were slightly more cardiac events reported in the Fenofibrate group as compared to the Placebo group, but the events in both groups occurred at <1.0%. Congestive heart failure was the most frequently reported event under the Cardiac System Order Class (SOC).

Gallbladder-related events occurred at similar rates in both treatment groups; there were 7 (0.3%) events in the Fenofibrate group and 6 (0.2%) events in the Placebo group. Pancreatitis also occurred at similar rates in both treatment groups; there were 5 events in the Fenofibrate group and 4 events in the Placebo group.

There were no reported pulmonary emboli or deep vein thromboses in either group.

There were two cases of ‘acute renal failure’ reported by study investigators during the course of the trial; both reports were of patients randomized to the Fenofibrate group (Table 25).

Table 25: Patients Reported with acute renal failure by ACCORD-Lipid Study Investigators

Patient ID	Serious Adverse Event	Treatment Arm	Creatinine	Outcome
14419	acute renal failure	Fenofibrate	4.2 mg/dL (changed from 1.3 mg/dL)	Recovered; all meds discontinued, last Cr = 1.96 mg/dL Taking herbal medications
15041 59 yo Asian woman	acute renal failure	Fenofibrate	5.2 mg/dL (changed from 1.23 mg/dL 3 months previously)	Outpatient follow-up to assess etiology of ARF

The narratives of these two patients are summarized below.

Patient narrative #14419:

Patient #1449 (randomized to Fenofibrate treatment arm) 68-year-old African American female who reports a hospitalization. She has a medical history of type 2 diabetes, hypertension, hyperlipidemia, and non-specific inflammation and septal fibrosis of the liver without cirrhosis. Participant was referred to the ED for several months with complaints of nausea, decreased energy, and generalized "lousy" feeling along with elevated BUN of 56 and creatinine of 4.2 [mg/dL]. Patient states the symptoms began in October 2005 after taking an herbal medication called "alkol". All medications were discontinued and patient was hydrated during stay. Patient improved and was discharged with creatinine of 3.0 [mg/dL] with prescriptions for insulin glargine, insulin aspart, esomeprazole, and diltiazem. The exact reason for acute renal failure not known but likely multifactorial; new herbal, drug-drug, drug-herb interaction, and/or polypharmacy. Recommended discuss with outside physician.
 Creatinine on 1/24/2006 1.67 mg/dL and 1.96 mg/dL on 5/16/2006.

LABORATORY/DIAGNOSTIC RESULTS

Date	Time	Test Name	Results	Normal Range
11/23/2005	13:56	calcium	10 mg/dL	
11/23/2005		chloride	100 mEq/L	

11/23/2005	creatinine	4.2 mg/dL	0.5 - 1.4
11/23/2005	glucose	118 mg/dL	70 -100
11/23/2005	potassium	4.0 mEq/L	
11/23/2005	sodium	141 mEq/L	
11/23/2006	BUN	56 mg/dL	6 - 20

Patient narrative #15041 is summarized below as submitted to the Agency:

Patient #15041 (randomized to Fenofibrate arm) is a 59-year-old Asian female who reports hospitalization. She has a medical history of type 2 diabetes, hyperlipidemia, and hypertension. Patient admitted (b) (6) from the IM clinic after having worsening renal function and nausea and vomiting. Patient started prilosec, amoxicillin, and biaxin on 5/16/2005 for post upper endoscopy and colonoscopy. Patient discontinued drugs 5 days later and starting taking son's compazine which relieved the nausea and allowed her to tolerate oral intake. Patient's creatinine on 5/26/06 visit reported at 5.2 mg/dL and 3.9 mg/dL at repeat on 6/1/2006. Patient remained stable with no episodes of nausea and vomiting. Renal function improved moderately with IV hydration but did not return to baseline. Diagnostic results suggest possible intrinsic process. Patient was discharged in stable condition with instructions to stop metformin, HCTZ, and lisinopril until she follows up with nephrology, her primary care physician and ACCORD physician. Metformin and fenofibrate/placebo study drug discontinued. Recommended discuss whether to continue taking lisinopril and HCTZ with outside physician. Outpatient follow-up to assess etiology of acute renal failure.

DATE	TIME	TEST NAME	RESULTS	NORMAL RANGE
6/1/2006	8:36	glucose	122 mg/dL	79 - 115
6/1/2006		BUN	63 mg/dL	8 - 26
6/1/2006		calcium	10 mg/dL	
6/1/2006		chloride	101 mmol/L	
6/1/2006		CO2	24 mmol/L	
6/1/2006		creatinine	3.9 mg/dL	.4 -1.0
6/1/2006		GFR	13 ml/min/m2	>60
6/1/2006		potassium	4.7 mmol/dL	
6/1/2006		sodium	135 mmol/L	136 - 144
6/1/2006		urine eosinophils	negative	
6/2/2006	04:43	glucose	86 mg/dL	
6/2/2006		BUN	55 mg/dL	8 - 26
6/2/2006		calcium	9.2 mg/dL	
6/2/2006		chloride	111 mmol/L	
6/2/2006		CO2	23 mmol/L	
6/2/2006		creatinine	3.4 mg/dL	.4 -1.0
6/2/2006		GFR	15 ml/min/m2	>60
6/2/2006		potassium	4.4 mmol/dL	
6/2/2006		sodium	139 mmol/L	

Although the data is not complete, the narrative for Patient # 15041 is concerning for a possible drug –induced process.

ACCORD-Lipid Safety Conclusions

The ACCORD-Lipid trial was conducted in the spirit of a ‘large simple’ trial. Therefore, the collection of safety data was in some sense limited. Since complete data were not available, it is difficult to definitively assess the safety profile of fenofibrate plus simvastatin versus simvastatin plus placebo.

For example, although three cases of hepatitis were reported in the Fenofibrate group (and none in the Placebo group), bilirubin, AST, and alkaline phosphatase were not obtained. Therefore the verification of hepatitis is difficult. However, Patient # 14762’s narrative made a strong case for drug-induced hepatitis with a description of a positive re-challenge when fenofibrate was added to simvastatin.

ALT increases > 5XULN were statistically significantly higher in the Fenofibrate group than in the Placebo group (p=0.03). The current labeling for all fenofibrate products describes transaminase elevations under Warnings and Precautions. Regular monitoring of liver function, including ALT, is recommended for the duration of fenofibrate therapy and therapy discontinuation if enzyme levels persist > 3XULN.

Muscle toxicity occurred at similar rates in the Fenofibrate group as compared to the Placebo group during the ACCORD-Lipid trial. Mild-to-moderate CPK elevations occurred at 6.5% in the Fenofibrate group and 6.0% in the Placebo group. Of the seven reported myopathy/rhabdomyolysis cases, complete information was not available to make conclusive determinations, but a few cases were suspicious for rhabdomyolysis. Patient #10303 met the Agency’s definition of rhabdomyolysis, but the etiology was unclear and drug-induced rhabdomyolysis could not be established.

Increases in serum creatinine were more common in the Fenofibrate group. Altogether 18% of patients in the Fenofibrate treatment arm as compared to 8% in the Placebo treatment arm were either on a reduced dose or had to be discontinued from the masked medication because of low eGFR or elevated creatinine. There were two reported cases of acute renal failure in the Fenofibrate treatment arm as compared to zero in the Placebo arm. Although the data are not complete, the narrative for Patient # 15041 is concerning for a possible drug–induced process.

Trilipix Development Program

Abbott Laboratories submitted a New Drug Application (NDA) for fenofibric acid (Trilipix®) in 2007. Three double-blind, controlled Phase 3 studies (M05-748, M05-749, and M05-750) and one long-term, open-label extension study (M05-758) were conducted in support of the proposed indication for use of Trilipix in combination with a statin.

Study Design

Studies M05-748, M05-749, and M05-750 had similar designs, differing primarily in the statin used for combination therapy/monotherapy. All were multi-center, randomized, double-blind,

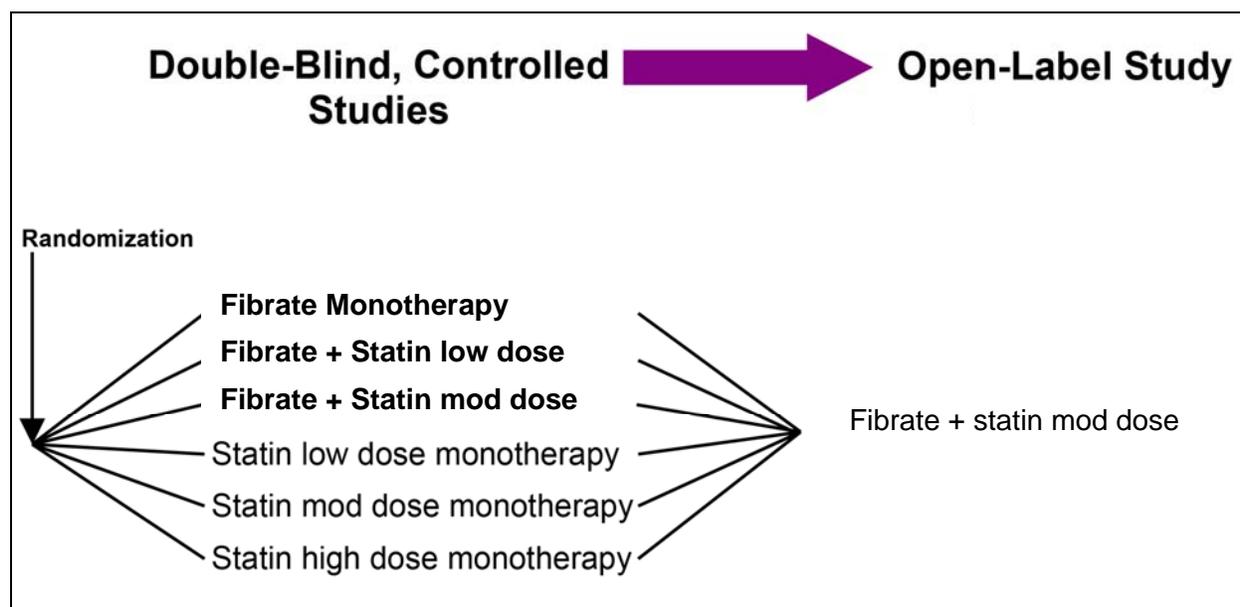
prospective, comparative studies in mixed dyslipidemic adults (Fredrickson Type IIb) conducted at sites in the United States, Canada, and Puerto Rico. All studies assessed the lipid-altering efficacy and safety of once daily treatment with fenofibric acid in combination with either a low or a moderate dose of a statin compared to fenofibric acid monotherapy and statin monotherapy.

The statins in the three Phase 3 studies were rosuvastatin (10 mg, 20 mg, and 40 mg) in Study M05-748, simvastatin (20 mg, 40 mg, and 80 mg) in Study M05-749, and atorvastatin (20 mg, 40 mg, and 80 mg) in Study M05-750.

The statins were categorized further into the following categories:

- Low-dose statins= 10 mg rosuvastatin, 20 mg simvastatin, and 20 mg atorvastatin
- Moderate-dose statins= 20 mg rosuvastatin, 40 mg simvastatin, and 40 mg atorvastatin
- High-dose statins= 40 mg rosuvastatin, 80 mg simvastatin, and 80 mg atorvastatin

The planned duration of each double-blind study was approximately 22 weeks, consisting of a 42-day diet run-in/hypolipidemic washout period (Screening Period), a 12-week Treatment Period, and a 30-day Safety Follow-up Period (only if not entering the open-label safety extension study). The following figure depicts the parallel treatment arm design of the three controlled studies in the Trilipix program.



Source: Sponsor's NDA 22224 Integrated Summary of Efficacy pg. 42.

Inclusion Criteria

1. Men or women ≥ 18 years of age
2. Subjects must have the following fasting lipid results following ≥ 12 hour fasting period before the Baseline Visit (measured at the Screening Visit):
 - TG level ≥ 150 mg/dL (≥ 1.69 mmol/L), and
 - HDL-C < 40 mg/dL (< 1.02 mmol/L) for males and < 50 mg/dL (< 1.28 mmol/L) for females, and

- LDL-C \geq 130 mg/dL (\geq 3.35 mmol/L).
3. Subject must be willing to observe the diet recommended by the American Heart Association entitled "An Eating Plan for Healthy Americans: Our American Heart Association Diet."

Exclusion Criteria

1. Subject is of Asian ancestry (having Filipino, Chinese, Japanese, Korean, Vietnamese or Asian-Indian origin).
2. Subject has any of the following diabetic conditions
 - Type I diabetes mellitus,
 - A history of diabetic ketoacidosis, or
 - Uncontrolled type II diabetes mellitus (defined as hemoglobin A_{1c} of $>$ 8.5%)
3. Subject has a history of pancreatitis or gallbladder disease. Subjects with gallbladder who have previously undergone a cholecystectomy will be allowed to enroll.
4. Subject has evidence of unstable cardiovascular disease:
 - Myocardial infarction, coronary bypass surgery, or angioplasty within 12 months of the Pre-screening Visit.
 - Severe peripheral artery disease as evidenced by intermittent claudication within 3 months of the Pre-screening Visit.
 - Unstable angina pectoris or uncontrolled cardiac arrhythmias within 3 months of the Prescreening Visit.
 - Congestive heart failure (CHF) as defined by the New York Heart Association (NYHA) – Class III or IV.
5. Subject has a history of diagnosed hereditary or acquired myopathy.
6. Subject received coumarin anticoagulants, cyclosporine, nicotinic acid, bile acid binding resins, HMG-CoA reductase inhibitors (statins), fibric acid derivatives, ezetimibe, sibutramine, orlistat, oral corticosteroids, oral garlic supplements, fish oil, plant stanols or other agents/supplements specifically to alter lipid levels within six weeks of enrollment (Baseline Visit).
7. Screening Laboratory analyses show any of the following abnormal laboratory results:
 - ALT/SGPT or AST/SGOT $>$ 1.5 X Upper Limit of Normal (ULN)
 - Creatine phosphokinase (CPK) level $>$ 3 X ULN.
 - Calculated creatinine clearance $<$ 50 mL/min (0.83 mL/s).
 - Thyroid Stimulating Hormone (TSH) level that is outside the central laboratory reference range.

Demographics and other Subject Characteristics

Of the 2698 randomized and treated subjects, 1393 (51.6%) were women (Table 26) and 1305 (48.4%) were men. A total of 92.6% of all subjects were White, 4.7% were Black, and 2.8% were of other races. The majority of subjects (81.8%) were younger than 65 years of age. Most (87.5%) subjects weighed \geq 70 kg at baseline. Mean weight was 91.4 kg overall, 85.5 kg among females, and 97.8 kg among males.

Table 26: Demographic and Baseline Characteristics Trilipix Clinical Trials

Demographic Characteristic	Fenofibric Acid (N=490)	Low-dose statin (N=493)	Fenofibric Acid + Low statin (N=490)	Moderate-dose statin (N=491)	Fenofibric Acid + Moderate statin (N=489)	High-dose statin (N=245)
Sex						
Female	277 (56.5)	234 (47.5)	263 (53.7)	245 (49.9)	249 (50.9)	125 (51.0)
Male	213 (43.5)	259 (52.5)	227 (46.3)	246 (50.1)	240 (49.1)	120 (49.0)
Race						
White	461 (94.1)	460 (93.3)	446 (91.0)	458 (93.3)	445 (91.0)	227 (92.7)
Black	18 (3.7)	19 (3.9)	29 (5.9)	22 (4.5)	27 (5.5)	11 (4.5)
Other	11 (2.2)	14 (2.8)	15 (3.1)	11 (2.2)	17 (3.5)	7 (2.9)
Ethnicity						
Hispanic	51 (10.4)	51 (10.3)	51 (10.4)	48 (9.8)	45 (9.2)	21 (8.6)
No ethnicity	439 (89.6)	442 (89.7)	439 (89.6)	443 (90.2)	444 (90.8)	224 (91.4)
Age Group (years)						
< 65	402 (82.0)	419 (85.0)	394 (80.4)	408 (83.1)	389 (79.6)	195 (79.6)
≥ 65	88 (18.0)	74 (15.0)	96 (19.6)	83 (16.9)	100 (20.4)	50 (20.4)
Body Weight (kg)						
< 70	68 (13.9)	55 (11.2)	70 (14.3)	59 (12.0)	56 (11.5)	30 (12.2)
≥ 70	422 (86.1)	438 (88.8)	420 (85.7)	432 (88.0)	433 (88.5)	215 (87.8)
Tobacco Use						
User	108 (22.0)	92 (18.7)	106 (21.6)	103 (21.0)	95 (19.4)	60 (24.5)
Ex-User	135 (27.6)	152 (30.8)	142 (29.0)	152 (31.0)	149 (30.5)	72 (29.4)
Non-User	247 (50.4)	249 (50.5)	242 (49.4)	236 (48.1)	245 (50.1)	113 (46.1)
Alcohol Use						
Drinker	257 (52.4)	254 (51.6)	245 (50.0)	248 (50.5)	258 (52.8)	126 (51.4)
Ex-Drinker	38 (7.8)	33 (6.7)	41 (8.4)	31 (6.3)	31 (6.3)	28 (11.4)
Non-Drinker	195 (39.8)	205 (41.7)	204 (41.6)	212 (43.2)	200 (40.9)	91 (37.1)

Source: NDA 22-224, Summary of Integrated Efficacy.

Overall, Baseline Lipid Parameters

At baseline, the overall study population had a mean HDL-C level of 38.4 mg/dL, a mean TG level of 282.2 mg/dL and a mean LDL-C of 157.3 mg/dL (Table 27). Approximately 32% of subjects had baseline TG levels ≤ 200 mg/dL and 68% of subjects had baseline TG levels > 200 mg/dL.

Table 27: Lipid Parameters at Baseline Trilipix Clinical Trials

Treatment Arms							
	Fenofibric Acid N=490	Low-Dose Statin N=493	Fenofibric Acid + Low Dose	Moderate Dose Statin	Fenofibric Acid +Moderate	High Dose Statin	P=Value

			Statin N=490	N=491	Dose Statin N=489	N=245	
HDL-C mg/dL	n=477	n=481	n=467	n=470	n=467	n=234	0.876
Mean	38.6	38.4	38.3	38.4	38.3	37.9	
Median	38.0	38.0	37.0	37.9	38.0	37.0	
Min, Max	19, 60	19, 60	22, 62	12, 61	18, 71	26, 62	
TG mg/dL	n=490	n=493	n=490	n=491	n=489	n=245	0.875
Mean	280.9	284.1	281.2	290.0	287.2	280.4	
Median	236.5	248.7	233.3	247.0	245.0	248.0	
Min, Max	55, 1700	64, 1282	73, 1236	72, 1704	44, 1238	95, 1140	
LDL-C mg/dL	N=490	N=492	N=489	N=488	N=487	N=245	0.497
Mean	158.6	154.0	156.1	156.7	156.8	155.8	
Median	158.0	151.0	151.0	154.0	154.0	155.0	
Min, Max	48, 296	74, 325	65, 325	66, 266	61, 350	80, 278	

Source: NDA 22-224 clinical review, pg.39.

Other secondary lipid parameters, non-HDL-C, VLDL-C, TC, and apo B were also similar at baseline between the treatment arms. Mean values overall for the secondary efficacy parameters were 220.8 mg/dL for non-HDL-C, 65.6 mg/dL for VLDL-C, 259.6 mg/dL for TC, and 146.4 mg/dL for apo B; mean value for hsCRP was 0.48 mg/dL.

Subjects in the clinical trials were categorized into the following three Framingham risk categories as defined in NCEP ATP III:

- High (CHD or CHD risk equivalents)
- Moderate (multiple [2+] risk factors)
- Low (zero to one risk factor)

Overall, 35.4% were classified as having high risk, 43.9% were classified as having moderate risk, and 20.8% were classified as having low risk.

Primary Efficacy Endpoints

- TG: Fenofibric acid in combination with each dose of statin versus statin monotherapy at the corresponding dose.
- HDL-C: Fenofibric acid in combination with each dose of statin versus statin monotherapy at the corresponding dose.
- LDL-C: Fenofibric acid in combination with each dose of statin versus fenofibric acid monotherapy

Table 28: Mean Percent Change from Baseline to Final Value in HDL-C, TG, and LDL-C in Trilipix Clinical Trials

	Fenofibric Acid N=490	Low-dose Statin N=493	Fenofibric Acid + Low-dose Statin N=490	P-value	Moderate-dose Statin N=491	Fenofibric Acid + Moderate-dose Statin N=489	P value	High-dose Stain N=245
HDL-C mg/dL	n=420	n=455	n=423		n=430	n=422		n=217
BL mean	38.4	38.4	38.2		38.4	38.1		38.0
Final mean	44.3	40.7	44.8		41.1	44.3		40.6
Mean % change	16.3%	7.4%	18.1%	<0.001^a	8.7%	17.5%	<0.001^a	7.9%
TG mg/dL	n=459	n=477	n=470		n=472	n=462		n=235
BL mean	280.7	286.1	282.1		287.9	286.1		282.5
Final mean	177.3	217.6	146.7		202.5	147.5		186.1
Mean % change	-31.0%	-16.8%	-43.9%	<0.001^a	-23.7%	-42.0%	<0.001^a	-28.1%
LDL-C mg/dL	n=427	n=463	n=436		n=439	n=434		n=225
BL mean	158.4	153.8	155.7		158.0	156.4		156.1
Final mean	146.1	100.6	101.9		91.6	99.1		81.7
Mean % change	-5.1%	-33.9%	-33.1%	<0.001^b	-40.6%	-34.6%	<0.001^b	-47.1%

Source: NDA 22-224 Integrated Summary of Efficacy.

a. Fenofibric acid in combination with statin vs. corresponding statin monotherapy

b. Fenofibric acid in combination with statin vs. fenofibric acid monotherapy

As per Table 28, the addition of fenofibric acid to a low-dose statin and a moderate-dose statin resulted in a significant decrease in TG over the corresponding statin monotherapy. The combination of fenofibric acid and statin also resulted in greater HDL-C improvements than the corresponding statin monotherapy. However, for LDL-C reduction high-dose statin monotherapy showed the greatest percent reduction, although a statistical comparison with other treatment groups was not conducted.

Table 29: Mean Percent Change from Baseline to Final Value in Non-HDL-C, VLDL-C, TC, in Trilipix Clinical Trials

	Fenofibric Acid N=490	Low-dose Statin N=493	Fenofibric Acid + Low-dose Statin N=490	P-value	Moderate-dose Statin N=491	Fenofibric Acid + Moderate-dose Statin N=489	P value	High-dose Stain N=245
Non-HDL-C	n=420	n=454	n=422		n=431	n=420		n=217

	Fenofibric Acid N=490	Low-dose Statin N=493	Fenofibric Acid + Low-dose Statin N=490	P-value	Moderate-dose Statin N=491	Fenofibric Acid + Moderate-dose Statin N=489	P value	High-dose Stain N=245
mg/dL								
BL mean	222.5	217.6	219.9		222.4	218.9		220.2
Final mean	181.4	140.9	129.7	<0.001 ^a	127.0	125.6	<0.001 ^a	115.5
Mean % change	-17.3%	-34.9%	-40.4%	<0.001^b	-42.4%	-42.0%	0.710^b	-47.3%
VLDL-C mg/dL	n=449	n=463	n=455		n=458	n=449		n=232
BL mean	65.0	66.0	65.5		67.8	64.5		66.1
Final mean	36.1	40.2	28.4		36.7	26.8		33.6
Mean % change	-34.2%	-32.1%	-50.0%	<0.001^b	-38.9%	-51.2%	<0.001^b	42.1%
Total C	n=459	n=477	n=469		n=472	n=462		n=235
BL mean	260.9	257.0	258.6		261.3	257.3		258.5
Final mean	225.8	182.4	175.4		169.2	170.3		155.8
Mean % change	-12.4%	-28.7%	-31.5%	<0.001^b	-34.7%	-33.3%	0.093^b	-39.5%
Apo B	n=455	n=470	n=465		n=468	n=455		n=229
BL mean	146.2	145.0	146.1		147.1	145.0		146.0
Final mean	122.1	99.1	92.0		91.6	90.7		83.6
Mean % change	-15.6%	-31.1%	-36.3%	<0.001^b	-36.9%	-36.7%	0.817^b	-42.4%

Source: NDA 22-224 Integrated Summary of Efficacy.

a. Fenofibric acid in combination with statin vs. fenofibric acid monotherapy

b. Fenofibric acid in combination with statin vs. corresponding statin monotherapy

Source: NDA 22-224.

In all three studies, both doses of combination therapy resulted in greater mean percent decreases in non-HDL-C compared to fenofibric acid monotherapy (Table 29). Compared to the corresponding low-dose statin monotherapy, fenofibric acid in combination with each low-dose statin resulted in greater mean percent decreases in non-HDL-C, VLDL-C, and apo B in all three studies.

High-dose statin monotherapy was associated with the greatest non-HDL-C, Total-C, and apo B lowering. As with the primary endpoints, although the individual statins imparted different mean percent changes in these parameters based on the statin's potency (rosuvastatin > atorvastatin > simvastatin), the impact of adding fenofibric acid to each statin was similar.

Summary of Safety Results

The safety review of the Trilipix program focused on issues that are well-known to occur with fenofibrates and stains, and are likely to be enhanced with combination therapy: hepatic, muscle, and renal events.

- **Hepatobiliary:** Overall, subjects treated with fenofibric acid, either alone or in combination with statins demonstrated more frequent increase in transaminases than subjects treated with statins alone. The incidence with fenofibric acid monotherapy and in

combination with a statin was 3.9 to 6.3% as compared to 0.6-0.8% with low-dose and moderate-dose statin monotherapy. No subject treated with fenofibric acid met criteria for Hy's law and no subject experienced hepatic failure. Biliary events, such as cholelithiasis and cholecystitis were infrequent (<1%).

- Muscle: Combination therapy with fenofibric acid and statin did not result in higher incidences of muscle events than statin therapy alone. The majority of subjects who reported muscle-related AEs did not prematurely discontinue due to the event. There were no cases of rhabdomyolysis or myopathy in any of the submitted AE datasets. There was one case of rhabdomyolysis in a narrative of a patient hospitalized with gastroenteritis and dehydration, who ultimately remained on the study drug.
- Renal: Modest renal laboratory changes (increase in BUN and creatinine >ULN) were relatively common in the fenofibric acid groups, but events of renal failure or insufficiency occurred infrequently.

Table 30: Adverse Events of Special Interest, 12-Week Phase 3 Trials

	Fenofibric acid N=49 n (%)	Low-dose statin N=493 n (%)	Fenofibric acid + low-dose statin N=490 n (%)	Moderate-dose statin N=491 n (%)	Fenofibric acid + moderate-dose statin N=489 n (%)	High-dose statin N=245 n (%)
Any AE of special interest	54 (11.0)	37 (7.5)	71 (14.5)	45 (9.2)	50 (10.2)	33 (13.5)
Hepatic events	19 (3.9)	3 (0.6)	31 (6.3)	4 (0.8)	22 (4.5)	6 (2.4)
Muscle events	27 (5.5)	32 (6.5)	38 (7.8)	41 (8.4)	26 (5.3)	25 (10.2)
Renal events	9 (1.8)	2 (0.4)	10 (2.0)	0	8 (1.6)	3 (1.2)

Source: NDA 22-224, Integrated Summary of Efficacy.

- Venous thrombosis: Two of 490 subjects in the fenofibric acid monotherapy treatment group developed venous thrombosis. There were no reports of venous thrombosis in any of the combination therapy or statin monotherapy groups.
- Pancreatitis: There was one case of pancreatitis in a patient on fenofibric acid and statin combination therapy.

Fibrate Trials

Brief Description of Major Fibrate Trials

Coronary Drug Project (CDP)

The results of the CDP were first published in 1975.³⁶ The primary objective of this trial was to determine the safety and efficacy of several different treatments in preventing recurrent CHD events among men with a previous myocardial event. In the group randomized to clofibrate, the

³⁶ Clofibrate and niacin in coronary heart disease. JAMA 1975;231:360-81.

relative risk reduction of CHD events was 9%, but did not reach statistical significance. All-cause mortality rates were similar to placebo. There was a significantly higher rate of cholelithiasis (3%) compared to placebo (1%). The authors concluded that the CDP results provided no evidence with which to recommend the use of clofibrate among men with CHD.³⁷

World Health Organization Cooperative Trial on Primary Prevention of Ischemic Heart Disease with Clofibrate to Lower Serum cholesterol (WHO-clofibrate)

The results of the WHO-clofibrate were first published in 1978.³⁸ In this primary prevention trial of 15,575 men, there was a 25% reduction in non-fatal myocardial infarction in the clofibrate-treated group compared to placebo (p<0.05). However mortality from all causes and causes other than ischemic heart disease was significantly higher in the clofibrate-treated group.³⁹

Helsinki Heart Study (HHS)

Gemfibrozil, a fibric acid derivative that is structurally different and possesses biologic actions distinct from those of clofibrate, was investigated in the Helsinki Heart Study (HHS), a primary prevention trial.⁴⁰ The study was a randomized, double-blind, placebo-controlled trial of gemfibrozil (600 mg twice daily) against placebo in 4081 men lasting five years. Fatal and non-fatal myocardial infarction and cardiac deaths were the principal end points. At baseline, mean TG levels were 175 mg/dL, HDL-C was 47 mg/dL, and TC was 289 mg/dL. LDL-C was 189 mg/dL at baseline. Treatment with gemfibrozil produced a 34% relative risk (RRR) reduction (P<0.002) in coronary heart disease events in the study population. Gemfibrozil lowered LDL-C modestly (~ 10%) but also lowered triglycerides (~ 43%) and raised HDL-C (~ 10%); the reduction in cardiac events in HHS was linked by multiple regression analysis to the rise in HDL-C.

Table 31: Cardiac Outcomes by Treatment Group- HHS

Coronary Event	Gemfibrozil N=2051 n (rate/1000 person years)	Placebo N=2030 n (rate/1000 person years)
Nonfatal myocardial infarction	45 (21.9)	71 (35.0)
Fatal myocardial infarction	6 (2.9)	8 (3.9)
Sudden cardiac death	5 (2.4)	4 (2.0)
Unwitnessed death	0	1 (0.5)
Total	56 (27.3)	84 (41.4)*
*Log rank chi-square=6.0; nominal P value<0.02 (two tailed)		

Source: Frick et al. Helsinki Heart Study. *NEJM* 1987; 317:1237-45.

³⁷ Ibid.

³⁸ Committee of Principal Investigators. A co-operative trial on primary prevention of ischemic heart disease using clofibrate. *Br Heart J* 1978; 40:1069-1118.

³⁹ Committee of Principal Investigators. WHO cooperative trial on primary prevention of ischemic heart disease with clofibrate to lower serum cholesterol: final mortality follow-up. *Lancet* 1984;2:600-604.

⁴⁰ Frick MH, et al. Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *NEJM* 1987;317: 1237-45.

Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT)

In VA-HIT, 2531 patients with mean LDL-C levels of 112 mg/dL, mean HDL-C levels of 32 mg/dL, and mean TG levels of 161 mg/dL were randomized to either 1200 mg gemfibrozil or placebo for an average of five years. Gemfibrozil produced a 24% relative risk reduction on the combination of nonfatal MI, death due to CHD, or confirmed stroke (95% CI 11 to 36, $p < 0.001$).⁴¹ The effects of gemfibrozil in VA-HIT were dependent on baseline and change in HDL-C, but independent of baseline or change in TG.⁴² Gemfibrozil treatment was associated with a 25% lowering of TG, a 7% increase in HDL-C, and no change in LDL-C.

Table 32: Major Cardiovascular Event According to Treatment Group-VA-HIT

Event	Placebo N=1267	Gemfibrozil N=1264	Relative Risk Reduction	p-value/nominal p-value
	n (%)	n(%)	(95% CI)	
Nonfatal myocardial infarction or death due to CHD	275 (21.7)	219 (17.3)	22 (7 to 35)	0.006
Nonfatal myocardial infarction or death due to CHD (excluding silent myocardial infarction)	241 (19)	195 (15.4)	21 (4 to 34)	0.02
Nonfatal myocardial infarction, death due to CHD, or confirmed stroke	330 (26)	258 (20.4)	24 (11 to 36)	<0.001
Nonfatal myocardial infarction	184 (14.5)	146 (11.6)	23 (4 to 38)	0.02
Death due to CHD	118 (9.3)	93 (7.4)	22 (-2 to 41)	0.07
Death from any cause	220 (17.4)	198 (15.7)	11 (-8 to 27)	0.23
Investigator-designated stroke	88 (6.9)	64 (5.1)	29 (2 to 48)	0.04
Confirmed stroke	76 (6.0)	58 (4.6)	25 (-6 to 47)	0.10
Transient ischemic attack	53 (4.2)	22 (1.7)	59 (33 to 75)	<0.001
CABG	173 (13.7)	164 (13.0)	6 (-17 to 24)	0.60
PTCA	147 (11.6)	120 (9.5)	21 (-1 to 38)	0.06
CABG or PTCA	287 (22.7)	266 (21.0)	9 (-8 to 23)	0.29
Peripheral vascular surgery	28 (2.2)	19 (1.5)	33 (-20 to 63)	0.18
Carotid endarterectomy	44 (3.5)	16 (1.3)	65 (37 to 80)	<0.001
Hospitalization for unstable angina	453 (35.8)	457 (36.2)	-0.4 (-14 to 12)	0.95
Hospitalization for congestive heart failure	168 (13.3)	134 (10.6)	22 (2 to 38)	0.04

⁴¹ Rubins et al., Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. *NEJM* (1999); 341:410-418.

⁴² Robins et al., Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT. *JAMA* (2001);285:1585-1591.

*CI denotes confidence interval, CHD coronary heart disease, CABG coronary-artery bypass graft, and PTCA percutaneous transluminal coronary angioplasty. Relative risk reductions, 95 percent confidence intervals, and P values are derived from Cox models. For risk reductions, negative numbers indicate an increase in risk.

†Confirmed stroke was judged by a blinded adjudication panel of three neurologists.

Source: Robins et al., JAMA (2001);285:1585-1591

Bezafibrate Infarction Prevention Study (BIP)

In the BIP trial, 3090 men and women with a previous history of CVD and mean LDL-C of 148 mg/dL, mean HDL-C of 35 mg/dL, and mean TG of 145 mg/dL were randomized to either bezafibrate 400 mg or placebo once daily for an average of 6.2 years.⁴³ Main exclusion criteria were insulin-dependent diabetes mellitus and current use of lipid-modifying agents.

The primary end point of the study was fatal MI, nonfatal MI, or sudden death (occurring within 24 hours of onset of symptoms).

Among patients treated with bezafibrate, the rate of primary end points was 13.6% versus 15.0% in the placebo group (9.4% relative risk reduction; P=0.26) (Table 33). Thus, although bezafibrate substantially increased HDL-C and reduced TG (as compared to minimal change or even worsening of lipid profiles in the placebo group, see below), the primary endpoint was not met.

Bezafibrate treatment increased HDL-C by 18%, and decreased TG by 21% and LDL-C by 7% (approximately). In the placebo group, TG increased by 5%, LDL-C decreased by 1% and HDL-C increased approximately 4%.⁴⁴

In subgroup analyses, among those whose baseline TG levels were ≥ 200 mg/dL, there was a 40% relative risk reduction in the primary endpoint (nominal p=0.02) in bezafibrate-treated subjects. If the baseline HDL-C was < 35 mg/dL and TG > 200 mg/dL, the relative risk reduction was reported to be 42% (nominal p=0.02) in bezafibrate-treated subjects.

Table 33: BIP Clinical Outcomes

	Bezafibrate n=1548	Placebo n=1542	Risk Reduction, %	p-value/ nominal p-value
Primary Endpoint	211 (13.6)	232 (15.0)	-9.4	0.26
Non-fatal MI	150 (9.7)	172 (11.2)	-12.8	0.18
Fatal MI	18 (1.2)	17 (1.1)		0.87
Sudden death	43 (2.8)	43 (2.8)		0.98
Secondary Endpoint	311 (20.1)	327 (21.2)	-4.9	0.44
Unstable angina pectoris	76 (4.9)	82 (5.3)		0.61

⁴³ The BIP Study Group. Secondary prevention by raising HDL-C and reducing TG in patients with coronary artery disease: the Bezafibrate Infarction Prevention (BIP) Study. *Circulation* 2000; 102:21-27.

⁴⁴ The BIP Study Group. Secondary prevention by raising HDL-C and reducing TG in patients with coronary artery disease: the Bezafibrate Infarction Prevention (BIP) Study. *Circulation* 2000; 102:21-27.

	Bezafibrate n=1548	Placebo n=1542	Risk Reduction, %	p-value/ nominal p-value
CABG	144 (9.3)	157 (10.2)		0.41
PTCA	91 (5.9)	88 (5.7)		0.84
All Endpoints Combined	522 (33.7)	559 (36.3)	-6.6	0.14
Mortality	161 (10.4)	152 (9.9)		0.62
Cardiac	95 (6.1)	88 (5.7)		0.61
Non-cardiac	66 (4.3)	64 (4.2)		0.87
Stroke	72 (4.6)	77 (5.0)		0.66
Ischemic Stroke	59 (3.8)	69 (4.5)		0.36

Secondary end points were the first event in patients free of the primary end points. CABG, coronary artery bypassgraft; and PTCA, percutaneous transluminal coronary angioplasty. Values are n(%) unless otherwise indicated.

Source: *Circulation* 2000;102:21-27.

Fenofibrate Intervention in Endpoint Lowering in Diabetes (FIELD)

In FIELD, 9795 patients with T2DM with mean LDL-C of 118 mg/dL, HDL-C of 42 mg/dL, and TG levels of 153 mg/dL were randomized to either 200 mg of fenofibrate or placebo once daily for the study duration of five years. The primary endpoint was coronary heart disease death or non-fatal MI (coronary events).

Although the patients in FIELD were randomized to masked study drug, decisions about changes in therapy for diabetes or lipid-lowering therapy were at the discretion of the patient's primary care physician.⁴⁵ By the end of the study, of the 4900 patients assigned to the Placebo treatment arm 1776 (36%) were on an additional lipid-lowering therapy. Of the 4895 patients assigned to the Fenofibrate arm, 944 (19%) patients were on an additional lipid-lowering therapy.

In the full cohort (4895 patients in the Fenofibrate arm and 4900 in the Placebo arm), treatment with fenofibrate reduced LDL-C by 6%, TG by 22%, and increased HDL-C by 2% (relative to placebo) at study close. There were 256 primary end-point events (256/4895 or 5.2%) in the Fenofibrate group as compared to 288 events (288/4900 or 5.9%) in the Placebo group. (HR 0.89 [95% CI 0.75-1.05], p=0.16).

Among patients who did not start other lipid-lowering therapy and only remained on the randomized masked study drug (3951 patients in the Fenofibrate arm and 3124 in the Placebo arm), treatment with fenofibrate decreased LDL-C by 15%, TG by 27%, and increased HDL-C by 2% (relative to those in the Placebo group) at study close. There were 222 primary end-point events (222/3951 or 5.6%) in the Fenofibrate group from subjects who did not start any other lipid-lowering therapy. There were 232 primary end-point events (232/3124 or 7.4%) in the Placebo group from subjects who did not start any other lipid-lowering therapy.

Among patients who started other lipid-lowering therapy in addition to the masked study medication (944 patients in the Fenofibrate group and 1776 patients in the Placebo group), those

⁴⁵ The FIELD Study Investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomized controlled trial. *Lancet* 2005; 366:1849-61.

assigned to the Fenofibrate arm decreased LDL-C by 0.7%, TG by 11%, and also decreased HDL-C by 0.5% (relative to those Placebo group) at study close. There were 34 primary end-point events (34/944 or 3.6%) in those assigned to the Fenofibrate arm. There were 56 primary end-point events (56/1776 or 3.2%) in those assigned to the Placebo arm.

Table 34: Incidence of Primary Endpoint in Patients on “Other” Lipid-Lowering Therapy by Randomized Treatment Arm

	Fenofibrate	Placebo
YES, started other lipid-lowering therapy (primarily statins)	34/944 (3.6%)	56/1776 (3.2%)
NO, did not start other lipid-lowering therapy	222/3951 (5.6%)	232/3124 (7.4%)
Total	256/4895 (5.2%)	288/4900 (5.9%)

Therefore, as shown in Table 34, of the patients taking “other” lipid-lowering treatment (primarily statins) those in the Placebo arm had a similar incidence of coronary events as compared to those in the Fenofibrate arm. The limitations of post-hoc subgroup analyses must be kept in mind when evaluating the clinical significance of these data.

Summary of Major Fibrate Trials

Over the last 40 years laboratory and clinical data have suggested the potential of fibrates to reduce cardiovascular risk. However, data from large clinical outcomes trials have produced mixed results. The inconsistent outcomes may be a result of differences in pharmacodynamic properties among individual fibrates or study populations or both.

The following tables summarize the study populations and the features of some of the major fibrate trials.

Table 35: Characteristics of the Study Populations of Major Fibrate Trials

Baseline Characteristics	HHS	VA-HIT	BIP	FIELD	ACCORD
Average age (years)	47	64	60	62	62
Population	Men; Primary Prevention	Men; Secondary Prevention	91% Men; Secondary Prevention	63% Men; Primary and Secondary Prevention	69% Men; Primary and Secondary Prevention
History of diabetes (%)	3	25	10	100	100
LDL-C mg/dL	189	111	148	119	101
TC mg/dL	270	175	212	195	175
HDL-C mg/dL	47	32	35	43	38
Triglycerides mg/dL	175	161	145	153	163

Adapted from: Saha et al., *International Journal of Cardiology* (2010) 141; 157-166 and Backes J, et al. *Pharmacotherapy* 2007;27 (3):412-424.

Table 36: Features of the Major Fibrate Outcomes Trials

Trial Characteristics	HHS	VA-HIT	BIP	FIELD	ACCORD
Drug	Gemfibrozil	Gemfibrozil	Bezafibrate	Fenofibrate	Fenofibrate
Dose	600 mg 2X/day	1200 mg/day	400 mg/day	200 mg/day	200 mg/day
Primary endpoint	MI (fatal and non-fatal), cardiac death	Combined incidence of nonfatal MI and death from CAD	MI (fatal and non-fatal), sudden death	CHD death, non-fatal MI	Non-fatal MI, non-fatal stroke, or CVD death
Mean duration of follow-up (years)	5	5	6	5	5
# of patients (total)	Fibrate= 2051 Placebo= 2030	Fibrate = 1264 Placebo = 1267	Fibrate = 1548 Placebo =1542	Fibrate =4895 Placebo=4900	Fibrate =2765 Placebo =2753
Effect on Lipid Levels (% change from baseline)	LDL-C: -10 TC: -11 TG: -43 HDL-C: +10	LDL-C: 0 TC: -4 TG: -31 HDL-C: +6	LDL-C: -6.5 TC: -4.5 TG: -21 HDL-C: +18	LDL-C: -12 TC: -11 TG: -29 HDL-C: +5	LDL-C: -19 TC: -14 TG: -22 HDL-C: +8.4
Outcomes	CHD: ↓ 34% Non-fatal MI: ↓37% Total mortality: no change	CHD and Non-fatal MI: ↓22% Total mortality: ↓ 11% (NS)	Fatal and nonfatal MI and sudden death: ↓ 9% (NS) Total mortality: no change	CHD and nonfatal MI: ↓11% (NS) ↑Total mortality: 19% (NS)	Nonfatal MI Nonfatal Stroke CVD Death: ↓8% (NS) Total mortality: ↓9 % (NS)

Adapted from: Saha et al., *International Journal of Cardiology* (2010) 141; 157-166 and Backes J, et al. *Pharmacotherapy* 2007;27 (3):412-424.

APPENDIX A: Schedule of Laboratory Procedures- ACCORD-Lipid

Evaluations	Schedule in Months																																																				
	Scrn ⁵	BL	0.5	1	2	3	4	5	6	7	8	9	10	11	12	14	16	18	20	22	24	Q2	Q4	Q12	Q24	36	40	48	prn ¹	Exit																							
Clinic Visit	X	X		X	X	X	X	prn	X	prn	X	prn	X	prn	X	X	X	X	X	X	X	X								X	X																						
BP/Pulse	X	X					X				X				X		X		X		X		X								X																						
Weight	X	X		X	X	X	X		X		X		X	X	X	X	X	X	X	X	X	X	X								X																						
BP Milepost ⁷			(none)																																																		
HbA1c (POC) ⁴		X		X	X	X	X	prn	X	prn	X	prn	X	prn	X	X	X	X	X	X	X	X									X																						
HbA1c		C					C				C				C		C		C		C		C								C																						
FPG		C					C				C				C						C				C						C																						
Potassium		C					C				C				C															C	C																						
Creatinine	L	C					C				C				C		C		C		C		C						C	C																							
Lipid Profile	L	C					C				C				C						C				C				C	C																							
ALT	L	C		C			C				C				C						C				C				C	C																							
CPK		C		C			C				C				C						C				C				C	C																							
Urinalysis	L	C																											C	C	C																						
ECG	L	C																											C		C																						
Events		X					X				X			X		X		X		X		X		X							X																						
Dist.Phys Actv ⁸		X													X												X		X																								
HRQL ⁶		X													X												X		X																								
Costs ⁹		X					X				X				X		X		X		X		X																														
Eye Substudy		C ¹⁰																												C																							
Visual Acuity		X																								X					X																						
MIND: Cognitive ¹¹				X																X								X																									
MIND: MRI				C ¹²																								C ¹³																									
Serum Storage		C													C														C		C																						
EDTA/Plasma Storage		C																																																			
Urine Storage		C																																																			
Phone Int ¹⁴			X					X		X		X		X																																							

Intensive Glyc Group: Phone calls must be made between all regularly scheduled clinic visits

X: This evaluation/procedure applies at this visit

1: prn ('as needed') includes:

- (a) Monitoring K⁺ and Creatinine after starting and/or significantly changing ACEI, ARB and thiazides
- (b) Patients initiated on thiazolidinediones will be monitored, as recommended by the manufacturer, with ALT levels every two months for the first 12 months after the initiation of this therapy, and annually thereafter.

γ: Milepost blood pressure visits are only for participants in the Intensive BP group.

Δ: Each participant in the Intensive Glycemic Group will have a point-of-care (POC) HbA1c measurement at each clinic visit.

* These evaluations will be done in a subset of participants (4288 participants in the Cost Study and, within this subset, 2000 will complete HRQL, diet and physical activity assessments [i.e., all 2000 participants are in HRQL/diet/physical activity])

φ For the Eye Substudy (in a subset of 4065 participants), the baseline eye exam/fundus photography can be performed up to 2 months post-randomization.

ξ For the clinics participating in the MIND Cognitive Substudy (conducted in a subset of 2,800 participants), a battery of cognitive neuropsychological tests

will be obtained at 1, 20 and 40 months post-randomization. (The 1 month visit will serve as the baseline visit.)

λ In addition to the neuropsych tests, a subsample of 640 MIND participants will have a baseline MRI within 45 days after the baseline neuropsych test date.

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Trilipix[®] (fenofibric acid)

λλ Participants in the MRI portion of MIND will have a follow-up MRI +/- 45 days around the 40 month neuropsych test date.

In addition to the phone contacts noted in the table, calls must also be made between all other regularly scheduled clinic visits.

† Measurement documented in source notes only.

σ An additional lipid profile would be required at the next 4 month visit (after dietary/adherence counseling) if notified by the Coordinating Center that the LDL-C has exceeded 130 mg/dl (3.36 mmol/L) and/or that the triglyceride level has exceeded 750 mg/dl (8.47 mmol/l) (see Section 3.3.c for details)

Scrn=Screening Visits; **B**L=Baseline Visit; **C**=Central reading center or lab; **P**OC=Point of Care; **L**=Local lab; **B**P=blood pressure; **C**PK=Creatine phosphokinase; **F**PG=fasting plasma glucose

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: April 7th, 2011

From: Nancy Xu, M.D.
Clinical Reviewer
Division of Cardiovascular and Renal Products /CDER

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Kati Johnson
Regulatory Project Manager
Division of Metabolism and Endocrinology Products

Subject: Consult Request, Division of Cardiovascular and Renal Products/CDER
Drug: Trilipix (fenofibric acid)

This memo contains the Division of Cardiovascular and Renal Products clinical consult review as per your consult request dated February 7th, 2011.

Documents used for review:

- Division of Cardiovascular and Renal Products (DCaRP) has reviewed the following:
 - IND 70345, supporting document 202, submitted on 12/30/2010: the analysis of creatinine, estimated glomerular filtration rate and albuminuria in the ACCORD LIPID and FIELD studies
 - The included medical literature on fibrate-induced deterioration of renal function
 - Pharmacology toxicology review by the Division of Metabolism and Endocrinology Products (DMEP)

Background

Fenofibrates are peroxisome proliferator receptor alpha (PPAR α) activators approved to reduce triglyceride (TGs), low density lipoprotein (LDL), and/or increase high density lipoprotein (HDL) cholesterol, alone or in combination with a statin.

Increases in serum creatinine (SCr) have been seen with fenofibrate use. Clinical trial data suggest that the change in SCr is reversible upon fenofibrate discontinuation and some published articles even suggest a protective effect of fenofibrate on renal indices. Questions remain, however, regarding the mechanism behind this rise in SCr as well as the long-term renal sequelae of fenofibrate use. An advisory committee meeting has been scheduled for May 29, 2011 to discuss the concomitant use of fenofibrate with a statin.

DMEP asks DCaRP to review the sponsor's submission and several included references to address the following questions:

1. What is the clinical relevance of the creatinine increases with fenofibrate?
 - a. Do the available data provide any insight into likely mechanisms?
 - b. What is the relevance of associated biomarker increases such as cystatin C?
2. Is there evidence of a renoprotective effect of fenofibrate (e.g., improvements in micro- and macroalbuminuria)?
3. Are there any nonclinical or clinical studies that you recommend be conducted to better assess fenofibrate's effect on renal function?

Executive Summary, Answers to Questions and Recommendations

Question #1:

The available data do not provide unequivocal evidence into the mechanism(s) of fenofibrate induced SCr elevation. However, the totality of the current data suggests that most consistent and parsimonious explanation of the elevation in SCr with fenofibrate is through a hemodynamic effect.

Short¹⁻³ (few weeks) and long^{4,5} (5-7 years) term trials have consistently demonstrated an early, modest increase in mean SCr that is stable over time on fenofibrate treatment but is reversible following discontinuation of treatment. The timing, magnitude, reversibility of the mean rise in SCr with fenofibrate is not consistent with drug mediated nephrotoxicity. With long term exposure, the incidence of ESRD was similar, or even numerically lower, in the fenofibrate as compared to the placebo arms of ACCORD-Lipid and FIELD trials, respectively. Moreover, of the potential novel biomarkers of early renal injury measured in the trials, only plasma cystatin C, also a filtration marker, showed a modest (20%) increase on fenofibrate.

The pattern of change in SCr may be consistent with drug induced increase in SCr production or decrease in clearance by glomerular filtration and/or tubular secretion. However, the hypothesis of increased creatinine production from muscle was not very compelling when the elevation in SCr was only associated with some but not all indices of muscle turnover in occasional subjects. Tubular creatinine secretion remained elevated on fenofibrate and therefore argued against impaired creatinine secretion as a cause of the transient increase in SCr level. Of note, while the measurement of renal indices on fenofibrate showed a trend toward decreased glomerular filtration rate (GFR) and renal plasma flow compared to placebo, the difference did not reach statistical significance. Nonetheless, the magnitude of increase in mean SCr and the number of subjects studied likely limited the ability to detect a corresponding small decrease in GFR or renal hemodynamic. Similarly, the above mentioned increase in plasma cystatin C levels may be consistent with in a small decrease in glomerular filtration rate; however, without concurrent urinary cystatin C levels, alternative causes, increased cystatin C production or decreased catabolism, can not be excluded. Lastly, the reduction in the albumin to creatinine ratio (ACR) on fenofibrate also appears consistent with a hemodynamic etiology.

Of the studies and trials reviewed, only one, single-center, observational case report study⁶ documented delayed and sometimes incomplete recovery of SCr after discontinuing fibrates for acute kidney injury, and raised concern about potential renal injury with long term (months) fibrate use. However, these findings appear inconsistent with those seen in the much larger (over

7000 subjects for 5-7 years) safety experience in randomized controlled trials. The interpretation of the findings in the case series is limited by the difficulties in ascertaining the causality of acute renal failure (in the presence of concomitant medications¹), the appropriateness of renal dose adjustment², and relationship of drug exposure to severity of SCr increase from this observational study.

In addition to the findings in the included literature outlined above, the animal studies conducted to support the marketing of Tricor or Trilipix reportedly did not show increases in SCr levels or concerning renal histopathological findings at clinically relevant doses. Moreover, published studies suggest that several members of the fibrate class, including fenofibrate, impair the generation of vasodilatory prostaglandins, probably via the activation of PPARs, which can downregulate the expression of the inducible COX-2 enzyme¹¹, and hence provide a possible mechanism for a hemodynamic effect.

Question #2:

There is no compelling finding of renal protection in FIELD and ACCORD. Though an on-treatment reduction in micro- and macro-albuminuria was seen in the fenofibrate arm in these trials, following the wash-out phase in FIELD, this effect disappeared. The reversible reduction in albuminuria on fenofibrate is consistent with a hemodynamic etiology.

Question #3:

Based on the review of the included medical literature, from a safety standpoint, we believe that no further studies are needed to assess fenofibrate's effect on renal function.

Review Findings of the Included References:

The DMEP consult request contains several published studies exploring fenofibrate's effects on SCr as well as an analysis of fenofibrate's effects on SCr, estimated glomerular filtration rate and albuminuria in the ACCORD LIPID and FIELD studies. The findings are reviewed below.

Published literature submitted for review:

Two small, short-terms trials (Hottelart 1999 and 2002³, Ansquer 2008¹) have explored the effects of fenofibrate on SCr levels. In all of these studies, the rise in creatinine was seen shortly after the initiation of therapy but is reversible following discontinuation of treatment.

- Hottelart 1999 and 2002 reported two parts of essentially the same trial design: an open-label uncontrolled trial with a 2-week on-therapy phase and a 2-week wash-out phase that assessed the effects of fenofibrate on electrolytes, liver and muscle enzymes, and/or

¹ If fenofibrate mediates SCr elevation via decrease renal perfusion, its concomitant use in the presence of drugs that also alter renal hemodynamics may influence rate of SCr elevation in vulnerable patients (e.g. those dependent on renal autoregulation for renal perfusion and/or prone to volume depletion).

² Fenofibrate is primarily excreted in the urine and according to the label, "dose reduction is required in patients with mild to moderate renal impairment and usage should be avoided in patients with severe renal impairment due to increased exposure, and dose selection for the elderly should be made on the basis of renal function".

measured renal function parameters. The trial enrolled subjects with normal renal function or moderate renal insufficiency previously treated with fenofibrate. Above mentioned laboratory values were obtained during the 2-week on-therapy phase and at the end of the 2-week wash out period. The dose of fenofibrate was adjusted to 200 mg every 2 days for creatinine clearance lower than 40 mL/min.

In this trial, subjects developed increased SCr and blood urea nitrogen (BUN) after two weeks of fenofibrate therapy without any detectable change in renal plasma flow and glomerular filtration rate. The mean percent increase in SCr was 15% (Table 1). An increase in SCr of at least 5% increase was observed in 23 (88%) patients, and an increase of at least 10% was present in 18 (62%) patients. Measured creatinine clearance (n=26), glomerular filtration rate (inulin clearance, n=13), renal plasma blood flow (para-aminohippurate [PAH] clearance, n=13) did not decrease in this trial. The observed increase in SCr was associated with a parallel increase in urinary creatinine excretion, arguing against an effect of fenofibrate on creatinine tubular secretion. Both Jaffe reaction colorimetric and high-performance liquid chromatography methods gave similar SCr values and therefore made it unlikely that the SCr increase was related to interference of fenofibrate or one of its metabolite with the colorimetric assay.

Table 1. Effect of fenofibrate on lipidic, renal, hepatic and muscular parameters

	First study (n = 13)*			2nd study (n = 13)			All patients (n = 26)		
	control	fenofibrate	p	control	fenofibrate	p	control	fenofibrate	p
Total cholesterol, mmol/l	6.4±0.3	5.3±0.2	0.0004	6.9±0.3	5.2±0.2	<0.0001	6.7±0.2	5.3±0.1	<0.0001
HDL cholesterol, mmol/l	1.2±0.1	1.2±0.1	n.s.	1.3±0.1	1.4±0.1	n.s.	1.2±0.1	1.3±0.1	n.s.
Triglycerides, mmol/l	1.9±0.3	1.4±0.2	0.009	1.9±0.2	1.0±0.1	<0.0001	1.9±0.2	1.2±0.1	<0.0001
p creatinine, µmol/l	147±12	170±15	0.014	132±11	150±13	<0.0001	139±8	160±10	<0.0001
p urea, mmol/l	10.4±1.3	11.8±1.3	0.03	8.9±1.2	9.8±1	0.002	9.6±0.9	10.8±0.8	0.006
p uric acid, mmol/l	454±30	370±20	0.03	408±29	290±22	<0.0001	427±21	327±17	<0.0001
Creatininuria, mmol/day	13.7±1.5	15.4±1.3	0.03	11.8±1.1	12.9±1	0.01	12.7±0.9	14.2±0.9	0.001
Urinary sodium, mmol/day	141±10	149±9	n.s.	169±21	156±19	n.s.	156±12	153±11	n.s.
Urinary urea, mmol/day	390±54	424±40	n.s.	422±32	433±38	n.s.	407±27	429±27	n.s.
Creatinine clearance, ml/min	69±8	68±8	n.s.	67±8	66±8	n.s.	68±6	67±6	n.s.
PAH clearance, ml/min	304±56	312±49	n.s.	-	-	-	-	-	-
Inulin clearance, ml/min	51.7±6	52.3±7	n.s.	-	-	-	-	-	-
AST, IU/l	-	-	-	23±0.9	30±3.3	0.034	-	-	-
GPT, IU/l	-	-	-	28±2.6	28±2.8	n.s.	-	-	-
CPK, IU/l	-	-	-	87±8	236±99	n.s.	-	-	-
LDH, IU/l	-	-	-	415±21	406±20	n.s.	-	-	-
Myoglobin, mg/ml	-	-	-	75±12	102±25	n.s.	-	-	-

* The data of the first arm of the study are reprinted from Hottelart et al, 1999, with permission. Values are mean±/SEM.

The authors use "control" to refer to the pre-baseline levels.

Source: table 1 of Hottelart et al, 2002

In the Hottelart 2002 (second part of the trial) that assessed effects on AST levels, a small (30%, still within normal range) but statistically significant elevation in AST was seen (Table 1). However, the increase was driven largely by two subjects (Table 2) who also developed a significant increase in muscle specific enzymes, CPK and myoglobin. Because the trial detected increases in muscle enzymes, urea, and decrease in uric acid, the authors concluded that fenofibrate might target diverse metabolic cellular pathways and that the increase in SCr likely reflected an increase in creatinine production from muscle. However, in most subjects, SCr increased in the absence of significant increases in the muscle parameters. Moreover,

the observed small increase in BUN would also be consistent with a hemodynamic effect.

Table 2. Detailed muscular, renal and hepatic parameters (Hottelart 2002)

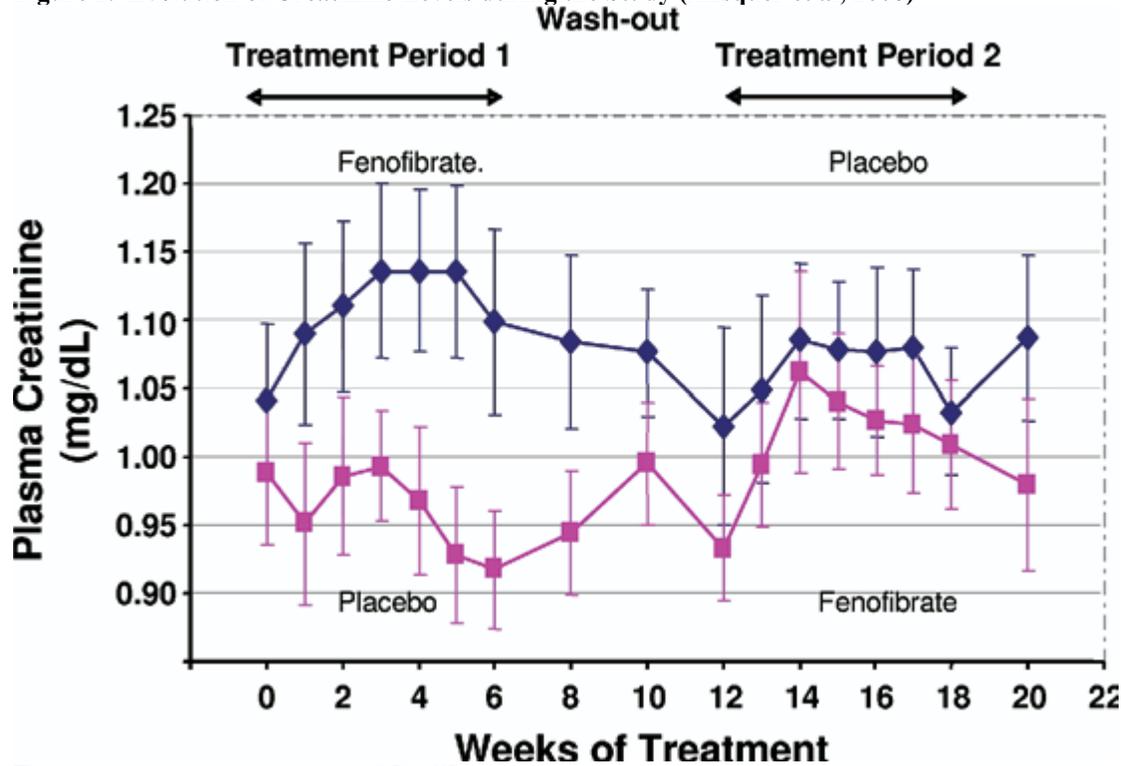
	Patient A		Patient B		Study 2 (patients A and B excluded)		p value
	pre- fenofibrate	post- fenofibrate	pre- fenofibrate	post- fenofibrate	pre- fenofibrate	post- fenofibrate	
Plasma creatinine	175	184	133	146	128 ± 12	148 ± 15	0.0005
AST, IU/l	23	58	26	45	23 ± 1	26 ± 2	0.2
GPT, IU/l	26	37	26	29	28 ± 3	27 ± 3	0.3
CPK, IU/l	95	1,290	109	673	85 ± 9	100 ± 15	0.1
Myoglobin, mg/ml	88	380	40	82	77 ± 13	76 ± 10	0.8
LDH, IU/l	480	553	351	387	415 ± 24	395 ± 20	0.5

Source: table 2 of Hottelart et al, 2002

- Ansquer 2008 trial: This trial was a double-blind, crossover, placebo-controlled trial of 24 “middle-aged” non-diabetic subjects with normal kidney function (estimated creatinine clearance >80 mL/min). Subjects were treated with fenofibrate (160 mg/d tablet) and placebo in two 6-week periods separated by a washout period of 6 weeks. The primary outcome measure was a comparison of the change from pre-treatment baseline in glomerular filtration rate (GFR) measured by inulin clearance between the two treatments groups: no decrease in GFR with fenofibrate was concluded if the lower limit of the 95% confidence interval (CI) of the mean difference between fenofibrate and placebo treatments was not greater than 20% of the pre-treatment baseline value. Secondary outcomes included effective renal plasma flow measured by means of PAH clearance, creatinine clearance, creatinine secretion (ratio of creatinine to inulin clearance), serum cystatin C, uric acid, and urinary excretion of creatinine. Markers of glomerular and tubular damage were evaluated by using albumin and retinol-binding protein (RBP) levels and *N*-acetyl-β-D-glucosaminidase (NAG) activity.

In this trial, the mean increase in SCr was small (mean 0.11 mg/dL, 15%), (see Figure 1) and levels started to plateau by 2-3 weeks on treatment. During the 6-week washout phase, SCr largely returned to pre-treatment levels. The changes in SCr observed in the placebo phase showed the level of variability/ noise in SCr measurements.

Figure 1. Evolution of Creatinine Levels during the Study (Ansquer et al, 2008)



The error bars indicate “mean +/- 95% CI”
 Source: Figure 2 of Ansquer et al, 2008

In this trial, slightly larger (n=24) than the 1999 Hottelart study which also assessed effects on measured GFR (n=13), a numerical (but not statistically significant) decrease in measured GFR and renal plasma flow was observed during fenofibrate therapy (see Table 3). Tubular creatinine secretion [assessed by the (urinary [U]/plasma [P] creatinine)/ (U/P inulin)] was not changed.

Table 3: Effect of 6 weeks of Fenofibrate Treatment on Glomerular Filtration Rate, Associated Markers, and Kidney Hemodynamic Markers in Subjects with Normal Kidney Function

	Placebo			Fenofibrate			Treatment Difference on End Point Values Estimate* (95% CI)
	Baseline	After Treatment	Change (%)	Baseline	After Treatment	Change (%)	
Inulin clearance (mL/min)	114.5 ± 18.8 (113.2)	116.1 ± 16.0 (116.4)	2 ± 10 (1)	115.5 ± 16.8 (112.1)	110.5 ± 19.6 (111.6)	-2 ± 9.0 (-4)	0.8 (-10.5 to 12.2)
PAH clearance (mL/min)	445 ± 74 (450)	477 ± 92 (469)	7 ± 14 (6)	469 ± 116 (407)	423 ± 96† (386)	-9 ± 16 (-4)	-33 (-66 to -1)‡
Plasma creatinine (mg/dL)	0.85 ± 0.12 (0.84)	0.83 ± 0.11 (0.84)	-1 ± 8 (-2)	0.84 ± 0.11 (0.82)	0.93 ± 0.13†§ (0.88)	9 ± 8 (9)	0.11 (0.05 to 0.18)§
Creatinine clearance (mL/min)	133.2 ± 19.4 (135.6)	136.8 ± 19.3 (136.2)	3 ± 10 (3)	133.4 ± 22.2 (132.7)	126 ± 20.5 (126.7)	-3 ± 9 (-6)	-9.5 (-14.4 to -4.7)
(U/P creatinine)/ (U/P inulin)	1.22 ± 0.21 (1.16)	1.25 ± 0.28 (1.17)	3 ± 9 (4)	1.19 ± 0.17 (1.18)	1.21 ± 0.24 (1.17)	3 ± 15 (0)	-0.05 (-0.11 to 0.02)
Urinary creatinine (g/24 h)	1.73 ± 0.76 (1.55)	1.43 ± 0.54 (1.27)	-8 ± 40 (-16)	1.45 ± 0.37 (1.45)	1.74 ± 0.78 (1.47)	28 ± 53 (16)	0.37 (-0.13 to 0.88)
Urine collection (L/24 h)	4.7 ± 1.3 (4.8)	4.5 ± 0.9 (4.4)	2 ± 29 (-3)	4.5 ± 1.1 (4.7)	4.4 ± 1.1 (4.4)	1 ± 36 (-2)	-0.1 (-0.5 to 0.3)

Source: table 1 of Ansquer et al, 2008

No changes were seen in potential biomarkers of renal injury, namely urinary albumin, retinol-binding protein (RBP) levels and N-acetyl-β-D-glucosaminidase (NAG) activity. Plasma cystatin

C, a filtration marker, increased 20% during therapy with fenofibrate (Table 3), suggesting a possible effect on GFR.

Table 4. Effects of 6 weeks of Fenofibrate Treatment on Tubular Function and Other Urinary Tests in Subjects with Normal Kidney Function.

	Placebo			Fenofibrate			Treatment Difference on
	Baseline	After Treatment	Change (%)	Baseline	After Treatment	Change (%)	End Point Values
Plasma cystatin C (mg/L)	0.85 ± 0.28 (0.85)	0.90 ± 0.20 (0.88)	20 ± 56 (5)	0.75 ± 0.22 (0.72)	0.94 ± 0.19†† (0.97)	34 ± 49 (20)	0.18 (0.03 to 0.34)‡
Serum uric acid (mg/dL)	5.7 ± 1.6 (5.9)	5.4 ± 1.3 (5.5)	-3 ± 15 (0)	5.6 ± 1.3 (5.7)	4.8 ± 1.4§ (4.5)	-14 ± 14 (-14)	-0.7 (-1.2 to -0.3)
Urinary albumin (mg/24 h)	12.9 ± 26.8 (6.4)	4.3 ± 6.5 (2.5)	-41 ± 100 (-62)	6.3 ± 6.8 (5.2)	3.0 ± 3.6 (2.6)	9 ± 125 (-44)	0.06 (-1.8 to 1.9)
Urinary RBP (mg/L)	0.12 ± 0.09 (0.10)	0.14 ± 0.14 (0.10)	102 ± 229 (17)	0.16 ± 0.18 (0.07)	0.13 ± 0.19 (0.10)	82 ± 313 (-38)	-0.74 (-7.02 to 5.54)
Urinary NAG# (μmol/h/ mmol creatinine)	20.0 ± 10.6 (15.9)	17.6 ± 7.5 (16.0)	5 ± 65 (-3)	18.3 ± 6.6 (18.8)	37.5 ± 24.6† (28.0)	122 ± 143 (82)	20.0 (9.3 to 30.7)
Urinary uric acid (g/24 h)	0.65 ± 0.27 (0.61)	0.54 ± 0.20 (0.49)	-8 ± 38 (-15)	0.58 ± 0.14 (0.53)	0.64 ± 0.35 (0.53)	15 ± 55 (-4)	0.14 (-0.05 to 0.33)
Sodium fractional excretion (%)	0.86 ± 0.21 (0.85)	0.93 ± 0.36 (0.87)	14 ± 52 (9)	0.91 ± 0.27 (0.89)	0.95 ± 0.22†† (0.92)	10 ± 35 (9)	0.25 (0.04 to 0.47)‡

Source: table 2 of Ansquer et al, 2008

Reviewer's comments:

Cystatin C, a low molecular weight protein, is thought to be largely produced by all nucleated cells at a constant rate and filtered freely by the kidney. Therefore, serum cystatin C has been proposed as a novel marker for GFR. If the current thinking holds true, the difference in the change from baseline by 20% in the cystatin C values between fenofibrate versus placebo arms may represent a small decrease in GFR. However, recent epidemiologic studies^{7,8} have suggested that factors other than GFR (including biomarkers of inflammation, smoking) may influence Cystatin C production and/or catabolism and limit the interpretation of a serum level as a measure of the change in GFR for a given subject. The addition of urinary cystatin C levels may help differentiate early, mild renal injury versus renal hemodynamic changes.

In addition to the above mentioned short-term trials, the consult request contained a single-center case series of 13 patients who developed acute renal failure between 2006 and 2008 following fibrate use (Polanco et al, 2009⁶). According to the publication, the following criteria were used to retrospectively identify potential case: the temporal relationship between fibrate use and a rise of greater than 20% in SCr, improvement of SCr upon fibrates suspension, and a “reasonable” exclusion of alternative causes of acute renal failure. However, nine subjects were concomitantly treated with renin-angiotensin system blocking agents.

Of these thirteen patients (mean age 65.5 ± 12.2 years), ten developed acute renal injury after receiving fenofibrate (other fibrates implicated were bezafibrate and gemfibrozil). Of the 13 patients whom received the fibrates, the onset of acute renal failure was delayed, with average time to diagnosis of 6.7 ± 5.8 months following initiation of therapy. The maximum on-treatment SCr was 2.22±0.49 mg/dL, which was increased from that of the pre-fibrate SCr levels 1.33±0.36 mg/dL (p<0.05). The average percent increase in SCr was 74.6±55.8%, with higher increase in SCr levels (up to 60%) seen in renal transplant patients. However, none of the patients required renal replacement therapy. After discontinuation of fibrate therapy, the improvement of renal function was delayed, an average of 3.8 ± 3.5 months. The average SCr fell to 1.45 ± 0.49 mg/dL. Four patients (31%) did not completely recover their pre-fibrate SCr level. Reversibility of fibrate induced renal injury appeared to be associated with the duration of fibrate therapy. The magnitude of SCr elevation, delayed and incomplete recovery raise concern

for fibrate induced renal injury with more prolonged use of fibrates, but renal biopsies performed in two of the thirteen patients identified no histologic “alterations”.

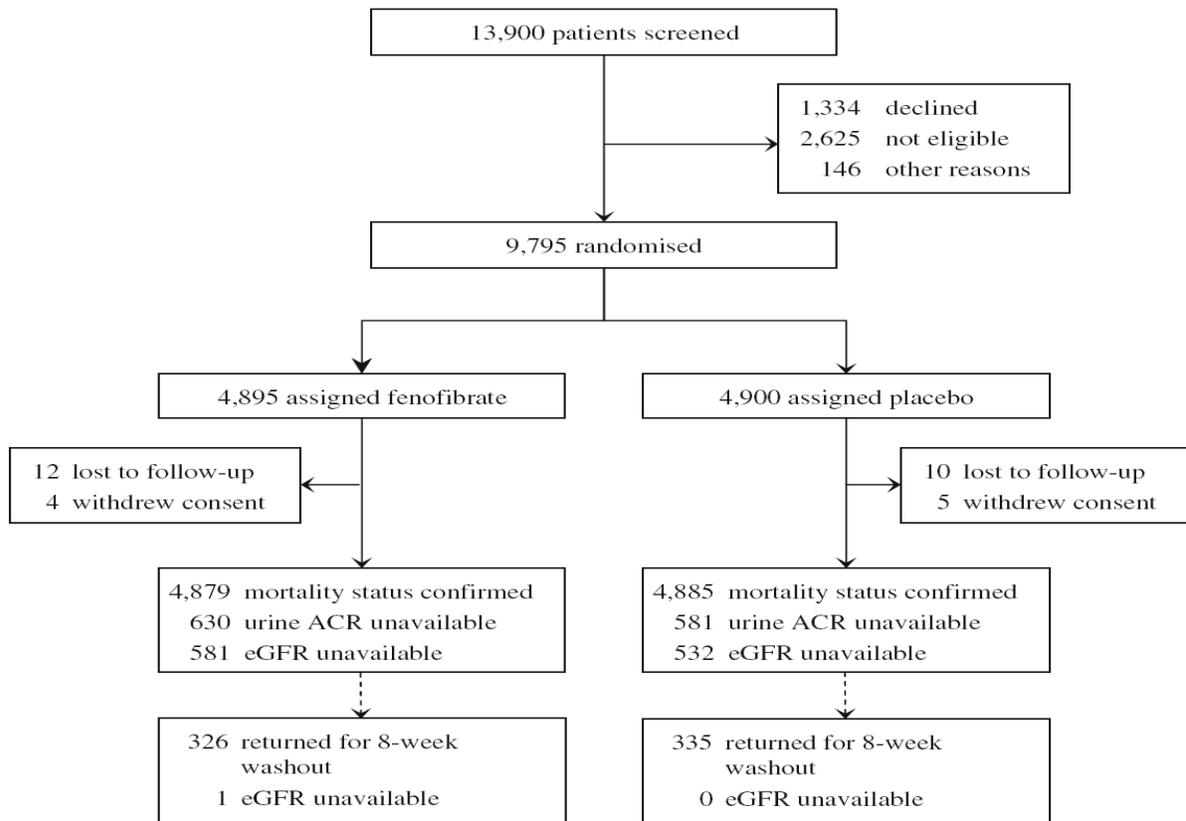
FIELD and ACCORD-Lipid Trials:

Two large, long term clinical trials, Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study and Action of Control Cardiovascular Risk in Diabetes – Lipid (ACCORD-Lipid) provide data that speak to the renal sequelae of long term exposure to fenofibrate. In these trials a total of 7,660 patients with type 2 diabetes mellitus were treated with fenofibrate for 5 to 7 years. The findings suggest that long-term use of fenofibrate in this population does not cause renal damage in the studied population.

The FIELD trial randomized 9,795 subjects with type 2 diabetes not previously treated with lipid-lowering agents to fenofibrate or placebo. The primary endpoint was coronary events after 5 years of randomized treatment. Pre-specified renal endpoints were: (1) renal function changes; (2) urinary albumin: creatinine ratio (ACR) changes; and (3) end-stage renal disease, defined as plasma creatinine >400 $\mu\text{mol/L}$ (or 4.5 mg/dL), dialysis, transplant or renal disease death. The trial included a run-in phase in which all subjects received fenofibrate. Effects on SCr following drug withdrawal were also obtained in a subset of subjects enrolled in a FIELD-washout substudy. The published report by Davis et al. (described below) provides results for both FIELD and the FIELD-washout substudy. Furthermore, a publication by Forsblom et al 2010⁹, describes the results FIELD (including the washout subset) at a single site (Helsinki). Reported in the Helsinki substudy, and presumably also reflective of the FIELD trial design overall, laboratory parameters were measured at baseline, 2- and 5-years of treatment. Serum, plasma, and urine creatinine were measured using the Jaffe method and later using an enzymatic method. Samples were randomly selected to perform parallel analyses with the Jaffe and enzymatic methods. The estimated GFR was calculated by the 4-variable Modification of Diet in Renal Disease equation (referred to as GFR-MDRD), and creatinine clearance by Cockcroft and Gault with additional normalized to body surface area by the DuBois formula (referred to as GFR-CG). The albumin creatinine ratio was determined from the spot samples. Cystatin C (not specified whether from serum, plasma or urine samples, presumably from serum or plasma) was also measured.

An overview of the FIELD trial is shown below (Figure 2)

Figure 2. An overview of the FIELD Trial



Source: Figure 1 of Davis et al, 2011.

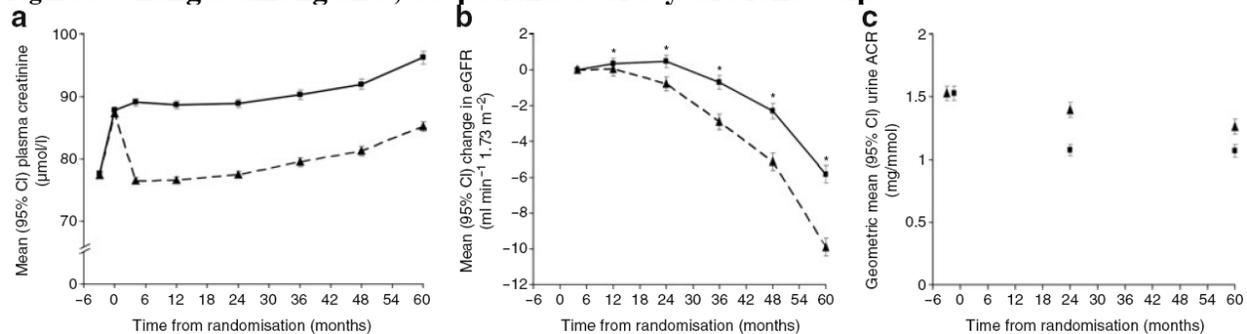
In FIELD, the randomized groups were well-matched (Table 5), and on average slightly younger than in the small case series of acute renal injury reported by Polanco 2009. The percentage of subjects on concomitant ACEI or ARB in the FIELD trial is lower than that reported in the case series. The baseline characteristics in FIELD withdrawal sub-study (n=661) were also similar to that of FIELD (Table 12, Appendix).

Table 5. Baseline Characteristics of All Patients the FIELD Trial by Treatment

Characteristic	Treatment	
	Placebo	Fenofibrate
<i>n</i>	4,900	4,895
General		
Male, <i>n</i> (%)	3,067 (62.6)	3,071 (62.7)
Age at visit 1 (years)	62.23 (6.91)	62.23 (6.83)
Duration of diabetes (years)	5.00 (2.00–10.00)	5.00 (2.00–10.00)
Clinical history		
Nephropathy, <i>n</i> (%) ^a	135 (2.8)	144 (2.9)
Laboratory data		
LDL-cholesterol (mmol/l)	3.07 (0.66)	3.07 (0.64)
HDL-cholesterol (mmol/l)	1.10 (0.26)	1.10 (0.26)
Triacylglycerol (mmol/l)	1.73 (1.34–2.30)	1.74 (1.35–2.34)
Marked dyslipidaemia, <i>n</i> (%) ^b	970 (19.8)	1,044 (21.3)
HbA _{1c} (%)	6.85 (6.10–7.75)	6.85 (6.05–7.80)
Plasma creatinine (μmol/l)	77.40 (15.66)	77.73 (15.91)
Urine ACR (mg/mmol)	1.10 (0.60–2.90)	1.15 (0.60–3.00)
Normoalbuminuria, <i>n</i> (%)	3,643 (74.5)	3,617 (74.1)
Microalbuminuria, <i>n</i> (%)	1,040 (21.3)	1,064 (21.8)
Macroalbuminuria, <i>n</i> (%)	204 (4.2)	200 (4.1)
eGFR (ml min ⁻¹ 1.73 m ⁻²)	87.8 (18.3)	87.6 (18.5)
eGFR <60, <i>n</i> (%)	224 (4.6)	295 (6.0)
eGFR 60–<90, <i>n</i> (%)	2,657 (54.2)	2,561 (52.3)
eGFR ≥90, <i>n</i> (%)	2,019 (41.2)	2,039 (41.7)
Medication		
ACE inhibitor, <i>n</i> (%)	1,653 (33.7)	1,628 (33.3)
ARB, <i>n</i> (%)	253 (5.2)	269 (5.5)
Any insulin, <i>n</i> (%) ^c	672 (13.7)	674 (13.8)

Source: Table 1 of Davis et al, 2011.

The changes among all 9,795 subjects over 5 years of follow-up in (a) plasma creatinine, (b) estimated GFR and (c) ACR in the fenofibrate (square) and placebo (triangles) groups are shown below (Figure 3). As illustrated below (Figure 3a), in the placebo group, the mean SCr quickly came down following the 6-week fenofibrate run-in phase. An increase in mean SCr values was evident in the fenofibrate arm by 6 months (presumably the first time point measured) after which SCr values appeared to stabilize. Values were ~ 10 to 12 μmol/L (0.11 to 0.14 mg/dL) higher compared to the placebo arm throughout the 5 years of treatment (Figure 3b). Moreover, no increase in albuminuria was seen with fenofibrate; in fact by the year-two on-treatment measurement, there was a small reduction in the ACR in the fenofibrate compared to the placebo arm (Figure 3c).

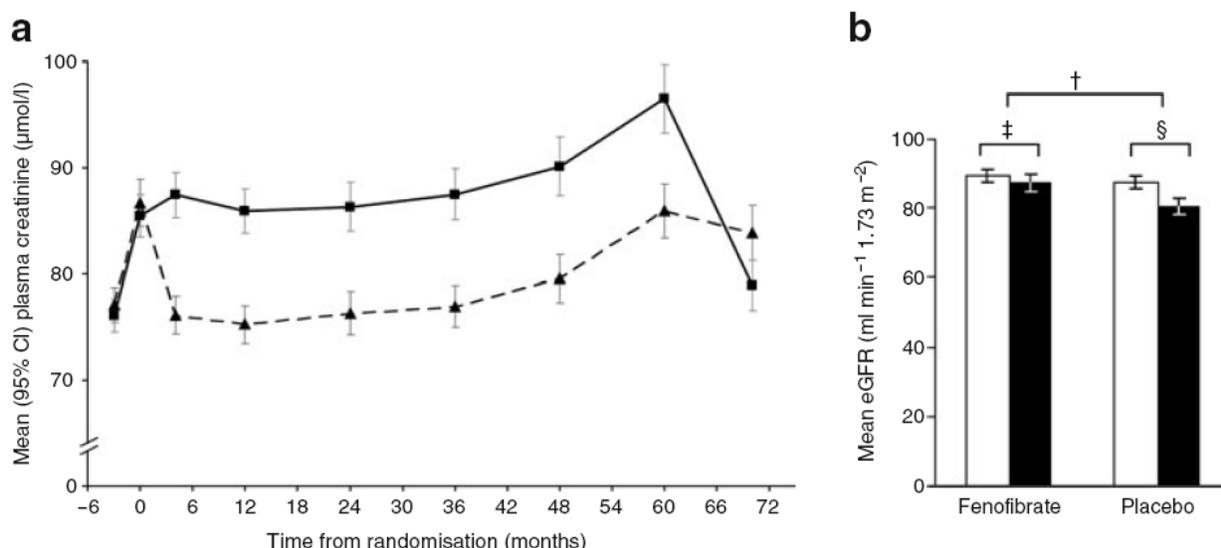
Figure 3. changes among all 9,795 patients over 5 years follow-up

Changes among all 9,795 patients over 5 years follow-up in (a) plasma creatinine, (b) estimated GFR and (c) ACR in the fenofibrate (squares) and placebo (triangles) groups. Changes are shown from screening for plasma creatinine and urinary ACR, and from 4 months for estimated GFR.

Source: Figure 2 of Davis et al, 2011.

Eight weeks after the withdrawing the treatment in the FIELD washout subset, the mean SCr significantly decreased in the fenofibrate treated arm (see Figure 4a). The exact values were not reported, but the 95% CI of the after wash-out values appeared to overlap between the two arms (Figure 4a). For an unclear reason, the SCr in the placebo arm also trended lower after withdrawal. After 8-week of wash-out, the decrease from baseline in estimated GFR was apparently less (-1.9 ml/min/1.73 m², from 89.2 to 87.3; p=0.07) in the fenofibrate group as compared to the placebo group (-6.9 ml/min/1.73 m², p<0.001).

Figure 4. Change among the 661 FIELD participants in the washout sub-study from “baseline” to 8 weeks after study close.



Changes among 661 participants in the washout substudy from baseline to 8 weeks after study close for (a) mean plasma creatinine in the fenofibrate group (continuous line) and placebo group (dashed line), and (b) for estimated GFR at baseline (white) and after washout (black). Values are mean (95% CI); †p=0.0003; ‡p=0.065; §p<0.0001

Source: Figure 3 of Davis et al, 2011.

In terms of incidence of renal events, the doubling of SCr, but not “ESRD”, was higher in fenofibrate as compared to placebo group (see Table 6).

Table 6. The Incidence of Renal Events by Treatment Group in FIELD

Variable	Placebo		Fenofibrate		Total	
	<i>n</i> ^a	%	<i>n</i> ^a	%	<i>n</i> ^a	%
Participants	4,900	100	4,895	100	9,795	100
Event						
Plasma creatinine >400 µmol/l	3	(0.1)	6	(0.1)	9	(0.1)
Renal replacement therapy	21	(0.4)	16	(0.3)	37	(0.4)
Renal transplant	0	(0.0)	0	(0.0)	0	(0.0)
Death from renal disease	4	(0.1)	1	(0.0)	5	(0.1)
Total patients with ESRD	26	(0.5)	21	(0.4)	47	(0.5)
Doubling of serum creatinine	90	(1.8)	148	(3.0)	238	(2.4)
Doubling of serum creatinine or ESRD ^{b,c}	103	(2.1)	152	(3.1)	255	(2.6)
Doubling of serum creatinine or ESRD ^{b,d}	105	(2.1)	152	(3.1)	257	(2.6)

ESRD, end-stage renal disease

^aCategories not mutually exclusive

^bPost hoc composite renal endpoints for comparison with other studies

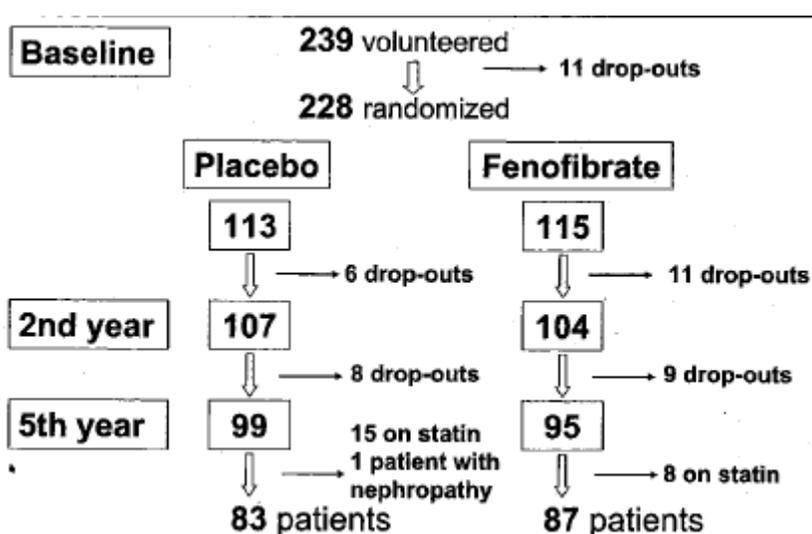
^cExcluding renal deaths

^dIncluding renal deaths

source: table 2 of Davis et al, 2011.

As previously noted, Forsblom 2010 describes the findings from FIELD and the washout phase at the Helsinki center. The baseline characteristics of subjects in this subset were reportedly similar to those in the larger FIELD trial. An overview of the disposition of subjects at this single center is shown below.

Figure 5. FIELD Helsinki Renal Substudy



Source: Figure 1 of Forsblom et al, 2010

While plasma creatinine increased during therapy in the fenofibrate but not placebo treatment arm ($p < 0.001$), no statistically significant difference was seen in urine creatinine levels between the two treatment arms (Figure 6). Thus, measured creatinine clearance trended downward in the fenofibrate compared to placebo treatment arm ($\Delta\Delta$, -1.78 mL/min/year). In addition, there was a statistically significant decrease in estimated renal function by CG ($\Delta\Delta$, -2.7 mL/min/ 1.73 m²/year) and MDRD ($\Delta\Delta$, -2.5 mL/min/ 1.73 m²/year) in the fenofibrate treatment group compared to the placebo as expected based on the reported changes in plasma creatinine values.

Figure 6. Creatinine levels and estimated renal function at baseline and on treatment in the FIELD-Helsinki substudy.

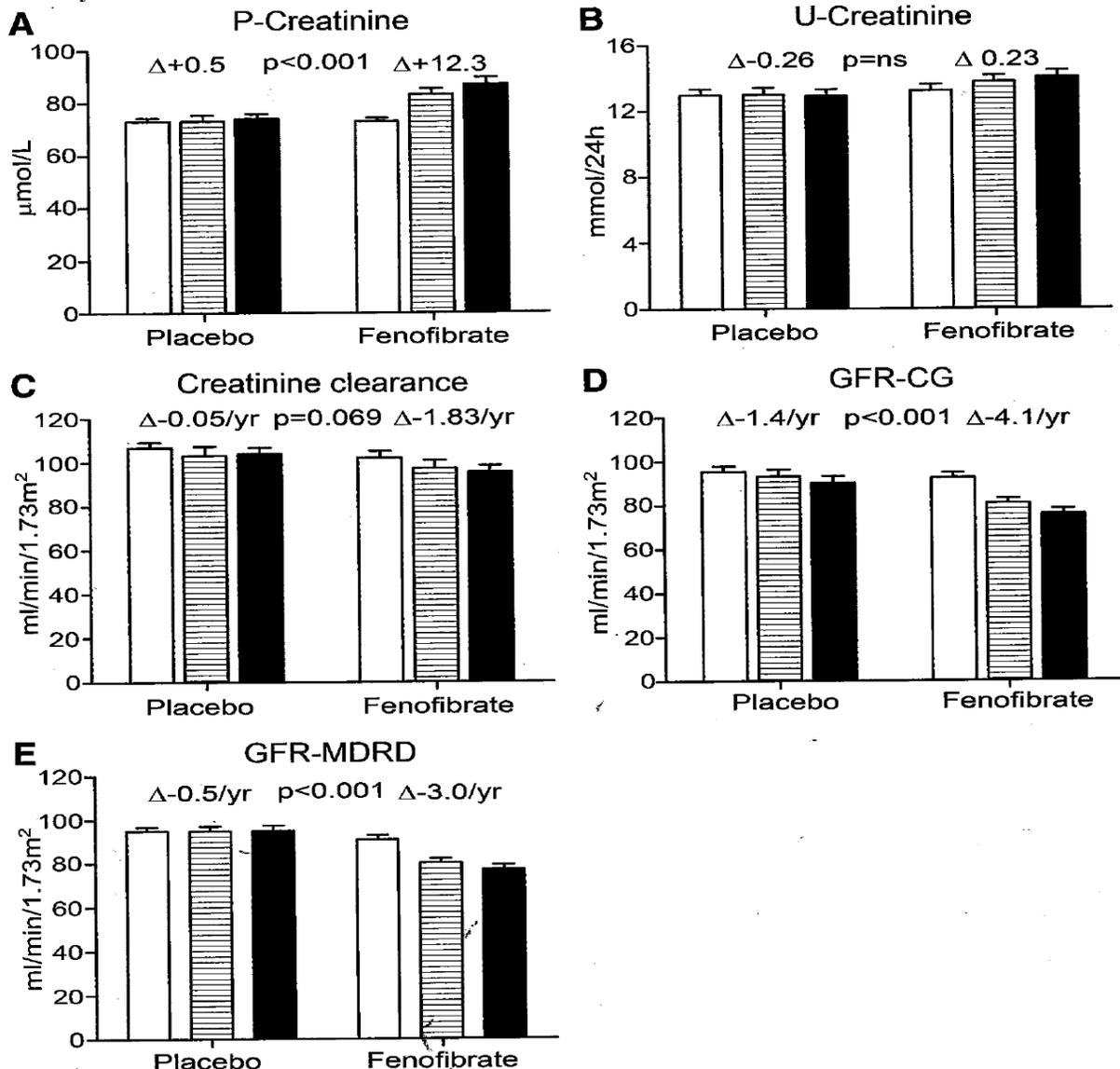


Figure 2: Creatinine levels in plasma (P-creatinine) and urine (U-creatinine) and markers of renal function during the study in placebo and fenofibrate groups. Clear box=baseline; striped box=2nd year; solid black box= 5th-year data (median). The change (Δ) during the study is expressed as total change for P- and U-creatinine and as annual change for the markers of renal function. These changes have been compared with the Mann-Whitney U test.

Source: Figure 2 of Forsblom et al, 2010

In concert with the increase in plasma creatinine in the Helsinki subset, cystatin C (Table 7) increased by 14.1% during fenofibrate treatment as compared with a 3.6% increase in the placebo group ($p < 0.001$). The on-therapy (measurements at close-out) albumin excretion rate (AER), 24-h urine protein and ACR were similar in the two treatment arms, in contrast to the reduction in albuminuria in the overall FIELD trial (see later discussion in appendix Table 13).

Table 7. Markers of albuminuria and renal function at baseline and at the 5th year (FIELD-Helsinki)

	Placebo		Fenofibrate		P§
	Baseline	5th year	Baseline	5th year	
n	83	83	87	87	
P-creatinine ($\mu\text{mol/l}$)	73 (66–78)	75 (63–85) ‡	73 (68–85)	87 (75–101)*	<0.001
U-creatinine (mmol/24 h)	13.0 (10.8–15.5)	12.9 (10.0–15.5)	13.2 (10.8–15.6)	14.0 (10.0–16.4)	NS
Creatinine clearance (ml/min per 1.73 m ²)	108 (95–119)	104 (89–127)	102 (87–118)	95 (77–112)*	0.027
eGFR-CG (ml/min per 1.73 m ²)	95 (83–109)	90 (75–108)	93 (80–104)	76 (59–89)*	<0.001
eGFR-MDRD (ml/min per 1.73 m ²)	95 ± 15	95 ± 23	91 ± 16	78 ± 20*	<0.001
Cystatin C (mg/l)	0.85 ± 0.13*	0.91 ± 0.17	0.92 ± 0.17	1.05 ± 0.25*	<0.001
AER ($\mu\text{g/min}$)	6.5 (5–11)	4 (2–11)‡	6 (4–12)	4 (2–13)	NS
dU-Prot (mg/day)	105 (82–190)	100 (70–150)	123 (78–184)	110 (73–190)	NS
ACR (mg/mmol)	1.0 (0.7–2.3)	1.1 (0.4–2.9)	1.1 (0.6–2.8)	1.0 (0.0–3.3)	NS
CPK (u/l)	92 (61–134)	98 (70–150)	84 (60–133)	84 (55–115)	0.05

Data are means ± SD or median (interquartile range). Between baseline and 5th year within each group, P values with Wilcoxon signed-rank test for two related variables. *P < 0.001, †P < 0.05, §P value from the repeated-measures ANOVA, except for AER for which Mann-Whitney U test was used to compare relative changes from baseline to 5th year between the groups. CG, Cockcroft-Gault; CPK, creatine phosphokinase; dU-Prot, 24-h urine protein excretion; P-creatinine, plasma creatinine; U-creatinine, urine creatinine.

Source: table 2 of Forsblom et al, 2010

ACCORD was a randomized, controlled trial of 10,251 subjects with type 2 diabetes who were at high risk for CVD events because of existing CVD or additional risk factors. The ACCORD-Lipid trial randomized a subgroup of subjects (n=5,518) to treatment with either fenofibrate alone or in combination with simvastatin for 7 years. The primary end point was the composite of nonfatal MI, nonfatal stroke, or CVD death. The trial excluded subjects with SCr > 1.5 mg/dL obtained within the previous 2 months. SCr and urinary ACR were obtained at baseline, every 1-2 years, and at the end of the trial¹⁰. There was no pre-specified renal endpoint in ACCORD-Lipid. However, in the entire ACCORD population, fatal or nonfatal renal failure, defined as initiation of dialysis or ESRD, or renal transplantation, or rise of SCr >3.3 mg/dL in the absence of an acute reversible cause, were assessed every 4 months as part of a composite secondary endpoint.

The baseline characteristics of the subjects in FIELD and Action of Control Cardiovascular Risk in Diabetes – Lipid (ACCORD-Lipid) submitted by Abbott are shown in Table 8. The mean SCr values were 81 $\mu\text{mol/L}$ (0.92 mg/dL) and 77 $\mu\text{mol/L}$ (0.87 mg/dL) in ACCORD-Lipid and FIELD, respectively (Table 8). Based on MDRD estimates of GFR, only small percentage (2.5% or 6.1%) of the subjects had moderate degree renal impairment (eGFR 30-49 mL/min/1.73 m²). Compared to the Polanco case series, the means of both SCr and age were lower in the two long-term clinical trials, implying a higher mean baseline renal function.

Table 8. Main Baseline Characteristics by Randomized Treatment Groups in ACCORD Lipid and FIELD

	ACCORD lipid		FIELD	
	Fenofibrate + Simvastatin n=2765	Simvastatin Monotherapy n=2753	Fenofibrate n=4895	Placebo n=4900
Age (year)	62.2 (6.7)	62.3 (6.7)	62.2 (6.8)	62.2 (6.9)
Gender				
Men	1914 (69.2%)	1910 (69.4%)	3071 (62.7%)	3067 (62.6%)
Women	851 (30.8%)	843 (30.6%)	1824 (37.3%)	1833 (37.4%)
Prior cardiovascular disease	1008 (36.5%)	1008 (36.5)	1068 (21.8%)	1063 (21.7%)
Current smoker	410 (14.8%)	393 (14.3%)	462 (9.4%)	460 (9.4%)
BMI (kg/m ²)	32.2 (5.4)	32.4 (5.4)	30.7 (5.6)	30.6 (5.5)
Duration of diabetes ^a (year)	10 (5-15)	9 (5-15)	5 (2-10)	5 (2-10)
Glycated hemoglobin ^a (%)	8.1 (7.6-8.8)	8.1 (7.5-8.8)	6.9 (6.1-7.8)	6.9 (6.1-7.8)
Blood pressure (mmHg)	134 (18)/74 (11)	134 (18)/ 74 (11)	140 (15)/ 82 (9)	141 (15)/82 (9)
Creatinine (µmol/L)	81.3	81.3	77.7 (15.9)	77.4 (15.7)
- Men	86.6	86.6	83.6 (14.1)	83.4 (13.9)
- Women	69.0	70.7	67.9 (13.8)	67.4 (13.2)
eGFR ^b (ml/min/1.73m ²)	30-49: 71 (2.6%) >50: 2668 (97.4%)	30-49: 70 (2.5%) >50: 2679 (97.5%)	30-59: 299 (6.1%) 60-89 2571 52.5%) ≥90 2025 (41.4%)	30-59: 226 (4.6%) 60-89 2660 54.3%) ≥90 2014 (41.1%)
Albuminuria ^c	NA	NA	Micro 19% Macro 3%	Micro 19% Macro 3%
TC (mmol/L)	4.52 (0.98)	4.54 (0.98)	5.04 (0.69)	5.03 (0.71)
LDL-C (mmol/L)	2.59 (0.79)	2.61 (0.80)	3.07 (0.64)	3.07 (0.66)
HDL-C (mmol/L)	0.98 (0.20)	0.99 (0.20)	1.10 (0.26)	1.10 (0.26)
TG ^a (mmol/L)	1.85 (1.29-2.62)	1.81 (1.26-2.56)	1.74 (1.34-2.34)	1.73 (1.34-2.30)

NA = not available. Data are number (%) or mean (standard deviation) except otherwise mentioned

a. median and interquartile range.

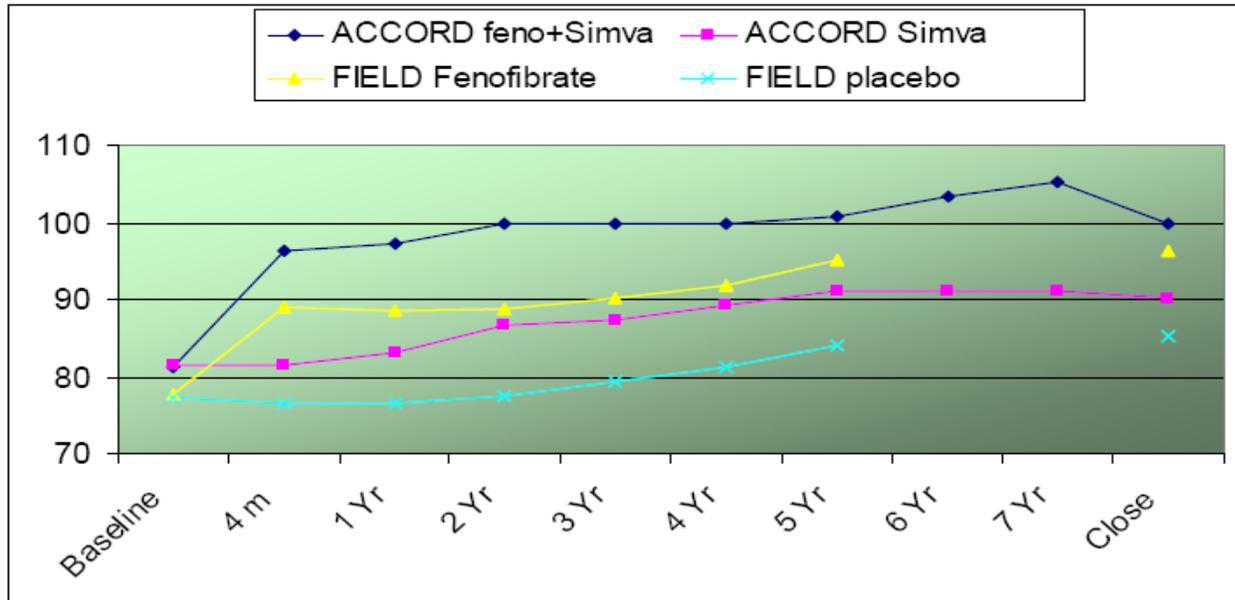
b. using MDRD in FIELD

c. Classification based on average of two UACR

Source: IND 70345 Abbott's submission 202, dated 12/30/2010, table 2.

As illustrated in Figure 7 below, in both two trials, SCr rose following initiation of fenofibrate. In both trials, by about 6 to 8 months after initiation, the rise in SCr began to plateau, and the rate of rise was similar to that observed in the non-fenofibrate treatment arms. In ACCORD-LIPID, although the mean SCr increased with fenofibrate, there was no difference in the incidence of ESRD between treatment arms⁵.

Figure 7. Evolution of creatinine levels in $\mu\text{mol/L}$ during ACCORD Lipid and FIELD overall



Source: IND 70345 Abbott's submission 202, dated 12/30/2010, figure 1.

Of note, in contrast to the close-out for the whole study population, in the FIELD withdrawal sub-study, the mean SCr was lower in the fenofibrate as compared to the placebo groups (Table 9). According to the sponsor, “six to eight weeks after the last study visit, the previous fenofibrate-treated subjects had eGFR 5 mL/min/1.73m² higher than previous placebo-treated subjects”, which the sponsor interpreted to represent “preservation of renal function by 1 mL/min/1.73m² per year.” However, this conclusion was projected based on a modest difference in the mean SCr from a small subgroup of a single trial at one time point. Therefore, the results would need to be replicated to provide assurance of renoprotection.

Table 9. Creatinine level by visit in the overall ACCORD-Lipid and FIELD populations

	Baseline	Randomization	4 months	1 Year	2 Years	3 Years	4 Years	5 Years	6 Years	7 Years	Close-out	Post study
ACCORD												
feno-Simva	N=2625		N=2625	N=2576	N=2487	N=2404	N=2346	N=1466	N=791	N=248	N=2253	
Mean	81.3		96.4	97.2	99.9	99.9	99.9	100.8	103.4	105.2	99.9	
ACCORD Simva	N=2620		N=2620	N=2576	N=2465	N=2363	N=2349	N=1469	N=796	N=240	N=2269	
Mean	81.3		81.3	83.1	86.6	87.5	89.3	91.1	91.1	91.1	90.2	
FIELD Fenofibrate	N=4895	N=4888	N=4815	N=4716	N=4580	N=4446	N=4313	N=1993			N=4250	
Mean (SD)	77.7 (15.9)	87.8 (20.6)	89.1 (22.0)	88.7 (22.6)	88.9 (24.3)	90.3 (27.0)	92.0 (28.9)	95.1 (29.2)			96.3 (33.9)	
FIELD placebo	N=4900	N=4889	N=4835	N=4734	N=4620	N=4473	N=4343	N=1991			N=4303	
Mean (SD)	77.4 (15.7)	87.3 (20.3)	76.6 (17.4)	76.6 (19.3)	77.5 (20.3)	79.5 (25.5)	81.3 (25.5)	84.2 (24.8)			85.2 (26.0)	
FIELD withdrawal sub-study Fenofibrate	N=326	N=325	N=324	N=325	N=322	N=324	N=324	N=189			N=326	N=325
Mean (SD)	76.1 (14.2)	85.5 (18.4)	87.4 (19.9)	85.9 (19.3)	86.3 (21.5)	87.5 (22.3)	90.1 (25.7)	94.1 (28.3)			96.3 (29.8)	78.9 (21.8)
FIELD withdrawal sub-study placebo	N=335	N=335	N=334	N=332	N=332	N=331	N=334	N=190			N=335	N=335
Mean (SD)	77.1 (15.4)	86.7 (20.8)	76.1 (16.5)	75.3 (16.3)	76.3 (19.1)	76.9 (18.2)	79.6 (21.0)	83.2 (21.2)			85.9 (23.8)	83.9 (24.3)

Source: IND 70345 Abbott's submission 202, dated 12/30/2010, table 5.

In ACCORD-Lipid (Table 10) trial, the percentage of subjects with microalbuminuria and macroalbuminuria was slightly lower in the fenofibrate plus simvastatin arm than simvastatin monotherapy. A similar finding was observed in FIELD (Table 13, appendix) using the categorization of albuminuria in contrast to the no difference found in the Helsinki subset when the amount of albuminuria was expressed as a continuous variable (Table 7).

Table 10. Micro- and Macroalbuminuria in ACCORD Lipid

	Fenofibrate + simvastatin (n=2765)	Simvastatin monotherapy (n=2753)	P value
Post-randomization incidence of microalbuminuria (≥ 30 mg/g)*	1050 (38.2%)	1137 (41.6%)	0.01
Post-randomization incidence of macroalbuminuria (≥ 300 mg/g)	289 (10.5%)	337 (12.3%)	0.04

* Urinary albumin/creatinine expressed as mg/g creatinine. Category described as (≥ 30 to <300 mg/g) in ACCORD Lipid publication

Source: IND 70345 Abbott's submission 202, dated 12/30/2010, table 10.

The reduction in ACR was not persistent after discontinuing fenofibrate therapy in the FIELD withdrawal subset and the percent subjects without albuminuria was higher in the placebo compared to the fenofibrate arm following withdrawal of therapy (Table 11).

Table 11. Albuminuria in FIELD withdrawal sub-study

Albuminuria	Fenofibrate n=326	Placebo n=335
Baseline Normal	256 (79.0%)	272 (78.6%)
Micro	57 (17.6%)	53 (15.9%)
Macro	11 (3.4%)	9 (2.7%)
Close -out Normal	271 (83.9%)	257 (78.6%)
Micro	40 (12.4%)	54 (16.5%)
Macro	12 (3.7%)	16 (4.9%)
Post-study Normal	174 (66.2)	202 (74.8%)
Micro	68 (25.9%)	55 (20.4%)
Macro	21 (8.0%)	13 (4.8%)

Source: adapted from IND 70345 Abbott's submission 202, dated 12/30/2010, table 13.

APPENDIX:

Table 12. Baseline Characteristics by Randomized Treatment Groups in FIELD Study and its Withdrawal Sub-study

	FIELD		FIELD withdrawal sub-study	
	Fenofibrate n=4895	Placebo n=4900	Fenofibrate n=326	Placebo n=335
Age (year)	62.2 (6.8)	62.2 (6.8)	61.6 (6.5)	62.2 (6.7)
< > 65				
older	1962 (40.1%)	1993 (40.7%)	120 (36.8%)	129 (36.8%)
younger	2933 (59.9%)	2907 (59.3%)	206 (63.2%)	206 (61.5%)
Gender				
Men	3071 (62.7%)	3071 (62.7%)	204 (62.6%)	206 (60.3%)
Women	1824 (37.3%)	1824 (37.3%)	122 (37.4%)	133 (39.7%)
Prior cardiovascular disease	1068 (21.8%)	1068 (21.8%)	50 (15.3%)	54 (16.1%)
Weight (kg)	88.3 (16.9)	88.0 (16.9)	88.0 (16.5)	87.1 (16.5)
Glycated hemoglobin ^a %	6.9 (6.1-7.8)	6.9 (6.1-7.8)	6.7 (5.9-7.6)	6.8 (6.0-7.7)
Blood pressure mmHg	140 (15)/ 82 (9)	140 (15)/ 82 (9)	138 (14)/ 88 (17)	139 (15)/87 (17)
Creatinine (µmol/L)	77.7 (15.9)	77.7 (15.9)	76.1 (14.2)	77.1 (15.4)
- Men	83.6 (14.1)	83.6 (14.1)		
- Women	67.9 (13.8)	67.9 (13.8)		
eGFR ^b (ml/min/1.73m ²)	87.6 (18.5)	87.8 (18.3)	89.2 (17.4)	87.4 (17.9)
Albuminuria	Micro 19% Macro 3%	Micro 19% Macro 3%	Micro 57 (17.6%) Macro 11 (3.4%)	Micro 53 (15.9%) Macro 9 (2.7%)
TC (mmol/L)	5.04 (0.69)	5.04 (0.69)	4.98 (0.67)	5.00 (0.69)
LDL-C (mmol/L)	3.07 (0.64)	3.07 (0.64)	3.01 (0.62)	3.03 (0.63)
HDL-C (mmol/L)	1.10 (0.26)	1.10 (0.26)	1.09 (0.26)	1.10 (0.26)
TG ^a (mmol/L)	1.74 (1.34-2.34)	1.74 (1.34-2.34)	1.73 (1.37-2.35)	1.77 (1.32-2.28)

NA = not available. Data are number (%) or mean (standard deviation) except otherwise mentioned

a. median and interquartile range.

b. using MDRD

Source: IND 70345 Abbott's submission 202, dated 12/30/2010, table 4.

Table 13. Albuminuria by visit in the FIELD trial, overall, in men and women and in the dyslipidemic population (TG ≥2.3 mmol/l and HDL-C <1.03 in men and <1.29 mmol/L in women)

	Visit 1 ^a	Visit 3 ^b	Baseline	2 years	5 years	Close_out
fenofibrate						
Overall	N=4895	N=4748	N=4881	N=4265	N=1842	N=3936
Normo	3866 (79.0%)	3736 (78.7%)	3800 (77.9%)	3521 (82.6%)	1379 (74.9%)	3132 (79.6%)
Micro	858 (17.5%)	869 (18.3%)	925 (19.0%)	626 (14.7%)	381 (20.7%)	662 (16.8%)
Macro	171 (3.5%)	143 (3.0%)	156 (3.2%) ^c	118 (2.8%)	82 (4.5%)	142 (3.6%)
Men	N=3071	N=2997	N=3065	N=2682	N=1151	N=2445
Normo	2377 (77.4%)	2308 (77.0%)	2347 (76.6%)	2179 (81.2%)	829 (72.0%)	1914 (78.3%)
Micro	576 (18.8%)	589 (19.7%)	614 (20.0%)	421 (15.7%)	264 (22.9%)	437 (17.9%)
Macro	118 (3.8%)	100 (3.3%)	104 (3.4%)	82 (3.1%)	58 (5.0%)	94 (3.8%)
Women	N=1824	N=1751	N=1816	N=1583	N=6919	N=1491
Normo	1489 (80.3%)	1428 (81.6%)	1453 (80.0%)	1342 (84.8%)	550 (79.6%)	1218 (81.7%)
Micro	282 (15.5%)	280 (16.0%)	311 (17.1%)	205 (13.0%)	117 (16.9%)	225 (15.1%)
Macro	53 (2.9%)	43 (2.5%)	52 (2.9%)	36 (2.3%)	24 (3.5%)	48 (3.2%)
Dyslipidemic population	N=1044	N=1013	N=1041	N=897	N=388	N=840
Normo	760 (72.8%)	745 (73.5%)	749 (72.0%)	698 (77.8%)	270 (69.6%)	633 (75.4%)
Micro	230 (22.0%)	221 (21.8%)	247 (23.7%)	161 (17.9%)	92 (23.7%)	161 (19.2%)
Macro	54 (5.2%)	47 (4.6%)	45 (4.3%)	38 (4.2%)	26 (6.7%)	46 (5.5%)
Placebo						
Overall	N=4900	N=4751	N=4883	N=4357	N=1859	N=4045
Normal	3833 (78.2%)	3737 (78.7%)	3801 (77.8%)	3361 (77.1%)	1341 (72.1%)	3081 (76.2%)
Micro	908 (18.5%)	854 (18.0%)	925 (18.9%)	835 (19.2%)	414 (22.3%)	792 (19.6%)
Macro	159 (3.2%)	160 (3.4%)	157 (3.2%)	161 (3.7%)	104 (5.6%)	172 (4.3%)
Men	N=3067	N=2971	N=3056	N=2728	N=1165	N=2508
Normal	2362 (77.0%)	2302 (77.5%)	2347 (76.8%)	2052 (75.2%)	802 (68.8%)	1832 (73.0%)
Micro	599 (19.5%)	557 (18.7%)	602 (19.7%)	565 (20.7%)	292 (25.1%)	555 (22.1%)
Macro	106 (3.5%)	112 (3.8%)	107 (3.5%)	111 (4.1%)	71 (6.1%)	121 (4.8%)
Women	N=1833	N=1780	N=1827	N=1629	N=684	N=1537
Normal	1471 (80.3%)	1435 (80.6%)	1454 (79.6%)	1309 (80.4%)	539 (77.7%)	1249 (81.3%)
Micro	309 (16.9%)	297 (16.7%)	323 (17.7%)	270 (16.6%)	122 (17.6%)	237 (15.4%)
Macro	53 (2.9%)	48 (2.7%)	50 (2.7%)	50 (3.1%)	33 (4.8%)	51 (3.3%)
Dyslipidemic population	N=970	N=932	N=962	N=870	N=343	N=803
Normal	704 (72.6%)	675 (72.4%)	693 (72.0%)	636 (73.1%)	233 (67.9%)	583 (72.6%)
Micro	221 (22.8%)	214 (23.0%)	224 (23.3%)	186 (21.4%)	86 (25.1%)	171 (21.3%)
Macro	45 (4.6%)	43 (4.6%)	45 (4.7%)	48 (5.5%)	24 (7.0%)	49 (6.1%)

^c Visit 1: entry visit after withdrawal of any lipid-lowering therapy

^d Visit 3 visit after 6-week placebo; visit 1 and visit 3 results were averaged to determine baseline albuminuria status (Normoalbuminuria: urinary albumin/creatinine ratio <3.5 mg/mmol; microalbuminuria UACR 3.5-35 mg/mmol; macroalbuminuria UACR>35 mg/mmol)

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Observational Safety Postmarketing Requirement for Trilipix

*Endocrinologic and Metabolic Drugs Advisory Committee Meeting
May 19, 2011*

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Background

With the approval of Trilipix in December 2008, FDA required the sponsor to conduct “an observational study to estimate the incidence and risk factors for hospitalized rhabdomyolysis in patients treated with a fibrate in combination with a statin, versus statin or fibrate monotherapy.” FDA recommended methodology used in the article “Incidence of Hospitalized Rhabdomyolysis in Patients Treated with Lipid-Lowering Drugs” by Graham et al (1).

Objectives

To present methodology and findings of the epidemiological study by Graham et al., followed by a critical appraisal of the study submitted by the sponsor to fulfill FDA’s postmarketing requirement (PMR), as well as an earlier epidemiological study conducted on behalf of the sponsor, which included additional safety endpoints (2).

Reviewed Studies

1. Incidence of Hospitalized Rhabdomyolysis in Patients Treated With Lipid-Lowering Drugs by Graham et al. (1)

Objectives and methodology

The study’s objectives were to estimate the incidence of hospitalized rhabdomyolysis in patients treated with statins and fibrates, alone and in combination. The study sample was based on 11 US health plans during the period from 1/1/1998 to 6/30/2001. Subjects were categorized as new users of a statin or fibrate if their first prescription of the respective drug was preceded by a 180 days baseline period without a prescription for that drug. Exposure duration was based on days of supply plus 30 days, to allow for minor gaps. The outcome was hospitalized rhabdomyolysis, identified from a claims data search, and validated through medical records review. Cases of rhabdomyolysis were defined as the presence of severe muscle injury in conjunction with either a diagnosis of rhabdomyolysis or a creatine phosphokinase (CPK) level of more than 10 times the upper limit of normal. The authors used a Poisson regression model to calculate relative risks, adjusted for age, sex, and diabetes mellitus.

Results

Major findings of the study are displayed in Table 1. A large increase in the risk for hospitalized rhabdomyolysis was found during exposure to cerivastatin, especially when cerivastatin was combined with gemfibrozil. After adjustment, the study found a 5.5-fold increase in risk for hospitalized rhabdomyolysis associated with fibrates (95% CI, 1.5 – 20.4) when compared to statins alone (atorvastatin, pravastatin, simvastatin), and a 12-fold increase (95% CI, 2.6 – 57.4) when statins other than cerivastatin were used in combination with fibrates, again compared to statins alone. However, the estimates were based on small case numbers: only two cases occurred during combination use, not including cerivastatin.

Table 1. Results for hospitalized rhabdomyolysis, Graham et al. (2004)

Exposure	Cases	IR /100,000 person-yrs	95% CI
None	0	0	0 – 4.8
Atorvastatin	7	5.4	2.2 – 11.2
Cerivastatin	4	53.4	16.4 – 136.8
Pravastatin	0	0	0 – 11.1
Fluvastatin	0	0	--
Lovastatin	0	0	--
Simvastatin	2	4.9	0.6 – 17.6
Fenofibrate	0	0	0 – 145.8
Gemfibrozil	3	37.0	7.6 – 108.2
Atorvastatin + fenofibrate	1	224.5	5.7 – 1250
Fenofibrate + atorvastatin		168.6	4.3 – 936.0
Cerivastatin + gemfibrozil	3	10 350.0	3890 – 21,170
Gemfibrozil + cerivastatin	3	7 890.0	1660 – 21,380
Simvastatin + gemfibrozil	1	187.3	4.7 – 1040

CI: confidence interval, IR: incidence rate

2. Occurrence of Rhabdomyolysis with Fibrate and Statin Use

Report by i3 drug safety for Abbott to fulfill FDA's postmarketing requirement, prepared 01/26/2010, revised 06/17/2010

Study objectives

The primary objectives of the study were to estimate and compare incidence rates of hospitalized rhabdomyolysis during periods of use of statins and fibrate monotherapy, and concomitant use of statins and fibrates. The secondary objective was to estimate and compare the incidence of rhabdomyolysis during periods of use of statins metabolized by CYP3A4 and statins not metabolized by CYP3A4.

Data source

The analysis was conducted in the proprietary Normative Health Informatics database, which is based on 44 major markets or health plans. From 1993 to 2009, it contained medical and pharmacy data for more than 60 million current and past members,

and outpatient laboratory data for about 30% of its members. In January 2006, 12 million current members (3-4% of US population) were represented in the dataset. The database underrepresents the population over 65, which constitute 8% of the membership vs. 12% of the US population. The average length of membership is 18 months. Medical record abstraction is possible.

Methodology

The investigators conducted a retrospective cohort study and described the design as a new user design. During the study period from 1/1/1998 through 12/31/2008, subjects were included if they were older than 17 years of age and had at least 183 days of continuous enrollment in commercial insurance with medical and pharmacy benefits. Subjects had to have at least one dispensing of a statin or fibrate and were excluded if they had received cerivastatin or clofibrate, or if they had a diagnosis of rhabdomyolysis during their baseline period of 183 days prior to the beginning of the study.

The investigators followed patients from their index date, which was defined as the first prescription of a statin, fibrate, or both, preceded by at least 183 days without use of the same drug. Each day of follow-up was then categorized based on current exposure to statin and/or fibrate. Exposure duration was based on days of supply of the last prescription plus 20%. Current exposure also included the possibility of no use of lipid-lowering drugs, that is, no prescription for either a statin or fibrate after a period of lipid-lowering drug use, since initial use was a requirement for inclusion in the study.

The endpoint of hospitalized rhabdomyolysis was identified in a 3-step process. First, potential cases were identified through a broad claims search in the first or second position of inpatient claims with any of the ICD-9-CM discharge diagnosis codes listed in Table 2. Second, a claims profile review was performed by a clinical consultant who determined potential false-positives based on coding errors or transposition of ICD-9-CM codes. As of the writing of this document, no details were provided on the criteria used for this determination. The third step included a medical records review for potential cases selected for review in the previous step and where medical records could be obtained. In this step, cases of hospitalized rhabdomyolysis were confirmed if they had 1) a laboratory value for creatine kinase increased to more than 10 times the upper limit of normal with concomitant muscle symptoms (e.g., weakness, aching, tenderness) and no obvious acute alternate etiology (e.g., burns, crush injury) AND 2) creatinine elevation above the upper limit of normal, or a new clinical diagnosis of renal insufficiency or renal failure. The second part of this definition, the requirement for renal involvement, was not applied in the Graham et al. study. This requirement selects more severe cases. In a study in a single hospital, only 33-51% of hospitalized rhabdomyolysis cases were found to have acute renal failure (3).

The investigators calculated incidence rates and adjusted incidence rate ratios using Poisson regression. Baseline values of the following characteristics were considered for multivariate adjustment: age, sex, region, year, total healthcare cost, statin use, fibrate use, diabetes, hypertension, hypothyroidism, renal or hepatic disease, exposure to contrast dye within 30 days prior to the index date, and number of: hospitalizations, primary care visits, specialty visits, prescription drugs, laboratory tests, and procedures during the baseline period. Covariates not meeting the definition of a confounder (>10% change in the risk estimate) were not included in the final model.

Table 2. ICD-9-CM codes used to identify potential rhabdomyolysis cases, i3 PMR study

ICD-9-CM code	ICD-9-CM description
710.4	Polymyositis
791.3	Myoglobinuria
728.88	Rhabdomyolysis
728.89	Other disorder of muscle, ligament, and fascia
728.9	Unspecified disorder of muscle, ligament, and fascia
729.1	Myalgia and myositis
729.8x	Musculoskeletal symptoms of the limb
359.4, 359.8, 359.9	Myopathy
E942.2	Adverse effect of antihyperlipidemic agents

Results

Approximately 1.1 million subjects were included in the study. Among these, 86.6% initiated a statin, 12.9% a fibrate, and 0.5% initiated both drugs at the same time. Almost 2.4 million person-years of follow-up were categorized as either statin monotherapy (47.6%), fibrate monotherapy (4.7%), statin and fibrate combination therapy (2.9%), or periods of no lipid-lowering drug use (44.8%).

The claims search of discharge diagnoses identified 2,309 potential cases of hospitalized rhabdomyolysis in 2,171 patients. Based on the review of claims data, 1,232 were selected for medical record review, of which 942 records were obtained. Among these, 70 were confirmed as cases of hospitalized rhabdomyolysis. Four of these confirmed cases died within 1 day to approximately 6 months of the case date; however, no causes of death were provided.

Table 3 lists case numbers and incidence rates based on current exposure. While incidence rates during periods of statin monotherapy were comparable to periods of no lipid-lowering drug use, fenofibrate monotherapy was associated with a higher incidence rate, albeit not statistically significant from statin monotherapy, as indicated by overlapping confidence intervals. Combination use of fibrates and statins was associated with statistically significantly higher rates of hospitalized rhabdomyolysis, when compared to no use or statin monotherapy.

Table 3. Results, hospitalized rhabdomyolysis, i3 PMR study

Current exposure	Cases	Person-yrs	IR, per 100.000 person-yrs	(95% CI)
No lipid-lowering drug use	24	1,069,324	2.24	1.44 - 3.34
Statin only	28	1,137,968	2.46	1.64 - 3.56
Fenofibrate only	5	80,654	6.20	2.01 - 14.47
Gemfibrozil only	1	31,964	3.13	0.08 - 17.43
Statin and Fenofibrate	7	56,593	12.37	4.97 - 25.48
Statin and Gemfibrozil	5	12,963	38.57	12.52 - 90.01

CI: confidence interval, IR: incidence rate

Adjusted incidence rate ratios are displayed in Table 4. Adjustment had a minor effect on the estimate for fibrate monotherapy; however, incidence rate ratio estimates for combination use were attenuated with adjustment, possibly indicating channeling of combination therapy to patients at higher risk for rhabdomyolysis. After adjustment, the use of combination therapy was associated with an increased risk for hospitalized rhabdomyolysis, when compared to statin monotherapy.

Table 4. Results, hospitalized rhabdomyolysis, i3 PMR study

Current exposure	Crude IRR	95% CI	Adj. IRR	95% CI
Statin only	ref	ref	ref	ref
Fenofibrate only	2.52	0.97 – 6.52	2.25	0.85 – 5.95
Gemfibrozil only	1.27	0.17 – 9.34	1.41	0.19 – 10.50
Statin + Fenofibrate	5.03	2.20 – 11.51	3.26	1.21 – 8.80
Statin + Gemfibrozil	15.68	6.05 – 40.60	11.93	3.96 – 35.93

CI: confidence interval, IRR: incidence rate ratio

Table 5 contrasts findings by Graham et al. with the i3 PMR study. Of note, this table provides only unadjusted incidence rate ratios, which most likely overestimate the effect. Estimates for incidence rates were higher in the Graham et al. study, possibly due to the stricter case definition used in the i3 PMR study. Crude incidence rate ratios were also higher in the Graham et al. study (i3: crude IRR=7.00 [3.56 – 13.77], Graham: crude IRR=13.50 [2.92 – 62.46]); however, small case numbers resulted in wide confidence intervals, which include the possibility of little disagreement between the two studies.

Crude rate differences for hospitalized rhabdomyolysis based on the i3 study suggest an attributable risk of 14.8 [95% CI, 5.00 – 24.6] additional cases per 100,000 person-yrs of statin and fibrate combination use vs. statin monotherapy. This results in a number needed to harm (NNH) of 6,757 person-yrs of exposure necessary to observe one additional case of hospitalized rhabdomyolysis with renal impairment.

Table 5. Comparison of results for hospitalized rhabdomyolysis

Exposure	Graham et al., 2004*			i3 report, 2010		
	Cases	IR 95% CI	Crude IRR 95% CI	Cases	IR 95% CI	Crude IRR 95% CI
Statin monotherapy	9	4.34 1.98 – 8.23	ref	28	2.46 1.64 – 3.56	ref
Fibrate monotherapy	3	28.2 5.67 – 82.45	6.51 1.76 – 24.0	6	5.32 1.95 – 11.60	2.17 0.90 – 5.23
Statin + fibrate	2	58.5 6.58 – 211.3	13.50 2.92 – 62.46	12	17.23 8.89 – 30.10	7.00 3.56 – 13.77

CI: confidence interval, IRR: incidence rate ratio, IR: incidence rate, per 100,000 person-years

*Graham et al.: statins included: atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin

CYP3A4 Metabolism

No difference in risk for hospitalized rhabdomyolysis was found based on CYP3A4 metabolism, when compared to no statin use. Statins metabolized by CYP3A4 had an adjusted IRR of 1.17 (95% CI, 0.71 – 1.93) compared to 1.22 (95% CI, 0.53 – 2.79) associated with statins not metabolized by CYP3A4.

Limitations

- a) Although the design was described as a new user design, this only applies to the drug initiated on the index date. To illustrate, had a fibrate been used before the index date until after a statin index drug was stopped, the patient would have been categorized as a fibrate monotherapy user after stopping the statin. However, the patient would not be a true new user of the fibrate. The concern is depletion of susceptibles, that is, continuing users have already shown sufficient effectiveness and tolerance of side effects. Side effects that occur close to drug initiation would be underestimated in a design that does not restrict to new users, as is the case with the i3 PMR study.
- b) The investigators provided baseline characteristics by drug initiated. However, since the incidence of rhabdomyolysis was compared between cohorts of current drug use, not by drug initiated, patient characteristics according to current drug use would be most relevant. To illustrate, a statin new user who added a fibrate a few months later, would be considered a statin initiator. In contrast, this patient's current exposure, would be statin monotherapy for the initial few months and combination therapy thereafter. His or her patient characteristics would be included with statin initiators, although most of the patient's follow-up time was during combination use. Since characteristics were not provided for the cohorts compared in the study, we are unable to compare risk factors for rhabdomyolysis and consequently, evaluate the appropriateness of multivariate adjustment.
- c) Age is a risk factor for hospitalized rhabdomyolysis (4). Because the database used in the study underrepresents the population over 65, incidence rates for hospitalized rhabdomyolysis may be underestimated.
- d) Graham et al. found evidence for exposure misclassification, especially in the no use cohort. When they examined medical records, they found evidence of current lipid-lowering drug use in patients classified as no-users based on claims data. A potential misclassification of users as no-users would offer an explanation to the observation of similar rates for hospitalized rhabdomyolysis found during periods of statin use and no-use in the i3 PMR study (Table 3), which is contrary to the commonly-associated risk increase with statins.
- e) The adjustment for confounders changed incidence rate ratios significantly for combination drug users. This indicates the presence of confounding before adjustment with the possibility of residual confounding after adjustment. If present, this would likely result in overestimated incidence rate ratios. Furthermore, information on some risk factors, e.g. alcohol use, strenuous physical activity, and body mass index was not included in the analysis, potentially resulting in residual confounding. Also, renal disease was not

included in the final model, which is a recognized risk factor for rhabdomyolysis.(4)

- f) Medical records could not be obtained for 24% (n=290) of potential cases of hospitalized rhabdomyolysis, who were subsequently treated as non-cases. If the same confirmation rate applies as in the medical records that were obtained, 22 cases would be expected in the 290 records that were not obtained. This would result in underestimated incidence rates.
- g) The case definition of rhabdomyolysis with the requirement of renal impairment was stricter than the one used by Graham et al. and probably contributed to lower incidence rate estimates.

Conclusion

Despite its limitations, the study provides evidence for an increased risk of hospitalized rhabdomyolysis associated with combination use of statins and fibrates, when compared to statin monotherapy. This increase was moderate to large on a relative scale (Crude IRR: 7.00 [95% CI, 3.56 – 13.77]) and small on an absolute scale (Crude rate difference: 14.8 [95% CI, 5.00 – 24.6] additional cases per 100,000 person-yrs of exposure, NNH = 6,757). Relative measures are likely overestimated and absolute measures likely underestimated.

3. Pharmacoepidemiology Safety Study of Fibrate and Statin Concomitant Therapy Published study (2) and Final Report by i3 drug safety for Abbott Laboratories, 7/31/2009

The Final Report of this study, dated 7/31/2009 and submitted to the FDA, describes two sub-studies, a cohort study with additional outcomes (rhabdomyolysis, myopathy, renal impairment, hepatic injury, and pancreatitis) but methodology comparable to the i3 PMR study described under section 2 (above), and a case-control study with similar objectives. The cohort study was published in the American Journal of Cardiology (2). This review briefly describes design limitations to the case-control study, but mainly concentrates on the cohort study.

Case-control study

The case-control selection was described in the study methodology as “incidence-density sampling” with 30 randomly selected controls (with replacement) per case. For six different outcomes, this would normally entail six different sets of controls, each matched to one of six sets of cases. In addition, incidence-density sampling, also known as risk set sampling, requires that potential controls had to be eligible at the time when a case occurred. Instead, the investigators created one set of controls that was used for all of the 6 outcomes. Therefore, in the analysis of any one outcome, most controls were not part of the risk set for the cases, thus violating a necessary condition for risk set sampling. Furthermore, the set of controls was not sampled based on the total 1,027 chart-confirmed cases for the six outcomes, but apparently based on 3,116 claims-based cases, 67% of which were later excluded.

Since commonly accepted case-control methodology was not applied, the results may not be interpretable and, therefore, no further discussion of the study is included in this review.

Cohort study

This study examined additional outcomes besides rhabdomyolysis, including myopathy, renal impairment, hepatic injury, and pancreatitis. The cohort study was conducted in the same database and differs in methodology from the i3 PMR study described under section 2 (above) only in the absence of a cohort not exposed to lipid-lowering drugs, additional adjustment for biliary disease in some outcomes, and the shorter study period (from 1/1/2004 to 12/31/2007, instead of 1/1/1998 to 12/31/2008). Because this study cohort was a subset of the cohort that provided rhabdomyolysis information discussed in section 2, this review only presents findings on the outcomes of renal impairment, renal failure requiring renal replacement (dialysis or transplant), hepatic injury, and pancreatitis. Of note, no adjustment for multiple testing was done; for this reason, statistical significance should be interpreted with caution.

Results, Renal impairment

Table 6 presents results for renal impairment, indicating a 33% and 61% statistically significant increase in risk associated with fenofibrate and gemfibrozil monotherapy, respectively, when compared to statin monotherapy. The risk was not further increased when fibrates were used in combination with statins, thus providing no evidence for an interaction effect.

Table 6. Results, renal impairment, i3 Final Report

Current exposure	Cases	Person-years	IR 95% CI	Crude IRR 95% CI	Adj. IRR 95% CI
Renal impairment					
Statin Only	494	453,744	108.87 99.59 - 118.79	ref	ref
Fenofibrate Only	53	35,831	147.92 112.00 - 191.90	1.36 1.02 - 1.80	1.33 1.00 - 1.77
Gemfibrozil Only	19	10,381	183.03 113.88 - 279.95	1.68 1.06 - 2.66	1.61 1.02 - 2.54
Statin and Fenofibrate	60	26,504	226.38 174.39 - 289.28	2.08 1.59 - 2.72	1.47 1.12 - 1.93
Statin and Gemfibrozil	12	4,808	249.58 136.29 - 422.73	2.29 1.29 - 4.06	1.49 0.84 - 2.65

CI: confidence interval, IR: incidence rate, per 100,000 person-years, IRR: incidence rate ratio

Renal failure requiring renal replacement (dialysis or transplant)

The analysis of renal failure requiring renal replacement was based on small case numbers (Table 7). Fibrate monotherapy was not associated with an increased risk, when compared to statin monotherapy. Fibrate and statin combination therapy was associated

with a 29% to 41% risk increase; however it was not statistically significant. Of note, cases of renal failure requiring renal replacement were a subset of the cases with renal impairment described above.

Table 7. Results, renal failure requiring renal replacement, i3 Final Report

Current exposure	Cases	Person-years	IR 95% CI	Crude IRR 95% CI	Adj. IRR 95% CI
Renal failure requiring renal replacement (dialysis or transplant)					
Statin Only	121	453,744	26.67 22.23 - 31.74	ref	ref
Fenofibrate Only	5	35,831	13.95 5.29 - 30.59	0.52 0.21 - 1.28	0.48 0.20 - 1.18
Gemfibrozil Only	3	10,381	28.90 8.00 - 77.1	1.08 0.34 - 3.41	0.98 0.31 - 3.08
Statin and Fenofibrate	14	26,504	52.82 30.25 - 86.26	1.98 1.14 - 3.44	1.29 0.74 - 2.26
Statin and Gemfibrozil	3	4,808	62.40 17.27 - 166.47	2.34 0.74 - 7.36	1.41 0.45 - 4.45

CI: confidence interval, IR: incidence rate, per 100,000 person-years, IRR: incidence rate ratio

Hepatic injury

Small case numbers limit the interpretation of hepatic injury associated with lipid-lowering drug use (Table 8). Increased incidence rate ratios were found for fenofibrate monotherapy and fibrate and statin combination therapy when compared to statin monotherapy. None of these association reached statistical significance.

Table 8. Results, hepatic injury, i3 Final Report

Current exposure	Cases	Person-years	IR 95% CI	Crude IRR 95% CI	Adj. IRR 95% CI
Hepatic injury					
Statin Only	39	454,846	8.57 6.19 - 11.59	ref	ref
Fenofibrate Only	5	35,943	13.91 5.28 - 30.49	1.62 0.64 - 4.12	1.65 0.65 - 4.20
Gemfibrozil Only	0	10,424	0 0 - 23.64	---	---
Statin and Fenofibrate	3	26,660	11.25 3.11 - 30.02	1.31 0.41 - 4.25	1.23 0.38 - 4.00
Statin and Gemfibrozil	1	4,833	20.69 1.88 - 96.47	2.41 0.33 - 17.56	2.31 0.32 - 16.88

CI: confidence interval, IR: incidence rate, per 100,000 person-years, IRR: incidence rate ratio

Pancreatitis

Fenofibrate alone or in combination with statins was associated with a more than 2.5-fold statistically significant increase in risk for pancreatitis when compared to statin monotherapy (Table 9). A trend towards elevated risk was associated with gemfibrozil use, alone or in combination with statins; however it was not statistically significant. Overlapping confidence intervals between incidence rate ratios associated with fenofibrate monotherapy and gemfibrozil monotherapy preclude interpretation of a differential risk. For both fenofibrate and gemfibrozil, the addition of a statin did not further increase the risk of pancreatitis, when compared to fibrate monotherapy.

Both fibrates are indicated in patients with high levels of triglycerides, a condition that is also associated with an increased risk for pancreatitis. Thus, the observed increase in risk for pancreatitis observed during fibrate use might reflect the background risk of this population.

Table 9. Results, pancreatitis, i3 Final Report

Current exposure	Cases	Person-years	IR 95% CI	Crude IRR 95% CI	Adj. IRR 95% CI
Pancreatitis					
Statin Only	208	454,531	45.76 39.86 - 52.3	ref	ref
Fenofibrate Only	45	35,879	125.42 92.66 - 166.23	2.74 1.99 - 3.78	2.67 1.93 - 3.69
Gemfibrozil Only	9	10,400	86.54 42.74 - 157.95	1.89 0.97 - 3.69	1.82 0.93 - 3.55
Statin and Fenofibrate	42	26,592	157.94 115.41 - 211.34	3.45 2.48 - 4.81	2.87 2.05 - 4.02
Statin and Gemfibrozil	4	4,813	83.11 27.78 - 197.59	1.82 0.68 - 4.88	1.45 0.54 - 3.92

CI: confidence interval, IR: incidence rate, per 100,000 person-years, IRR: incidence rate ratio

Limitations

The study is subject to similar limitations as the PMR study discussed in section 2; therefore, no separate discussion of limitations is provided here.

Summary

The Graham et al. study and the i3 PMR study reported an increased risk of hospitalized rhabdomyolysis associated with combination use of statins and fibrates compared to statin monotherapy. Relative and absolute risk estimates differ between the studies, as a potential consequence of different case definitions, different mean ages of the samples, and random error related to small case numbers, especially in the Graham et al. study. Study limitations make it difficult to provide a numeric estimate of risk for

hospitalized rhabdomyolysis associated with statin and fibrate combination therapy; however, evidence supports a moderate-to large increase in risk on a relative scale and a small increase on an absolute scale.

An increased risk of renal impairment associated with the use of fibrates, and pancreatitis associated with use of fenofibrate compared to statin monotherapy was found, but no further increase when combined with statins. The Trilipix label currently includes reports of pancreatitis and elevations in serum creatinine.

Reference List

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