# Advisory Committee Briefing Document

# Trilipix® (Fenofibric Acid) Delayed Release Capsules

## Endocrinologic and Metabolic Drugs Advisory Committee

## Meeting on 19 May 2011



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## Abbreviations and Definition of Terms

| | |
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| ACCORD (trial) | Action to Control Cardiovascular Risk in Diabetes |
| ALT | alanine transaminase |
| Apo | apolipoprotein |
| AST | aspartate transaminase |
| ATP III | Adult Treatment Panel III |
| BIP (trial) | Bezafibrate Infarction Prevention |
| BMI | body mass index |
| CHD | coronary heart disease |
| CHF | congestive heart failure |
| CHMP | Committee for Human Medicinal Products |
| CI | confidence interval |
| CK | creatine kinase |
| CVD | cardiovascular disease |
| EMR | electronic medical records |
| ETDRS | Early Treatment Diabetic Retinopathy Study |
| FDA | Food and Drug Administration |
| FIELD (trial) | Fenofibrate Intervention and Event Lowering in Diabetes |
| GFR | glomerular filtration rate |
| $HbA_{1c}$ | glycated hemoglobin |
| HDL-C | high-density lipoprotein cholesterol |
| HHS | Helsinki Heart Study |
| HR | hazard ratio |
| hsCRP | high-sensitivity C-reactive protein |
| LDL-C | low-density lipoprotein cholesterol |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MI | myocardial infarction |
| NCEP | National Cholesterol Education Program |
| NHANES | National Health and Nutrition Examination Survey |
| NHLBI | National Heart, Lung and Blood Institute |
| NNH | number needed-to-harm |
| NNT | number needed-to-treat |
| OR | odds ratio |
| PPAR$\alpha$ | peroxisome proliferator activated receptor $\alpha$ |


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| | |
|---|---|
| PROVE IT-TIMI 22 (trial) | Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction |
| T2DM | type 2 diabetes mellitus |
| TG | triglycerides |
| TNT (trial) | Treating to New Targets |
| Total-C | total cholesterol |
| ULN | upper limit of normal |
| VA-HIT | Veterans Affairs High-Density Lipoprotein Intervention Trial |
| VLDL-C | very–low-density lipoprotein cholesterol |


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## 1.0 Executive Overview

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was funded by the United States (US) National Institutes of Health and conducted by the National Heart, Lung and Blood Institute (NHLBI) at sites in the US and Canada. ACCORD Lipid, a component of the overarching ACCORD trial, was designed to evaluate whether treatment of lipid parameters with fenofibrate plus a statin reduces cardiovascular (CV) risk in patients with type 2 diabetes mellitus (T2DM) compared to statin monotherapy. Following the release of the ACCORD Lipid trial results at the American College of Cardiology meeting on 14 March 2010, the US Food and Drug Administration (FDA) publicly announced their plan to review the study's findings in relation to the approved prescribing information for Trilipix (fenofibric acid). The purpose of the 19 May Advisory Committee meeting is to further discuss appropriate use of Trilipix coadministered with a statin, in the context of the findings of ACCORD Lipid.

After a comprehensive review of available data, including ACCORD Lipid, Abbott concludes that the coadministration of Trilipix with a statin continues to have a favorable benefit-risk profile in patients with elevated triglycerides (TG) and/or low high-density lipoprotein cholesterol (HDL-C). This conclusion is supported by data illustrating the following points:

- Among patients whose low-density lipoprotein cholesterol (LDL-C) is successfully controlled with a statin, there is still risk of a CV event, and this risk increases with increasing levels of TG and/or decreasing levels of HDL-C.
- Results from CV outcomes trials with fibrate monotherapy conducted before the completion of ACCORD Lipid demonstrated that fibrates reduce CV risk in patients with elevated TG and low HDL-C.
- ACCORD Lipid confirms the results from these previous monotherapy trials, demonstrating that coadministration of fenofibrate with a statin reduces the risk of CV events in patients with elevated TG and low HDL-C compared to statin monotherapy.


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- The safety profile of fenofibrate/fenofibric acid is well defined, predictable, and consistent with the approved Trilipix prescribing information.

Statins reduce LDL-C and the risk of CV events, but patients receiving statin monotherapy have residual risk for these events, as approximately 20% of statin-treated patients with preexisting coronary heart disease have additional CV events within 5 years of their first event. Statin-treated patients with controlled LDL-C and elevated TG have greater risk of CV events than patients with controlled LDL-C and normal TG. Likewise, statin-treated patients with controlled LDL-C and low HDL-C have greater risk of CV events than patients with controlled LDL-C and normal HDL-C. Because residual risk in statin-treated patients is associated with elevated TG and low HDL-C, these patients may benefit from additional therapy to lower TG and increase HDL-C.

At the time the ACCORD Lipid results were released, data were available from 4 key fibrate outcomes trials: the Helsinki Heart Study (HHS, published in 1987), the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT, published in 1999), the Bezafibrate Infarction Prevention trial (BIP, published in 2000) and the Fenofibrate Intervention and Event Lowering in Diabetes trial (FIELD, published in 2005). Two of these trials were conducted with gemfibrozil (HHS and VA-HIT), one with bezafibrate (BIP), and one with fenofibrate (FIELD). In each of these trials, patients with elevated TG and low HDL-C consistently demonstrated a statistically significant reduction in risk of CV events with fibrate therapy. In contrast, in each trial, there was a nonsignificant reduction in the risk of CV events in patients without elevated TG and low HDL-C. In an analysis of patients with elevated TG and low HDL-C, combining results from all 4 trials, fibrate therapy reduced the odds of a CV event by 38% compared to placebo (odds ratio [OR] = 0.62; 95% CI: 0.49, 0.79; $P < 0.001$). In patients without elevated TG and low HDL-C, the combined analysis showed a nonsignificant reduction in the odds of a CV event (OR = 0.91; 95% CI: 0.82, 1.01; $P = 0.062$).


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## ACCORD Lipid Results in Patients with Dyslipidemia

ACCORD Lipid evaluated whether fenofibrate-simvastatin coadministration therapy reduced the risk of CV events in patients with T2DM compared to simvastatin monotherapy. The primary outcome in ACCORD Lipid was the time to the first occurrence of nonfatal myocardial infarction (MI), nonfatal stroke, or CV death. In the overall population, coadministration therapy provided a nonsignificant reduction in the risk of CV events compared to simvastatin monotherapy (hazard ratio [HR] = 0.92; 95% CI: 0.79, 1.08; $P = 0.32$). However, in the prespecified subgroup of patients with dyslipidemia (defined in this study as patients who were simultaneously in the highest baseline tertile of TG [≥ 204 mg/dL] and lowest baseline tertile of HDL-C [≤ 34 mg/dL]), a 31% reduction in risk of CV events was observed with fenofibrate-simvastatin coadministration therapy (HR = 0.69; 95% CI: 0.49, 0.97; $P = 0.032$). In all other patients, the risk of CV events was nearly identical in the 2 treatment groups (HR = 0.99; 95% CI: 0.83, 1.19; $P = 0.935$; $P = 0.06$ for test of interaction). The results in the prespecified subgroup with dyslipidemia correspond to a number needed-to-treat (NNT) of 20 patients over 4.7 years to prevent one CV event.

Therefore, results from ACCORD Lipid confirm the results observed in the 4 earlier CV outcomes trials (figure below). In patients with elevated TG and low HDL-C, fibrates consistently provide evidence of CV benefit regardless of gender, history of CV events, diabetic status, or concomitant statin therapy. In contrast, in patients without both elevated TG and low HDL-C, there was a nonsignificant reduction in CV events. When ACCORD Lipid was added to the analysis of earlier fibrate outcomes trials, the results were similar. Fibrate therapy significantly reduced the odds of a CV event in patients with elevated TG and low HDL-C (OR = 0.65; 95% CI: 0.55, 0.77; $P < 0.0001$), while the reduction in the odds of a CV event in patients without elevated TG and low HDL-C was nonsignificant (OR = 0.93; 95% CI: 0.85, 1.01; $P = 0.098$).


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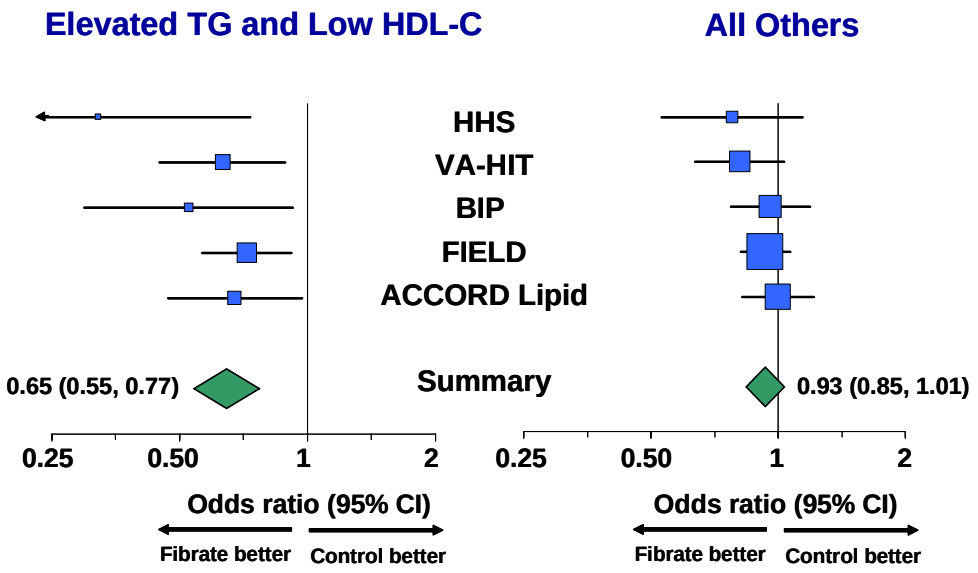


Both treatment guidelines and the Trilipix prescribing information indicate that patients should be receiving statin therapy before adding Trilipix. Because only 60% of patients enrolled in ACCORD Lipid were receiving a statin at baseline, Abbott conducted a sensitivity analysis evaluating patients in the prespecified subgroup with dyslipidemia who were receiving a statin at baseline. In this group, coadministration therapy significantly reduced the risk of CV events compared to simvastatin monotherapy (HR = 0.55; 95% CI: 0.35, 0.87; $P$ = 0.01).

To assess whether patients at other lipid thresholds would also derive CV benefit from fenofibrate-simvastatin coadministration therapy, a second sensitivity analysis was conducted examining results by alternative baseline TG and HDL-C cutoffs among patients receiving statins at baseline in ACCORD Lipid. As shown in the figure below, the risk of CV events in the simvastatin monotherapy group increased with increasing TG and with decreasing HDL-C (ranging from 13% to 21%), consistent with the increased CV risk known to be associated with these lipid abnormalities. In contrast, in the coadministration group, the risk of CV events remained lower and relatively uniform across baseline TG and HDL-C levels (ranging from 10% to 13%). For example, in the most dyslipidemic group (TG ≥ 200 mg/dL and HDL-C ≤ 34 mg/dL), the percentage of


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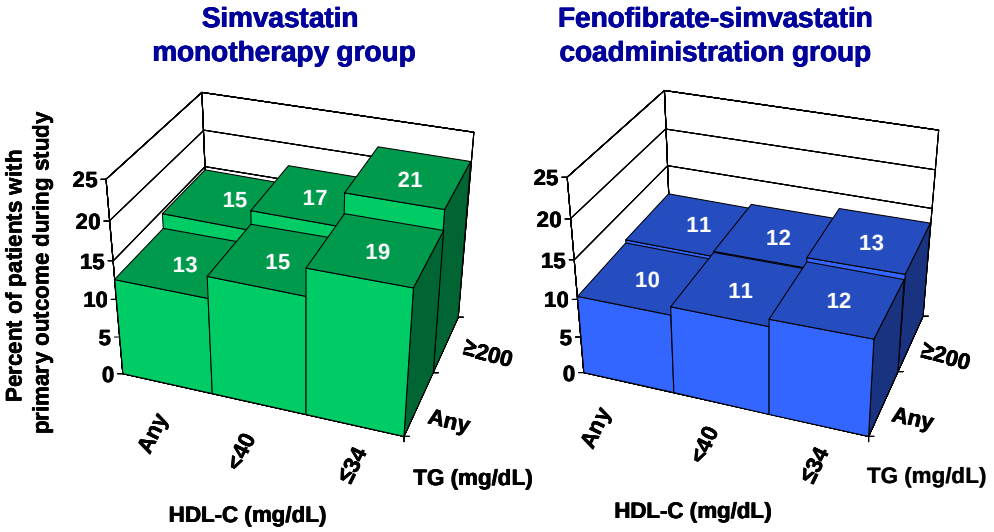
patients with an event was 21% in the simvastatin monotherapy group and 13% in the coadministration therapy group.




**Patients Receiving a Statin at Baseline**

These analyses demonstrate that in ACCORD Lipid, fenofibrate-simvastatin coadministration therapy consistently provided a reduction in the risk of CV events in patients with elevated TG and/or low HDL-C, both in the prespecified subgroup with dyslipidemia and in sensitivity analyses of that subgroup. In simvastatin-treated patients, the risk of a CV event increased with increasing TG levels and/or decreasing HDL-C levels, consistent with the CV risk known to be associated with these lipid abnormalities. In contrast, in the coadministration therapy group, event rates were consistently lower, suggesting a mitigation of the impact of elevated TG and/or low HDL-C on CV risk with the addition of fenofibrate to simvastatin therapy.

## ACCORD Lipid Results in Women

One of the findings in ACCORD Lipid was a significant treatment-by-gender interaction ($P$ = 0.01), with a significant reduction in the risk of a CV event with coadministration therapy in men (HR = 0.82; 95% CI: 0.69, 0.99; $P$ = 0.037) and a trend toward a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potentially higher risk of CV events in women treated with coadministration therapy compared to simvastatin monotherapy (HR = 1.38; 95% CI: 0.98, 1.95; *P* = 0.069). Abbott investigated the findings in women by evaluating the components of the primary endpoint and the results in women with dyslipidemia.

The results for the primary outcome in women were driven by the event of nonfatal MI, in which there was a greater—but nonsignificantly different—risk for this event with coadministration therapy. Notably, the risks for CV death and for all-cause death were not increased with fenofibrate-simvastatin coadministration therapy (table below).

**Primary Outcome Events and All-cause Mortality in Women in ACCORD Lipid**

| | Number of Events | | | |
|---|---|---|---|---|
| | **Fenofibrate-simvastatin** | **Simvastatin Monotherapy** | **HR** | **95% CI** |
| Primary outcome[a] | 77 | 56 | 1.38 | (0.98, 1.95) |
| Nonfatal MI – any | 52 | 36 | 1.43 | (0.93, 2.18) |
| Nonfatal stroke – any | 11 | 9 | 1.20 | (0.50, 2.91) |
| CV death | 18 | 18 | 0.98 | (0.51, 1.88) |
| All-cause death | 45 | 50 | 0.89 | (0.60, 1.34) |

a. The primary outcome was the first occurrence of any of the following outcomes: nonfatal MI, nonfatal stroke, CVD death. These individual events were secondary outcomes.

The increased risk of nonfatal MI in women receiving fenofibrate in ACCORD Lipid is inconsistent with results from FIELD, which enrolled more than twice as many women as in ACCORD Lipid. In the FIELD trial, the risk of nonfatal MI was reduced in the overall population (HR = 0.76; 95% CI: 0.62, 0.94; *P* = 0.010), with similar beneficial effects observed in both men (HR = 0.78; 95% CI: 0.62, 1.00; *P* = 0.048) and women (HR = 0.70; 95% CI: 0.47, 1.05; *P* = 0.086).

In the prespecified subgroup with dyslipidemia in ACCORD Lipid, there was not a significant treatment-by-gender interaction (*P* = 0.524). The absence of a treatment-by-gender interaction suggests that in this subgroup the significant reduction in CV risk observed for coadministration therapy was not different for men and women.



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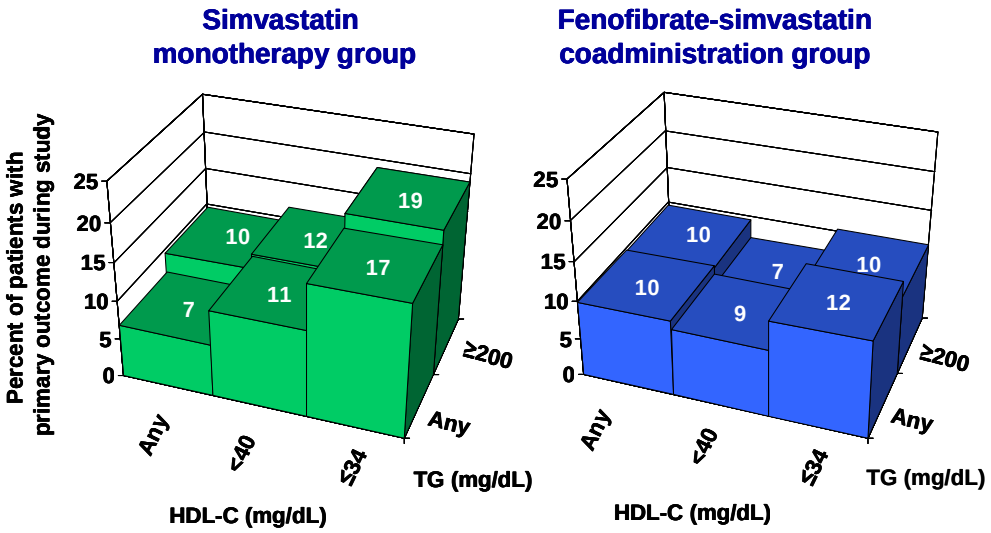
Women in this subgroup who received coadministration therapy had a numerically lower CV event rate compared to women who received simvastatin monotherapy (13.4% versus 15.2%; HR = 0.825; 95% CI: 0.379, 1.795; *P* = 0.627).

Similar to the analysis displayed in the preceding section, among women in ACCORD Lipid who were receiving a statin at baseline, the estimated treatment effect of coadministration therapy compared to simvastatin monotherapy improved with increasing TG and/or lower HDL-C (figure below).




**Women Receiving a Statin at Baseline**

Abbott investigated potential explanations for the significant treatment-by-gender interaction (*P* = 0.01) in ACCORD Lipid. These included evaluation of baseline imbalances, lipid changes, and pharmacokinetic interactions. Overall, demographics and baseline characteristics in women were well balanced between treatment groups, and adjustment for baseline factors associated with CV risk did not meaningfully alter the estimated treatment effect of coadministration therapy in women. Theoretically, the suggestion of harm observed in women treated with coadministration therapy compared to simvastatin monotherapy could arise if fenofibrate altered lipid parameters in women differently than in men, as this difference could affect CV outcomes. However, the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beneficial effects of fenofibrate on TG and HDL-C in ACCORD Lipid were similar in women and men.

If the treatment-by-gender interaction observed in ACCORD Lipid were a true clinical phenomenon, it would suggest a gender-specific pharmacologic interaction between fenofibrate and simvastatin. There were no statistically significant differences between females and males in pharmacokinetic interactions between fenofibrate and statins, suggesting that this was an unlikely explanation for the treatment-by-gender interaction.

Potential baseline imbalances between treatment groups for women, potential gender-specific effects of fenofibrate-mediated changes of lipid parameters, and potential gender-specific pharmacologic interventions were not identified and, thus, do not explain the observed results in women. Assessment of the multiplicity-adjusted *P* value for the treatment-by-gender interaction in ACCORD Lipid (*P* value of approximately 0.20) suggests that the observation may be a chance result.

**Safety Profile of Fenofibrate/Fenofibric Acid**

The safety of fenofibrate/fenofibric acid is well described and predictable and is based on results from the Trilipix clinical program, outcomes trials (including ACCORD Lipid and FIELD), other published clinical studies, and postmarketing safety reports.

Rhabdomyolysis, a rare but clinically significant muscle-related adverse event, has been reported coincident with the use of all classes of lipid-modifying drugs. To further investigate the incidence of this event with coadministration therapy, Abbott commissioned i3 (now i3 Innovus), a global health economics and outcomes research organization, to conduct 2 observational cohort studies to assess the occurrence of hospitalized rhabdomyolysis in patients receiving lipid-modifying therapies. The larger of these observational studies found that the rate of rhabdomyolysis was higher with fenofibrate monotherapy and fenofibrate-statin coadministration therapy compared to statin monotherapy, but overall, the rate was very low (approximately 1 per


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25,000 patient treatment-years), consistent with the rate in a similar previous observational cohort study.

Increases in serum creatinine are observed in some patients treated with fenofibrate/fenofibric acid. In ACCORD Lipid, mean serum creatinine increased from 0.93 at baseline to 1.10 mg/dL at end of therapy with fenofibrate-simvastatin coadministration and from 0.93 mg/dL to 1.04 mg/dL with simvastatin monotherapy. In both ACCORD Lipid and FIELD, observed increases in creatinine were reversible upon discontinuation of therapy and were not associated with an increase in important renal events, such as the need for hemodialysis.

In both ACCORD Lipid and FIELD, the percentages of patients with increases in alanine transaminase (ALT) to 3 to 5 times the upper limit or normal (ULN) were also low.

| **Percentage of Patients Meeting Laboratory Criteria for ALT Increases** | | | | | | | |
|---|---|---|---|---|---|---|---|
| **FIELD** | | | | **ACCORD Lipid** | | | |
| **3 to 5 × ULN** | | **> 5 × ULN** | | **> 3 × ULN** | | **> 5 × ULN** | |
| **Fenofibrate** | **Placebo** | **Fenofibrate** | **Placebo** | **Fenofibrate-simvastatin** | **Simvastatin** | **Fenofibrate-simvastatin** | **Simvastatin** |
| < 1% | < 1% | < 1% | < 1% | 1.9% | 1.5% | 0.6% | 0.2% |

## Real-World Use of Coadministration Therapy

To understand the real-world use of coadministration therapy, Abbott conducted analyses of patient-level clinical data from Centricity Physician Office® Electronic Medical Records (EMR). Among patients adding fenofibrate or fenofibric acid to existing statin therapy, the median TG was 303 mg/dL and the mean HDL-C was 39 mg/dL. Eighty-nine percent of patients had TG ≥ 200 mg/dL and/or HDL-C < 40 mg/dL.

Thus, prescription data indicate that for patients on statin therapy, fenofibrate/fenofibric acid is generally added in patients with elevated TG and/or low HDL-C, in accordance with treatment guidelines and also consistent with the Trilipix prescribing information. Importantly these patients can be identified by routine lipid analysis (elevated TG and/or low HDL-C) prior to and during treatment.


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**Benefit-Risk Summary**

Trilipix is indicated for coadministration with a statin to reduce TG and increase HDL-C in dyslipidemic patients who are on optimal statin therapy to achieve their LDL-C goal. In the Trilipix development program, the coadministration of Trilipix with a statin consistently demonstrated significant improvements in LDL-C, TG, and HDL-C in patients with dyslipidemia. The guidance to consider the use of Trilipix to treat TG and/or HDL-C abnormalities after optimal statin therapy for LDL-C control is consistent with current clinical treatment guidelines.

Among patients receiving a statin at baseline in ACCORD Lipid, the absolute CV risk for patients randomized to receive simvastatin monotherapy increased with increasing TG and/or decreasing HDL-C, consistent with epidemiological evidence associating both high TG and low HDL-C with risk of CV events. In contrast, in patients randomized to fenofibrate-simvastatin coadministration therapy, the incremental CV risk associated with increasing TG and/or decreasing HDL-C was largely eliminated.

The finding from ACCORD Lipid demonstrating a reduction in CV events in patients with elevated TG and low HDL-C confirms the findings from 4 earlier CV outcomes studies investigating the effect of fibrate therapy on CV risk reduction. In each of these 4 earlier CV outcomes trials, fibrate therapy demonstrated a statistically significant reduction in the risk of CV events in patients with elevated TG and low HDL-C. In these trials, there was not a significant reduction in CV events in patients without elevated TG and low HDL-C. The consistency of the results across these trials demonstrates that in a population with elevated TG and low HDL-C, fibrate therapy reduces CV risk regardless of whether the population has diabetes, has had previous CV events, or is receiving concomitant statin therapy.

Unique microvascular benefits have been demonstrated with fenofibrate therapy in patients with diabetes. Two of these, decreases in retinopathy and improvements in microalbuminuria, have been replicated in prespecified analyses from both FIELD and ACCORD Lipid.



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The safety profile of fenofibrate/fenofibric acid has been well-characterized with over 35 years of marketing experience and is appropriately described in the Trilipix prescribing information.

Events of rhabdomyolysis have been observed with lipid-modifying therapy, including statin monotherapy, fibrate monotherapy, and fibrate-statin coadministration therapy. Three large observational pharmacoepidemiological cohort studies consistently showed that events of hospitalized rhabdomyolysis are rare, although the risk is increased in patients receiving coadministration of fenofibrate/fenofibric acid with a statin compared to statin monotherapy. The risk of this event is even greater in patients who receive gemfibrozil coadministered with a statin, likely because of well-documented pharmacokinetic effects of gemfibrozil on statins. Advice is provided to prescribers and patients on the identification and management of rhabdomyolysis and other muscle-related adverse events in the Trilipix prescribing information and Medication Guide.

Taken together, these efficacy and safety data demonstrate that coadministration therapy of fenofibrate/fenofibric acid with a statin has a positive benefit-risk profile and remains an important therapeutic option for appropriately selected patients.

## Organization of this Briefing Document

The results described in this executive overview are outlined more fully in the complete briefing document.

**Section 2.0**
**The Scope of Dyslipidemia and the Role of Triglycerides and HDL-C in CV Disease**
This section begins with an overview of the scope of dyslipidemia in the US and the importance of lipid parameters, such as LDL-C (the primary target of lipid-modifying therapies) as well as TG and HDL-C, in contributing to CV risk.

**Section 3.0**
**The Role of Fenofibric Acid in the Treatment of Dyslipidemia**
The role of fenofibric acid in the treatment of dyslipidemia is discussed, with a summary of the lipid changes observed in the Trilipix clinical program. Results from the Trilipix


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clinical program are shown for the overall population and for subgroups that are relevant to the ACCORD Lipid trial, specifically patients with T2DM and women.

**Section 4.0**
**ACCORD Lipid**

The results of ACCORD Lipid are presented and compared to the results in earlier CV outcomes trials with fibrates. The consistency of results across these trials is presented, with the conclusion that fibrate-statin coadministered therapy is not appropriate in all patients, but it is appropriate and effective in reducing risk of CV events in those with elevated TG and/or low HDL-C who are already receiving a statin. This section presents results of ACCORD Lipid overall, in the prespecified subgroup with dyslipidemia, and in sensitivity analyses of this subgroup in patients receiving a statin at baseline.

**Section 5.0**
**ACCORD Lipid Subgroup Analysis by Gender**

The treatment-by-gender interaction observed in ACCORD Lipid is discussed, beginning with a summary of overall results in women, and a presentation of results in women in the subgroup with dyslipidemia and in women receiving a statin at baseline. These results showed that the reduction in CV risk with coadministration therapy in the prespecified subgroup with dyslipidemia was not different in women and men. Possible explanations for the overall significant treatment-by-gender interaction in ACCORD Lipid are also discussed.

**Section 6.0**
**Additional Evidence of the CV Benefits of Fibrate Therapy in Dyslipidemia Patients**

Additional evidence of the CV benefits of fibrate therapy in patients with dyslipidemia is presented. This includes results of an Abbott meta-analysis of 71 CV outcomes studies with lipid-modifying therapies and an independent published meta-analysis of 18 fibrate CV outcomes trials. The results of these meta-analyses further support the conclusion that patients with dyslipidemia are likely to receive CV benefit with fibrates that is incremental to the CV benefit received with statin therapy.


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**Section 7.0**
**Microvascular Benefits of Fenofibrate Therapy**

This section discusses the microvascular benefits of fenofibrate therapy in patients with diabetes, such as reductions in albuminuria, retinopathy, amputation, and neuropathy derived from analyses of the ACCORD Lipid and FIELD trials.

**Section 8.0**
**Safety of Fibrate-Statin Coadministration Therapy**

The safety of fenofibrate/fenofibric acid is presented in detail, with focus on renal, hepatic, and muscle events and pancreatitis. The safety profile is summarized from ACCORD Lipid, FIELD, the Trilipix clinical program, postmarketing surveillance, observational cohort studies, and a published meta-analysis of 18 trials with fibrates. In this section, Trilipix prescribing patterns are also presented.

**Section 9.0**
**Benefit-Risk Conclusions**

**Section 10.0**
**Recommendations to Guide Appropriate Usage**

**Appendices**

A list of cited literature is provided, followed by appendices with methodology for the Abbott meta-analysis, diagrams of the molecular structure of fenofibrate and fenofibric acid, the Trilipix prescribing information, and results from the Trilipix clinical program in the study conducted with simvastatin.


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## 2.0 The Scope of Dyslipidemia and the Role of Triglycerides and HDL-C in CV Disease

**Highlights:**

- Elevated TG and low HDL-C are independent risk factors for coronary heart disease (CHD).
- In meta-analyses of CV outcomes trials, larger decreases in TG were associated with greater reduction in the risk of a coronary event.
- Approximately 20% of statin-treated patients with preexisting CHD have additional CV events within 5 years of their first event, emphasizing the need for additional intervention.
- The residual risk for CV events in patients treated with statins is associated with elevated TG and/or low HDL-C, suggesting patients with persistent abnormal TG and/or HDL-C despite statin therapy may benefit from treatments that lower TG and raise HDL-C.

Dyslipidemia is a common condition in the US despite available treatments. Reported results from the Third National Health and Nutrition Examination Survey (NHANES) 2003–2004 found that 48% of the non-institutionalized US population aged 20 to 79 years (102.6 million people when standardized to the 2007 US population) had at least one abnormal lipid parameter (LDL-C, TG, and/or HDL-C).[1] Sixteen percent of US adults have 2 or more lipid abnormalities, including 7% (14.4 million) with both elevated TG and low HDL-C. Since these results are independent of treatment status, they underestimate the off-treatment prevalence of dyslipidemia.

There is extensive evidence that elevated LDL-C is a major risk factor for CV disease, and it is well established that statins effectively reduce LDL-C in patients with hypercholesterolemia and decrease morbidity and mortality associated with cardiovascular disease by 25% to 35%.[2–7] However, a published meta-analysis of 14 randomized controlled trials identified that, while statins provided significant


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reductions in CV events, substantial risk remained, as approximately 20% of statin-treated patients with preexisting CHD had further CV events within 5 years of their first event.[8,9]

The primary focus of the published National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines is to treat patients in order to achieve LDL-C goals and, thus, reduce the risk of CHD. The NCEP ATP III uses a risk-stratified approach to specify LDL-C treatment goals (Table 1). NCEP ATP III also designates the presence of T2DM as a CHD risk equivalent.[10]



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**Table 1. NCEP ATP III LDL-C Goals and Cut Points for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories**

| Risk Category | LDL-C Goal | Initiate TLC | Consider Drug Therapy |
|---|---|---|---|
| High risk: CHD* or CHD risk equivalents† (10-year risk > 20%) | < 100 mg/dL (optional goal: < 70 mg/dL)& | ≥ 100 mg/dL# | ≥ 100 mg/dL†† (< 100 mg/dL; consider drug options)** |
| Moderately high risk: 2+ risk factors‡ (10-year risk 10%–20%)§§ | < 130 mg/dL¶ | ≥ 130 mg/dL# | ≥ 130 mg/dL (100–129 mg/dL; consider drug options)‡‡ |
| Moderate risk: 2+ risk factors‡ (10-year risk < 10%)§§ | < 130 mg/dL | ≥ 130 mg/dL | ≥ 160 mg/dL |
| Lower risk: 0–1 risk factor§ | < 160 mg/dL | ≥ 160 mg/dL | ≥ 190 mg/dL (160–189 mg/dL; LDL-C–lowering drug optional) |

TLC = therapeutic lifestyle changes

* CHD includes history of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia.

† CHD risk equivalents include clinical manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease [transient ischemic attacks or stroke of carotid origin or > 50% obstruction of a carotid artery]), DM, and 2+ risk factors with 10-year risk for hard CHD > 20%.

‡ Risk factors include cigarette smoking, hypertension (BP ≥ 140/90 mmHg or on antihypertensive medication), low HDL cholesterol (< 40 mg/dL), family history of premature CHD (CHD in male first-degree relative < 55 years of age; CHD in female first-degree relative < 65 years of age), and age (men ≥ 45 years; women ≥ 55 years).

§§ Electronic 10-year risk calculators are available at www.nhlbi.nih.gov/guidelines/cholesterol.

§ Almost all people with zero or 1 risk factor have a 10-year risk < 10%, and 10-year risk assessment in people with zero or 1 risk factor is thus not necessary.

& Very high risk favors the optional LDL-C goal of < 70 mg/dL, and in patients with high triglycerides, non-HDL-C < 100 mg/dL.

¶ Optional LDL-C goal < 100 mg/dL.

\# Any person at high risk or moderately high risk who has lifestyle-related risk factors (e.g., obesity, physical inactivity, elevated triglyceride, low HDL-C, or metabolic syndrome) is a candidate for therapeutic lifestyle changes to modify these risk factors regardless of LDL-C level.

** When LDL-lowering drug therapy is employed, it is advised that intensity of therapy be sufficient to achieve at least a 30% to 40% reduction in LDL-C levels.

†† If baseline LDL-C is < 100 mg/dL, institution of an LDL-lowering drug is a therapeutic option on the basis of available clinical trial results. If a high-risk person has high triglycerides or low HDL-C, combining a fibrate or nicotinic acid with an LDL-lowering drug can be considered.

‡‡ For moderately high-risk persons, when LDL-C level is 100 to 129 mg/dL, at baseline or on lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL-C level < 100 mg/dL is a therapeutic option on the basis of available clinical trial results.

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Following treatment of LDL-C, non–HDL-C is a secondary therapeutic target in patients with hypertriglyceridemia (TG ≥ 200 mg/dL), with a goal of less than 30 mg/dL above the patient's LDL-C target. The importance of treating non–HDL-C was underscored by a recent meta-analysis of lipid-modifying CV outcomes trials, which found a direct and consistent relationship between non–HDL-C lowering and cardiovascular risk reduction.[12] The means by which non–HDL-C may be targeted in those patients with well-controlled LDL-C is to reduce TG. The NCEP ATP III also considers HDL-C < 40 mg/dL as low and encourages use of therapies that raise HDL-C.[10]

Epidemiologic investigations have established that CV morbidity and mortality vary directly with the levels of total cholesterol, LDL-C, and TG, and inversely with the level of HDL-C.[13,14] Furthermore, the presence of the lipid triad of elevated LDL-C, elevated TG, and low HDL-C confers additional CHD risk compared to elevated LDL-C alone.[15]

**Elevated Triglycerides as a Risk Factor for CV Outcomes**

A large body of epidemiological evidence supports elevated TG as an independent risk factor for CV disease.[13,14,16,17] A meta-analysis of 29 prospective epidemiological studies involving data from 262,525 patients, including 10,158 with CHD, reported a 72% higher risk for CHD for patients in the top third versus the bottom third of the TG values (adjusted OR = 1.72; 95% CI: 1.56, 1.90).[16] The impact of TG on CHD risk was similar in men and women, and a strong, statistically significant association between TG and CHD risk remained, after adjusting for HDL-C.[16]

These findings were supported by a recent analysis of the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction (PROVE IT-TIMI 22) trial, which compared intensive versus moderate statin monotherapy and demonstrated that on-treatment TG levels < 150 mg/dL were associated with a lower risk of recurrent CHD events, independent of the level of LDL-C.[18] For each 10-mg/dL decrease in TG, the incidence of death, MI, and recurrent acute coronary syndrome was lower by 1.4% to 1.6%, after adjustment for LDL-C and other covariates. Moreover, the combination of low LDL-C (< 70 mg/dL) and low TG (< 150 mg/dL) was


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associated with the lowest event rates compared with higher LDL-C, higher TG, or both (Table 2).[18]

**Table 2. Risk of Recurrent CHD Events by On-Treatment TG and LDL-C Values in PROVE IT-TIMI 22**

| Lipid Thresholds, mg/dL | | % of Subjects | | | |
|---|---|---|---|---|---|
| TG | LDL-C | with Event | Hazard Ratio | 95% CI | *P* value |
| < 150 | < 70 | 11.7% | 0.72 | (0.54, 0.94) | 0.017 |
| ≥ 150 | < 70 | 16.5% | 0.84 | (0.65, 1.09) | 0.192 |
| < 150 | ≥ 70 | 15.0% | 0.85 | (0.67, 1.08) | 0.180 |
| ≥ 150 | ≥ 70 | 17.9% | reference | | |

Source: Miller et al.[18]

## Low HDL-C as a Risk Factor for CV Outcomes

Data from the Framingham Heart Study indicate that there is a clear prognostic relationship between low HDL-C and increased CV morbidity and mortality, irrespective of LDL-C levels.[19,20] The incidence of CHD was more than 8-fold higher in patients with HDL-C levels < 35 mg/dL compared to patients in the highest HDL-C group. In addition, every 1-mg/dL decrease in HDL-C was associated with a consistent 2% to 3% increased risk of CHD.[20]

## Evidence that Treatment of TG and HDL-C Correlates with CV Outcomes

There is evidence that increasing HDL-C with lipid-modifying agents reduces the risk of atherosclerosis and CV events. Raising HDL-C by at least 7.5%, along with intensive reduction in LDL-C, was a predictor of clinical regression of atherosclerosis, as measured by intravascular ultrasound, in patients with CHD.[21] More recently, a post hoc analysis of the Treating to New Targets (TNT) trial demonstrated that the risk of CV events was lower in patients with higher on-treatment HDL-C levels compared to patients with lower HDL-C levels, in patients with LDL-C < 70 mg/dL (Figure 1).[22]


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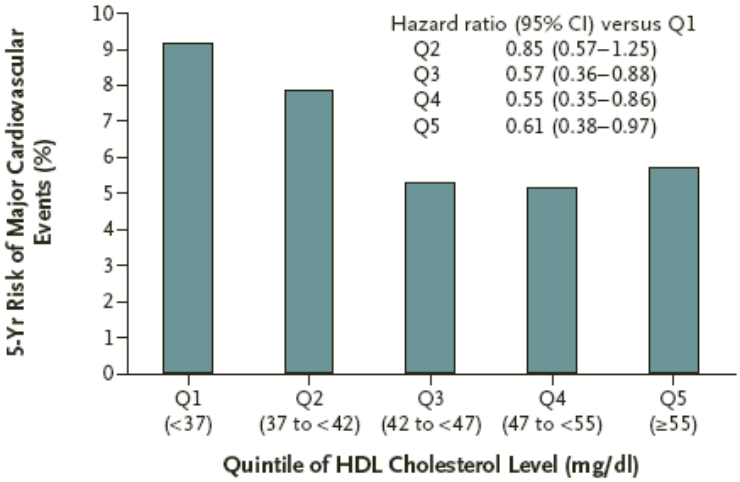
**Figure 1. Relationship of Quintiles of HDL-C Levels to CV Events in a Post Hoc Analysis of the TNT Trial in Patients with LDL-C < 70 mg/dL**




| | | | | | |
|---|---|---|---|---|---|
| No. of Events | 57 | 50 | 34 | 34 | 35 |
| No. of Patients | 473 | 525 | 550 | 569 | 544 |

Source: Barter et al.[22]

Similarly, a meta-analysis of 23 randomized lipid trials by Brown et al supported the hypothesis that patients with cardiovascular disease (CVD) benefit additively from LDL-C reduction and HDL-C elevation.[23] In another meta-analysis of 53 fibrate trials by Birjmohun et al, all of the fibrates evaluated, except clofibrate, significantly increased HDL-C by 10% ($P < 0.00001$). Eight of these studies included CV outcomes as an endpoint and were analyzed separately. In this analysis, fibrates significantly reduced the risk of a major coronary event by 25% (95% CI: 11%, 37%; $P < 0.001$) but did not affect the risk of coronary death.[24]

A meta-analysis by Jun et al of 18 fibrate outcomes trials encompassing 45,058 patients demonstrated that fibrate therapy conferred a 10% relative risk reduction for major CVD events (95% CI: 0%, 18%; $P = 0.048$) and a 13% relative risk reduction for coronary events (95% CI: 7%, 19%; $P < 0.0001$).[25] For coronary events, the benefit of fibrate therapy was larger in trials with a higher mean baseline TG level ($P = 0.030$). In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addition, a correlation between the TG reductions and risk of coronary events was noted ($P$ = 0.026), with larger risk reductions associated with larger TG decreases.[25]

Abbott conducted a meta-analysis of CV and/or coronary outcomes in over 215,000 patients in 71 outcomes trials (Appendix A), including statin, fibrate, and niacin trials. This meta-analysis evaluated the correlation between lipid parameters (i.e., LDL-C, TG, and HDL-C) and outcomes. The magnitudes of decrease in LDL-C and TG were independent and additive contributors to decreases in risk. In addition, baseline HDL-C was also a significant contributor to CV risk, with increased risk noted with lower baseline HDL-C.

In summary, the therapeutic benefit of adding a fibrate such as fenofibric acid to a statin is supported in patients with elevated TG and/or low HDL-C because elevated TG and low HDL-C are independent risk factors for and predictors of CHD.[13,16,19,26,27]



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# 3.0 The Role of Fenofibric Acid in the Treatment of Dyslipidemia

**Highlights:**

- Fenofibrate/fenofibric acid has more than 35 years of clinical use worldwide.
- Trilipix® (fenofibric acid) coadministered with a statin is highly effective in lowering elevated TG and raising low HDL-C, improving these parameters more than treatment with statins alone.
- In the Trilipix clinical program, patients with T2DM and those without T2DM had similar improvements in TG, HDL-C, and LDL-C, while females generally showed similar or greater mean improvements in lipid parameters than males.

The lipid-modifying effects of fenofibric acid are caused by the activation of peroxisome proliferator activated receptor α (PPARα). Fenofibric acid thereby increases lipolysis and elimination of TG-rich particles from plasma by activating lipoprotein lipase and inhibiting production of apolipoprotein (Apo) CIII. PPARα also mediates the increased production of hepatic Apo AI and Apo AII, major constituents of HDL-C.[28]

## 3.1 Regulatory History

Fenofibrate, first marketed in Europe in 1975 and in the US in 1998 as TriCor®, has been available for more than 35 years and is marketed in more than 80 countries worldwide. Fenofibrate is indicated as adjunctive therapy to diet to reduce elevated LDL-C, total cholesterol, TG, Apo B, and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia and for adult patients with hypertriglyceridemia.

Fenofibric acid is the active moiety of fenofibrate and Trilipix® (fenofibric acid choline salt; see Appendix B). Trilipix was approved by the US FDA on 15 December 2008


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(NDA 22-224) with all the indications currently approved for TriCor® on the basis of demonstrated bioequivalence between Trilipix 135 mg and the reference micronized 200 mg fenofibrate capsules. Trilipix is currently only marketed in the US. After the conduct of a large Phase 3 program, including 3 randomized controlled trials in 2,698 patients followed for up to 2 years, an additional indication was granted for Trilipix to be coadministered with a statin:

> **Coadministration Therapy with Statins for the Treatment of Mixed Dyslipidemia**
>
> Trilipix is indicated as an adjunct to diet 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.

In the US, Trilipix is the only fibrate with an indication for coadministration with statins for the treatment of mixed dyslipidemia. The US prescribing information for Trilipix is provided in Appendix C.

Following the release of the ACCORD Lipid trial results on 14 March 2010,[29] the FDA posted a Public Statement on www.fda.gov to advise that they would review the findings from ACCORD Lipid,[30] and that part of this review would be to determine how the trial's findings relate to the approved indication and labeling for Trilipix. The 19 May 2011 advisory committee meeting has been convened as part of the FDA review.

On the basis of the ACCORD Lipid findings in the prespecified subgroup with dyslipidemia and supportive data, the European Committee for Human Medicinal Products (CHMP) issued a Positive Opinion on 21 October 2010 to amend labeling for fenofibrate in the European Union to add the following indication for coadministration with a statin:


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**Coadministration Therapy with Statins for the Treatment of Mixed Dyslipidemia**

Fenofibrate is indicated as an adjunct to diet and other non-pharmacological treatment (e.g., exercise, weight reduction) for mixed hyperlipidaemia in patients at high cardiovascular risk in addition to a statin when triglycerides and HDL cholesterol are not adequately controlled.

This indication is consistent with the Trilipix coadministration indication.

## 3.2 Efficacy in the Trilipix Clinical Program

The coadministration indication for Trilipix was supported by the findings from 3 12-week randomized, controlled clinical studies, comparing the effect of coadministration therapy with fenofibric acid and a statin versus fenofibric acid monotherapy and statin monotherapy on key lipid parameters. Each study evaluated 1 of 3 statins (simvastatin, atorvastatin, or rosuvastatin; Figure 2). The development program also included a 1-year open-label extension study. A subset of these patients receiving coadministration therapy were followed for up to 116 weeks of treatment. Altogether, 2,698 patients were treated in the Trilipix clinical program.



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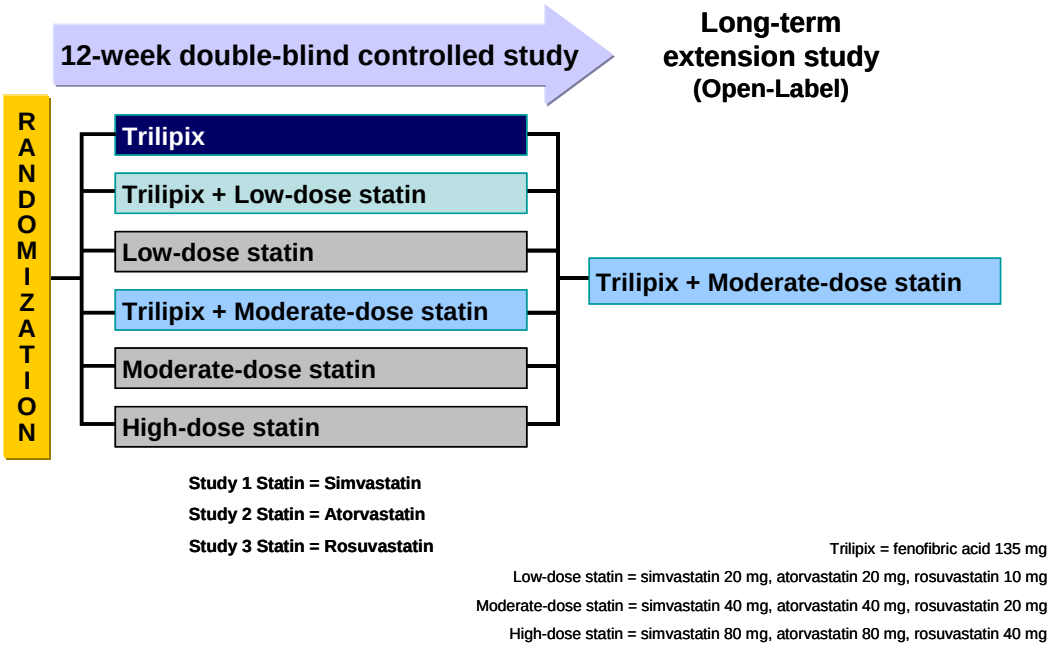
**Figure 2. Design of Studies in the Trilipix Clinical Program**




The data supporting the indication for the use of Trilipix coadministered with a statin demonstrate that adding fenofibric acid to a statin in patients with mixed dyslipidemia (defined by the study entry criteria as TG ≥ 150 mg/dL, HDL-C < 40 mg/dL for men and < 50 mg/dL for women, and LDL-C ≥ 130 mg/dL) resulted in statistically significantly greater improvements with coadministration therapy in the prespecified primary endpoints for the 3 main lipid parameters after 12 weeks of therapy (results for all 3 endpoints had to be statistically significant in order for coadministered therapy to be considered superior to monotherapy):

- Greater reductions in LDL-C compared to fenofibric acid monotherapy
- Greater reductions in TG compared to the corresponding dose of statin monotherapy
- Greater elevations in HDL-C compared to the corresponding dose of statin monotherapy

Results are presented for pooled data across the 3 statins/studies.

Detailed baseline characteristics are shown in Table 3 for the 3 pooled studies. At baseline (after a 6-week washout of lipid-modifying therapy), the Trilipix clinical program population overall had high TG (mean of 282.2 mg/dL), high LDL-C (mean of 157.3 mg/dL), and low HDL-C (mean of 38.4 mg/dL).



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**Table 3. Demographic and Baseline Characteristics for Patients from Pooled Trilipix Clinical Studies**

| | Treatment Group n (%) | | | | | |
|---|---|---|---|---|---|---|
| **Demographic Characteristic** | **Fenofibric Acid (N = 490)** | **Low-dose Statin (N = 493)** | **Fenofibric Acid + Low-dose Statin (N = 490)** | **Moderate-dose Statin (N = 491)** | **Fenofibric Acid + Moderate-dose 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) |
| Mean body weight (SD), kg | | | | | | |
| Females | 84.6 (18.6) | 85.9 (19.2) | 84.6 (17.9) | 85.5 (19.7) | 86.2 (19.8) | 86.6 (20.0) |
| Males | 99.8 (21.5) | 97.8 (19.6) | 96.4 (18.8) | 97.6 (16.8) | 97.5 (18.5) | 97.9 (15.2) |
| Diabetic history | | | | | | |
| With T2DM | 105 (21.4) | 105 (21.3) | 106 (21.6) | 107 (21.8) | 110 (22.5) | 53 (21.6) |
| Mean lipid parameters (SD), mg/dL | | | | | | |
| LDL-C | 158.6 (35.4) | 154.0 (34.2) | 156.1 (37.2) | 156.7 (34.2) | 156.8 (35.3) | 155..8 (32.8) |
| TG | 280.9 (162.7) | 284.1 (150.7) | 281.2 (147.5) | 290.0 (162.3) | 287.2 (160.4) | 280.4 (142.6) |
| HDL-C | 38.6 (6.8) | 38.4 (6.9) | 38.3 (7.1) | 38.4 (7.3) | 38.3 (7.3) | 37.9 (6.9) |

T2DM = type 2 diabetes mellitus

Results in each individual trial were statistically significant for each of the 3 components of the prespecified primary endpoint (Table 4), and results were consistent regardless of whether the statin coadministered with fenofibric acid was simvastatin, atorvastatin, or rosuvastatin. Results for the study conducted with simvastatin, the statin used in



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ACCORD Lipid, are provided in Appendix D, along with a brief description of statistical methods used in the Trilipix clinical program. Importantly, 12 weeks of coadministration therapy resulted in mean values for all 3 primary lipid parameters that were at or within the recommended optimal therapeutic targets.[10,31,32] These data provide substantial clinical evidence that adding Trilipix to a statin in patients with mixed dyslipidemia improves TG and HDL-C more than treatment with statins alone. Significant improvements were also observed in prespecified secondary endpoints of non–HDL-C, Apo B, and high-sensitivity C-reactive protein (hsCRP) (Table 5).[33]

**Table 4. Prespecified Primary Endpoint from Pooled Trilipix Clinical Studies**

| | Treatment Group | | | | | |
|---|---|---|---|---|---|---|
| **Parameter** | **Fenofibric Acid (N = 490)** | **Low-dose statin (N = 493)** | **Fenofibric Acid + Low-dose statin (N = 490)** | **Moderate-dose statin (N = 491)** | **Fenofibric Acid + Moderate-dose statin (N = 489)** | **High-dose statin[a] (N = 245)** |
| Mean HDL-C, mg/dL | | | | | | |
| Baseline | 38.4 | 38.4 | 38.2 | 38.4 | 38.1 | 38.0 |
| Final | 44.3 | 40.7 | 44.8 | 41.1 | 44.3 | 40.6 |
| % Change | +16.3% | +7.4% | +18.1%* | +8.7% | +17.5%* | +7.9% |
| Mean TG, mg/dL | | | | | | |
| Baseline | 280.7 | 286.1 | 282.1 | 287.9 | 286.1 | 282.5 |
| Final | 177.3 | 217.6 | 146.7 | 202.5 | 147.5 | 186.1 |
| % Change | –31.0% | –16.8% | –43.9%* | –23.7% | –42.0%* | –28.1% |
| Mean LDL-C, mg/dL | | | | | | |
| Baseline | 158.4 | 153.8 | 155.7 | 158.0 | 156.4 | 156.1 |
| Final | 146.1 | 100.6 | 101.9 | 91.6 | 99.1 | 81.7 |
| % Change | –5.1% | –33.9% | –33.1%& | –40.6% | –34.6%& | –47.1% |

a. No statistical comparisons were made between the high-dose statin arm and other treatment arms.

* Statistically significant difference between coadministration therapy and statin monotherapy at $P \leq 0.05$.

& Statistically significant difference between coadministration therapy and fenofibric acid monotherapy at $P \leq 0.05$.

Note: Only subjects with both a baseline and at least 1 postbaseline value are included in the analyses.



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## Table 5. Prespecified Secondary Endpoints from Pooled Trilipix Clinical Studies

| | Treatment Group | | | | | |
|---|---|---|---|---|---|---|
| **Parameter** | **Fenofibric Acid (N = 490)** | **Low-dose statin (N = 493)** | **Fenofibric Acid + Low-dose statin (N = 490)** | **Moderate-dose statin (N = 491)** | **Fenofibric Acid + Moderate-dose statin (N = 489)** | **High-dose statin[a] (N = 245)** |
| Mean non-HDL-C, mg/dL | | | | | | |
| Baseline | 222.5 | 217.6 | 219.9 | 222.4 | 218.9 | 220.2 |
| Final | 181.4 | 140.9 | 129.7 | 127.0 | 125.7 | 115.5 |
| % Change | –17.3% | –34.9% | –40.4%*& | –42.4% | –42.0%& | –47.3% |
| Mean VLDL-C, mg/dL | | | | | | |
| Baseline | 65.0 | 66.0 | 65.5 | 67.8 | 64.5 | 66.1 |
| Final | 36.1 | 40.2 | 28.4 | 36.7 | 26.8 | 33.6 |
| % Change | –34.2% | –32.1% | –50.0%* | –38.9% | –51.2%* | –42.1% |
| Mean total cholesterol, mg/dL | | | | | | |
| Baseline | 260.9 | 257.0 | 258.6 | 261.3 | 257.3 | 258.5 |
| Final | 225.8 | 182.4 | 175.4 | 169.2 | 170.3 | 155.8 |
| % Change | –12.4% | –28.7% | –31.5%* | –34.7% | –33.3% | –39.5% |
| Mean Apo B, mg/dL | | | | | | |
| Baseline | 146.2 | 145.0 | 146.1 | 147.1 | 145.0 | 146.0 |
| Final | 122.1 | 99.1 | 92.0 | 91.6 | 90.7 | 83.6 |
| % Change | –15.6% | —31.1% | –36.3%* | –36.9% | –36.7% | –42.4% |
| Median hsCRP, mg/L | | | | | | |
| Baseline | 0.29 | 0.27 | 0.31 | 0.29 | 0.30 | 0.30 |
| % Change | –13.1% | –20.5% | –31.2%* | –27.7% | –37.3%* | –28.4% |

a. No statistical comparisons were made between the high-dose statin arm and other treatment arms.

* Statistically significant difference between coadministration therapy and statin monotherapy at $P \leq 0.05$.

& Statistically significant difference between coadministration therapy and fenofibric acid monotherapy at $P \leq 0.05$.

Note: Only subjects with both a baseline and at least 1 postbaseline value are included in the analyses.



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### 3.2.1 Efficacy in Key Subgroups

The 3 randomized controlled trials in the Trilipix clinical program included 1,393 females and 1,305 males, among whom 586 had T2DM.

In the pooled studies, baseline characteristics were similar between males and females (data not shown). Efficacy results in patients with T2DM were similar to results in patients without T2DM and in the overall population, as were results in both males and females. More than half (51.6%) of the patients treated in the Trilipix clinical program were women, and the observed improvements in lipid parameters with coadministration therapy were generally better in women than in men. Notably, results in women showed numerically greater mean percent reductions in LDL-C and TG and numerically greater mean percent increases in HDL-C compared to results in men (no statistical tests were performed comparing results between these groups) (Table 6). As with the overall population, the gender subgroups and the T2DM subgroups showed improvements in primary and secondary efficacy endpoint results (Table 6 and Table 7).[34–36]



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## Table 6. Prespecified Primary Endpoint from Pooled Trilipix Clinical Studies in Subgroups

| | Treatment Group | | | | | |
|---|---|---|---|---|---|---|
| **Parameter** | **Fenofibric Acid** | **Low-dose statin** | **Fenofibric Acid + Low-dose statin** | **Moderate-dose statin** | **Fenofibric Acid + Moderate-dose statin** | **High-dose statin[a]** |
| **Females** | N = 277 | N = 234 | N = 263 | N = 245 | N = 249 | N = 125 |
| Mean HDL-C, mg/dL | | | | | | |
| Baseline | 41.1 | 41.6 | 41.2 | 41.8 | 41.4 | 41.0 |
| Final | 48.3 | 44.2 | 49.0 | 44.5 | 49.4 | 44.1 |
| % Change | +18.3% | +8.1% | +19.9%* | +7.9% | +21.1%* | +8.7% |
| Mean TG, mg/dL | | | | | | |
| Baseline | 269.2 | 275.5 | 281.6 | 279.2 | 282.2 | 262.2 |
| Final | 160.2 | 204.8 | 138.3 | 190.4 | 137.9 | 185.3 |
| % Change | –35.7% | –20.2% | –45.6%* | –26.0% | –44.2%* | –24.9% |
| Mean LDL-C, mg/dL | | | | | | |
| Baseline | 161.3 | 159.9 | 161.0 | 163.3 | 161.4 | 165.8 |
| Final | 141.8 | 101.2 | 98.8 | 92.0 | 95.3 | 84.8 |
| % Change | –11.1% | –35.8% | –37.2%[&] | –42.5% | –39.0%[&] | –47.2% |
| **Males** | N = 213 | N = 259 | N = 227 | N = 246 | N = 240 | N = 120 |
| Mean HDL-C, mg/dL | | | | | | |
| Baseline | 34.8 | 35.3 | 34.5 | 35.0 | 34.5 | 34.5 |
| Final | 38.9 | 37.4 | 39.7 | 37.7 | 38.8 | 36.8 |
| % Change | +12.9% | +7.3% | +15.3%* | +9.8% | +13.3%* | +6.8% |
| Mean TG, mg/dL | | | | | | |
| Baseline | 295.7 | 296.9 | 283.6 | 297.0 | 290.8 | 304.1 |
| Final | 198.1 | 230.0 | 156.0 | 212.9 | 157.6 | 186.7 |
| % Change | –25.2% | –13.5% | –42.0%* | –21.9% | –39.8%* | –31.4% |
| Mean LDL-C, mg/dL | | | | | | |
| Baseline | 154.4 | 148.2 | 149.6 | 152.7 | 151.0 | 146.3 |
| Final | 151.6 | 100.0 | 105.5 | 91.6 | 102.8 | 78.5 |
| % Change | 2.3% | –31.8% | –28.6%[&] | –38.4% | –30.1%[&] | –47.2% |

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## Table 6. Prespecified Primary Endpoint from Pooled Trilipix Clinical Studies in Subgroups (Continued)

| | Treatment Group | | | | | |
|---|---|---|---|---|---|---|
| **Parameter** | **Fenofibric Acid** | **Low-dose statin** | **Fenofibric Acid + Low-dose statin** | **Moderate-dose statin** | **Fenofibric Acid + Moderate-dose statin** | **High-dose statin[a]** |
| **T2DM** | N = 105 | N = 105 | N = 106 | N = 107 | N = 110 | N = 53 |
| Mean HDL-C, mg/dL | | | | | | |
| Baseline | 38.0 | 38.0 | 38.4 | 38.5 | 38.6 | 38.3 |
| Final | 43.9 | 39.4 | 44.6 | 40.9 | 44.2 | 40.4 |
| % Change | +15.6% | +4.7% | +16.8%* | +8.7% | +16.3%* | +7.7% |
| Mean TG, mg/dL | | | | | | |
| Baseline | 293.0 | 293.7 | 299.9 | 294.4 | 283.6 | 250.0 |
| Final | 179.8 | 234.0 | 158.4 | 206.6 | 149.8 | 158.3 |
| % Change | –31.9% | –18.1% | –43.9%* | –24.2% | –43.4%* | –34.1% |
| Mean LDL-C, mg/dL | | | | | | |
| Baseline | 159.8 | 153.2 | 149.5 | 154.2 | 156.9 | 158.4 |
| Final | 145.5 | 95.2 | 97.4 | 88.9 | 101.0 | 76.1 |
| % Change | –5.3% | –37.5% | –34.0%& | –41.5% | –32.6%& | –50.2% |
| **Non-T2DM** | N = 385 | N = 388 | N = 384 | N = 384 | N = 379 | N = 192 |
| Mean HDL-C, mg/dL | | | | | | |
| Baseline | 38.5 | 38.4 | 38.1 | 38.4 | 38.0 | 37.8 |
| Final | 44.6 | 41.4 | 45.1 | 41.5 | 44.6 | 41.0 |
| % Change | +17.2% | +9.0% | +19.3%* | +9.4% | +18.5%* | +8.8% |
| Mean TG, mg/dL | | | | | | |
| Baseline | 272.8 | 279.7 | 272.4 | 281.4 | 282.2 | 286.4 |
| Final | 170.7 | 198.5 | 137.2 | 195.3 | 140.8 | 186.9 |
| % Change | –32.0% | –20.9% | –45.2%* | –24.7% | –42.6%* | –27.5% |
| Mean LDL-C, mg/dL | | | | | | |
| Baseline | 159.3 | 155.2 | 158.8 | 160.4 | 157.6 | 156.8 |
| Final | 148.6 | 104.5 | 105.6 | 94.9 | 101.0 | 85.7 |
| % Change | –3.7% | –31.5% | –31.5%& | –38.9% | –33.7%& | –44.7% |

a. No statistical comparisons were made between the high-dose statin arm and other treatment arms.

* Statistically significant difference between coadministration therapy and statin monotherapy at $P \leq 0.05$.

& Statistically significant difference between coadministration therapy and fenofibric acid monotherapy at $P \leq 0.05$.

Notes: Only subjects with both a baseline and at least 1 postbaseline value are included in the analyses. Diabetic status was determined from subject's medical history.



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## Table 7. Prespecified Secondary Endpoints from Pooled Trilipix Clinical Studies in Subgroups

| | Treatment Group | | | | | |
|---|---|---|---|---|---|---|
| **Parameter** | **Fenofibric Acid** | **Low-dose statin** | **Fenofibric Acid + Low-dose statin** | **Moderate-dose statin** | **Fenofibric Acid + Moderate-dose statin** | **High-dose statin[a]** |
| **Females** | N = 277 | N = 234 | N = 263 | N = 245 | N = 249 | N = 125 |
| Mean non–HDL-C, mg/dL | | | | | | |
| Baseline | 226.8 | 221.4 | 225.9 | 224.6 | 223.0 | 226.9 |
| Final | 174.4 | 138.8 | 125.4 | 126.4 | 119.8 | 120.1 |
| % Change | –22.1% | –37.3% | –43.7%*[&] | –43.6% | –45.9%[&] | –46.2% |
| Mean VLDL-C, mg/dL | | | | | | |
| Baseline | 65.0 | 64.2 | 64.9 | 65.6 | 62.5 | 63.6 |
| Final | 32.8 | 39.5 | 26.8 | 36.1 | 24.8 | 34.7 |
| % Change | –39.8% | –32.0 | –49.9%* | –38.4% | –52.6%* | –36.7% |
| Mean total cholesterol, mg/dL | | | | | | |
| Baseline | 266.7 | 263.9 | 267.1 | 266.9 | 264.5 | 268.8 |
| Final | 221.7 | 184.2 | 175.5 | 172.8 | 169.7 | 163.0 |
| % Change | –16.2% | –30.0% | –33.5%* | –35.0% | –35.5% | –38.5% |
| Mean Apo B, mg/dL | | | | | | |
| Baseline | 148.2 | 147.2 | 149.5 | 149.1 | 148.7 | 151.4 |
| Final | 116.4 | 98.3 | 89.3 | 92.3 | 86.8 | 85.8 |
| % Change | –21.3% | –32.7% | –39.4%* | –37.3% | –40.5%* | –42.2% |
| Median hsCRP, mg/L | | | | | | |
| Baseline | 3.68 | 3.59 | 4.44 | 3.89 | 3.93 | 3.70 |
| % Change | –15.7% | –23.7% | –33.5% | –28.9% | –39.0%* | –28.5% |

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## Table 7. Prespecified Secondary Endpoints from Pooled Trilipix Clinical Studies in Subgroups (Continued)

| | Treatment Group | | | | | |
|---|---|---|---|---|---|---|
| **Parameter** | **Fenofibric Acid** | **Low-dose statin** | **Fenofibric Acid + Low-dose statin** | **Moderate-dose statin** | **Fenofibric Acid + Moderate-dose statin** | **High-dose statin[a]** |
| **Males** | N = 213 | N = 259 | N = 227 | N = 246 | N = 240 | N = 120 |
| Mean non–HDL-C, mg/dL | | | | | | |
| Baseline | 216.5 | 214.1 | 212.7 | 220.2 | 214.7 | 213.7 |
| Final | 190.5 | 143.1 | 134.9 | 127.5 | 131.7 | 110.7 |
| % Change | –11.1% | –32.4% | –36.3%*[&] | –41.3% | –38.0%*[&] | –48.4% |
| Mean VLDL-C, mg/dL | | | | | | |
| Baseline | 65.0 | 67.9 | 66.2 | 70.1 | 66.7 | 69.2 |
| Final | 40.3 | 40.9 | 30.2 | 37.1 | 28.8 | 32.3 |
| % Change | –27.0% | –32.4% | –50.3%* | –39.9% | –50.2%* | –48.3% |
| Mean total cholesterol, mg/dL | | | | | | |
| Baseline | 252.7 | 250.7 | 248.3 | 255.4 | 249.6 | 248.1 |
| Final | 230.8 | 180.7 | 175.3 | 165.5 | 170.7 | 148.3 |
| % Change | –7.8% | –27.3% | –29.1% | –34.4% | –31.1%* | –40.4% |
| Mean Apo B, mg/dL | | | | | | |
| Baseline | 143.4 | 143.0 | 142.2 | 145.1 | 141.2 | 140.8 |
| Final | 129.5 | 99.9 | 95.2 | 90.9 | 94.8 | 81.3 |
| % Change | –8.3% | –29.5% | –32.7%* | –36.7% | –32.7%* | –42.6% |
| Median hsCRP, mg/L | | | | | | |
| Baseline | 2.16 | 2.03 | 2.15 | 2.11 | 2.15 | 2.38 |
| % Change | –7.3% | –16.7% | –26.5% | –26.0% | –35.%* | –27.5% |

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## Table 7. Prespecified Secondary Endpoints from Pooled Trilipix Clinical Studies in Subgroups (Continued)

| | Treatment Group | | | | | |
|---|---|---|---|---|---|---|
| **Parameter** | **Fenofibric Acid** | **Low-dose statin** | **Fenofibric Acid + Low-dose statin** | **Moderate-dose statin** | **Fenofibric Acid + Moderate-dose statin** | **High-dose statin[a]** |
| **T2DM** | N = 105 | N = 105 | N = 106 | N = 107 | N = 110 | N = 53 |
| Mean non–HDL-C, mg/dL | | | | | | |
| Baseline | 223.0 | 217.6 | 217.2 | 221.2 | 218.6 | 212.6 |
| Final | 180.1 | 139.4 | 125.5 | 126.3 | 127.7 | 103.2 |
| % Change | –17.9% | –35.9% | –41.8%*[&] | –42.5% | –40.9%[&] | –52.0% |
| Mean VLDL-C, mg/dL | | | | | | |
| Baseline | 65.9 | 68.6 | 66.5 | 69.6 | 63.5 | 61.0 |
| Final | 36.2 | 43.8 | 28.7 | 38.6 | 27.6 | 27.0 |
| % Change | –37.2% | –31.2% | –49.7%* | –41.3% | –52.0%* | –52.7% |
| Mean total cholesterol, mg/dL | | | | | | |
| Baseline | 260.0 | 257.3 | 255.6 | 259.4 | 259.4 | 253.1 |
| Final | 224.7 | 181.7 | 169.8 | 167.0 | 172.7 | 142.7 |
| % Change | –12.6% | –29.3% | –33.2%* | –35.3% | –32.6% | –43.7% |
| Mean Apo B, mg/dL | | | | | | |
| Baseline | 147.3 | 144.8 | 144.7 | 144.6 | 146.5 | 140.1 |
| Final | 122.4 | 97.2 | 91.3 | 91.3 | 92.9 | 75.1 |
| % Change | –15.6% | –32.7% | –36.2% | –36.3% | –35.3% | –46.8% |
| Median hsCRP, mg/L | | | | | | |
| Baseline | 3.05 | 3.27 | 3.66 | 3.58 | 3.92 | 4.25 |
| % Change | –12.1% | –25.5% | –25.0% | –33.8% | –39.3% | –28.9% |

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## Table 7. Prespecified Secondary Endpoints from Pooled Trilipix Clinical Studies in Subgroups (Continued)

| | Treatment Group | | | | | |
|---|---|---|---|---|---|---|
| **Parameter** | **Fenofibric Acid** | **Low-dose statin** | **Fenofibric Acid + Low-dose statin** | **Moderate-dose statin** | **Fenofibric Acid + Moderate-dose statin** | **High-dose statin[a]** |
| **Non-T2DM** | N = 385 | N = 388 | N = 384 | N = 384 | N = 379 | N = 192 |
| Mean non–HDL-C, mg/dL | | | | | | |
| Baseline | 223.4 | 218.6 | 221.6 | 223.8 | 220.0 | 223.1 |
| Final | 183.9 | 143.5 | 133.1 | 129.3 | 127.2 | 120.8 |
| % Change | –16.3% | –33.8% | –39.1%*& | –41.6% | –41.5%& | –45.3% |
| Mean VLDL-C, mg/dL | | | | | | |
| Baseline | 64.2 | 64.7 | 64.5 | 66.6 | 64.2 | 66.8 |
| Final | 35.8 | 38.9 | 28.0 | 35.8 | 26.2 | 34.9 |
| % Change | –32.7% | –31.7% | –49.5%* | –37.5% | –50.2%* | –38.6% |
| Mean total cholesterol, mg/dL | | | | | | |
| Baseline | 261.9 | 257.7 | 260.2 | 262.7 | 257.5 | 260.7 |
| Final | 228.4 | 184.8 | 179.3 | 172.2 | 172.0 | 161.6 |
| % Change | –11.6% | –27.7% | –30.1%* | –33.7% | –32.7% | –37.5% |
| Mean Apo B, mg/dL | | | | | | |
| Baseline | 146.5 | 145.6 | 147.0 | 148.3 | 145.1 | 148.1 |
| Final | 123.0 | 100.6 | 93.2 | 92.7 | 91.1 | 86.9 |
| % Change | –15.0% | –30.1% | –35.8%* | –36.5% | –36.5% | –40.7% |
| Median hsCRP, mg/L | | | | | | |
| Baseline | 2.91 | 2.55 | 2.96 | 2.67 | 2.80 | 2.76 |
| % Change | –14.5% | –19.6% | –33.6%* | –26.0% | –37.0%* | –27.5% |

a. No statistical comparisons were made between the high-dose statin arm and other treatment arms.

* Statistically significant difference between coadministration therapy and statin monotherapy at $P \leq 0.05$.

& Statistically significant difference between coadministration therapy and fenofibric acid monotherapy at $P \leq 0.05$.

Notes: Only subjects with both a baseline and at least 1 postbaseline value are included in the analyses. Diabetic status was determined from subject's medical history.



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Results in these subgroups, along with results in the overall population of patients treated in the Trilipix clinical program, support the approved indication for Trilipix (Section 3.0).

The overall safety profile of Trilipix, as assessed in the clinical program, is presented in Section 8.0, along with safety results from ACCORD Lipid and FIELD.



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# 4.0 ACCORD Lipid

**Highlights:**

- ACCORD was designed and conducted by the National Heart, Lung and Blood Institute, independently of Abbott.
- ACCORD Lipid was designed to evaluate the effect of coadministration therapy in a general T2DM population.
- The absence of a statistically significant reduction in CV risk with fenofibrate-simvastatin coadministration therapy in ACCORD Lipid overall is consistent with the modest degree of dyslipidemia at baseline.
- A prespecified subgroup of patients in ACCORD Lipid with elevated TG and low HDL-C demonstrated a statistically significant reduction in CV risk with coadministration therapy, in agreement with the results of previous fibrate CV outcomes trials.
- In sensitivity analyses conducted by Abbott, the statistically significant reduction in the risk of CV events observed in the subgroup with dyslipidemia was confirmed in a group of patients in this subgroup who were also receiving a statin at baseline and in patients receiving a statin at baseline but with alternative thresholds of TG and HDL-C abnormalities.
- In ACCORD Lipid, CV risk increased with more severe degrees of dyslipidemia (elevated TG and/or low HDL-C) in the simvastatin monotherapy group, while this risk was mitigated with fenofibrate-simvastatin coadministration therapy.

## 4.1 Design of the ACCORD Trial

The ACCORD trial was funded by the US National Institutes of Health and conducted by the National Heart, Lung and Blood Institute (NHLBI) beginning in 2001 at sites in the US and Canada. The ACCORD trial was designed to answer whether any of 3 therapeutic strategies could reduce the risk of major CVD events in patients with T2DM who are at especially high risk of CVD:


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- Intensive lowering of blood sugar levels (ACCORD Glycemia),
- Intensive lowering of blood pressure (ACCORD Blood Pressure), or
- Treatment of lipids with a fibrate drug plus a statin (ACCORD Lipid).

The results of the overall ACCORD (ACCORD Glycemia) and ACCORD Blood Pressure studies are not presented in this document. The protocol for ACCORD is available online.[37] In ACCORD Lipid, the effect of fenofibrate-simvastatin coadministration therapy on CV outcome events was compared to the effect of simvastatin monotherapy. Abbott provided fenofibrate for the ACCORD Lipid trial.

The ACCORD trial was designed to evaluate 3 medical strategies to reduce risk of CV events in patients with T2DM, as listed above.[29] The study population comprised patients with T2DM, with glycated hemoglobin ($HbA_{1c}$) of 7.5% or more and at high risk of CV events. Additional eligibility requirements were as follows:

- Patients aged 40 to 79 years who had clinical CVD or
- Patients aged 55 to 79 years who had subclinical CVD or had at least 2 cardiovascular risk factors

High risk of CV events was defined as at least 1 of the following:

- Presence of clinical CVD, or
- If no clinical CVD was present, evidence in the last 2 years suggesting a high likelihood of CVD, or
- Presence of at least 2 of the following factors that increase CV risk:
  - Use of lipid-lowering medication or untreated LDL-C > 130 mg/dL
  - Low HDL-C (< 40 mg/dL for men and < 50 mg/dL for women)
  - Use of blood pressure–lowering medication or untreated systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 95 mmHg


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- Current cigarette smoker, or
- Body mass index (BMI) > 32 kg/m$^2$

All patients in ACCORD were randomly assigned to receive either intensive glycemic control (targeting $HbA_{1c}$ below 6.0%) or standard therapy (targeting $HbA_{1c}$ of 7.0 to 7.9%) (ACCORD Glycemia). One subgroup of patients was also randomized in ACCORD Blood Pressure to receive either intensive blood pressure control (targeting SBP < 120 mmHg) or standard therapy (targeting SBP < 140 mmHg). The other subgroup of patients was randomized in ACCORD Lipid to receive simvastatin plus either fenofibrate or placebo (Figure 3).

**Figure 3. 2 x 2 Factorial Design of ACCORD Blood Pressure and ACCORD Lipid**

| | Blood Pressure | | Lipid | | |
|---|---|---|---|---|---|
| | Intensive (SBP<120) | Standard (SBP<140) | Simvastatin + Placebo | Simvastatin + Fenofibrate | |
| Intensive Glycemia ($HbA_{1c}$ <6%) | 1,178 | 1,193 | 1,383 | 1,374 | 5128 |
| Standard Glycemia ($HbA_{1c}$ 7% to 7.9%) | 1,184 | 1,178 | 1,370 | 1,391 | 5123 |
| | 2,362 | 2,371 | 2,753 | 2,765 | 10,251 |

Source: Elam et al.[38]

Participants in the ACCORD trial had to be eligible for the overarching Glycemia trial and for either the Blood Pressure or Lipid trial (or both). A total of 5,518 patients were enrolled in ACCORD Lipid. Patients in ACCORD Lipid were allowed, but not required,


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to be on statin therapy prior to study participation and there was no washout period prior to enrollment.

The ACCORD Lipid trial recruited a general T2DM population rather than a population with dyslipidemia. Specifically, patients were eligible to participate in ACCORD Lipid if they had the following:

- Observed LDL-C level of 60 to 180 mg/dL (or estimated if currently on lipid-modifying medication),
- HDL-C level < 55 mg/dL for women and Black subjects or < 50 mg/dL for all other groups, and
- TG level below 750 mg/dL if they were not receiving lipid therapy or below 400 mg/dL if they were receiving lipid therapy. No minimum value for TG was specified.

For all patients in the ACCORD trial, the primary outcome was:

- The first occurrence of a major adverse CV event, defined as:
  - Nonfatal MI,
  - Nonfatal stroke, or
  - CV death.

The following were secondary outcomes:

- A combination of the primary outcome plus any revascularization or hospitalization for congestive heart failure (termed the "expanded macrovascular outcome")
- Major coronary disease events
  - Fatal coronary events,
  - Nonfatal MI, or
  - Unstable angina


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- Nonfatal MI
- Total stroke (combined fatal and nonfatal stroke)
- Nonfatal stroke
- Total mortality
- CV mortality
- Congestive heart failure (death or hospitalization for heart failure).

The ACCORD trial investigators conducted additional prespecified analyses on microvascular endpoints, such as diabetic nephropathy, eye complications, and neuropathy.[39,40]

## 4.2 Fibrate Outcomes Trials Prior to ACCORD Lipid

At the time the ACCORD Lipid results were released, data were available from 4 key fibrate outcomes trials, the Helsinki Heart Study (HHS, published in 1987), the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT, published in 1999), the Bezafibrate Infarction Prevention trial (BIP, published in 2000) and the Fenofibrate Intervention and Event Lowering in Diabetes trial (FIELD, published in 2005). FIELD was designed to evaluate fenofibrate monotherapy and provides important insights into the effect of fenofibrate on CV outcomes. FIELD is particularly relevant to a discussion of ACCORD Lipid because FIELD is the only other major CV outcomes trial to evaluate fibrates in a diabetic patient population.

All trials were placebo controlled. The fibrate used, sample size, and patient population were different across the 4 trials (Table 8). All 4 trials showed a reduction in the risk of a CV outcome; the reduction was statistically significant in 2 of the 4 trials.


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**Table 8. Consistency of Results in 4 Fibrate Outcomes Trials Before ACCORD Lipid**

| Trial | N | Fibrate | Population | Duration | Risk Reduction (*P* value) |
|---|---|---|---|---|---|
| HHS[41,42] | 4081 | Gemfibrozil | Men, primary prevention | 5 years | –34% (< 0.02) |
| VA-HIT[43,44] | 2531 | Gemfibrozil | Men, secondary prevention | 5.1 years | –22% (0.006) |
| BIP[45] | 3090 | Bezafibrate | Men and women, secondary prevention | 6.2 years | –7% (0.24) |
| FIELD[46,47] | 9795 | Fenofibrate | Men and women with T2DM | 5 years | –11% (0.16) |

Not all patients enrolled in these trials had dyslipidemia at baseline. In each trial, a subgroup of patients with dyslipidemia was defined on the basis of elevated TG and low HDL-C levels (shown in Table 9). Across the 4 trials, the proportion of patients included in the subgroup with dyslipidemia ranged from 11% (BIP) to 33% (VA-HIT). In these subgroups, treatment with fibrates consistently demonstrated significant reduction in CV events (Table 9 and Figure 4, left panel). In contrast, in the complementary group of patients who did not have both elevated TG and low HDL-C, fibrates provided a nonsignificant reduction in the risk of CV events (Figure 4, right panel).

**Table 9. CV Outcomes in Dyslipidemic Population in 4 Fibrate Outcomes Trials**

| Trial | Fibrate | Dyslipidemia Subgroup Definition | Dyslipidemia Subgroup Risk Reduction (*P* value) |
|---|---|---|---|
| HHS | Gemfibrozil | TG > 204 mg/dL<br>HDL-C < 42 mg/dL | –68% (0.01) |
| VA-HIT | Gemfibrozil | TG ≥ 180 mg/dL<br>HDL-C ≤ 40 mg/dL | –37% (0.01) |
| BIP | Bezafibrate | TG ≥ 200 mg/dL<br>HDL-C < 35 mg/dL | –47% (0.02) |
| FIELD | Fenofibrate | TG ≥ 204 mg/dL<br>HDL-C < 40/50 mg/dL[a] | –28% (0.01) |

a. < 40 mg/dL for males and < 50 mg/dL for females.



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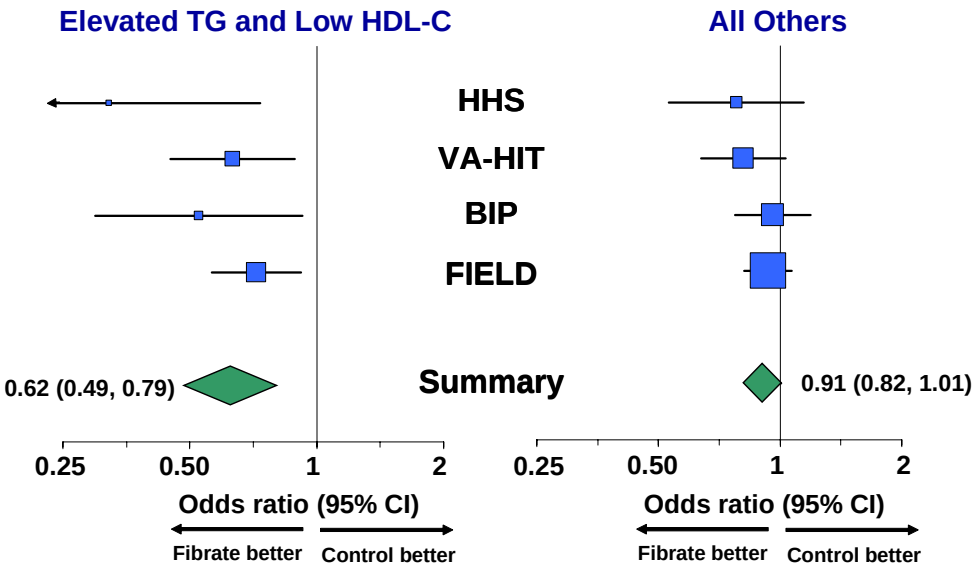
**Figure 4. Fibrates Reduced CV Events in Patients with Elevated TG and Low HDL-C in 4 Fibrate Outcomes Trials Conducted Before ACCORD Lipid**




Data on file at Abbott.

The odds ratio of 0.62 for patients with elevated TG and low HDL-C represents a significant 38% reduction in the odds of a CV event with fibrate therapy, while the odds ratio of 0.91 in all other patients represents a nonsignificant 9% reduction in the odds of a CV event.

The results of these previously conducted fibrate CV outcomes trials support 2 conclusions:

- In patients with elevated TG and low HDL-C, fibrate therapy significantly reduces the risk of CV events.
- In patients without elevated TG and low HDL-C, fibrate therapy does not provide a meaningful reduction in the risk of CV events.



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## 4.3 ACCORD Lipid Overall Results

On 14 March 2010, the results of the ACCORD Lipid trial were published. Select results are summarized below:

- The trial showed a trend toward reduction in cardiovascular events for coadministration therapy compared to statin monotherapy (HR = 0.92; 95% CI: 0.79, 1.08), although this finding was not statistically significant.
- Fenofibrate-simvastatin coadministration therapy resulted in a significant reduction in the risk of cardiovascular events, compared to simvastatin monotherapy when a prespecified subgroup with elevated TG (≥ 204 mg/dL) and low HDL-C (≤ 34 mg/dL) was examined (HR = 0.69; 95% CI: 0.49, 0.97; $P$ = 0.032; $P$ = 0.057 for interaction).
- A statistically significant treatment-by-gender interaction for the primary outcome was observed in the overall population ($P$ = 0.011).
- No significant treatment-by-gender interaction was observed in the prespecified subgroup with dyslipidemia ($P$ = 0.524).

The ACCORD investigators planned to enroll 5,800 patients into ACCORD Lipid. Of the 5,518 patients actually enrolled, the majority were white (68.4%) and male (69.3%) (Table 10).[29] The patients' mean age was 62.3 years, median duration of diabetes was 9 years, and 60% of patients were receiving a statin prior to study entry. Importantly, the overall ACCORD Lipid population did not have a significant degree of dyslipidemia, with a mean baseline LDL-C level of 101 mg/dL and a median baseline TG level of 162 mg/dL. This near-normal TG value is likely a result of the absence of a minimum TG level for enrollment into ACCORD Lipid. Thus, the overall ACCORD Lipid population does not represent the patients recommended for coadministration therapy per current lipid treatment guidelines.[10,48]


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**Table 10. Demographic and Baseline Characteristics of Patients in ACCORD Lipid**

| Characteristic | Overall Population (N = 5518) | Fenofibrate-Simvastatin (N = 2765) | Simvastatin Monotherapy (N = 2753) |
|---|---|---|---|
| **Categorical Variable** | | **n (%)** | |
| Gender | | | |
| Female | 1694 (30.7) | 851 (30.8) | 843 (30.6) |
| Male | 3824 (69.3) | 1914 (69.2) | 1910 (69.4) |
| Race | | | |
| White | 3774 (68.4) | 1909 (69.0) | 1865 (67.7) |
| Black | 834 (15.1) | 392 (14.2) | 442 (16.1) |
| Hispanic | 407 (7.4) | 213 (7.7) | 194 (7.0) |
| Had previous CVD event | 2016 (36.5) | 1008 (36.5) | 1008 (36.6) |
| Statin use at baseline | 3299 (59.8) | 1641 (59.3) | 1658 (60.2) |
| **Numeric Variable** | | **Mean (SD)** | |
| Age, years | 62.3 (6.8) | 62.2 (6.7) | 62.3 (6.9) |
| Duration of diabetes, years (median) | 9 | 10 | 9 |
| Baseline lipid values, mg/dL | | | |
| LDL-C | 100.6 (30.7) | 100.0 (30.3) | 101.1 (31.0) |
| HDL-C | 38.1 (7.8) | 38.0 (7.8) | 38.2 (7.8) |
| TG, median (Q1, Q3) | 162 (113, 229) | 164 (114, 232) | 160 (113, 227) |
| Total-C | 175.2 (37.3) | 174.7 (36.8) | 175.7 (37.9) |

The results of ACCORD Lipid demonstrated a nonsignificant reduction in the primary outcome (CV events) for fenofibrate-simvastatin coadministration therapy compared to simvastatin monotherapy (HR = 0.92; 95% CI: 0.79, 1.08; $P$ = 0.32).[29] Primary and secondary outcomes are displayed in Table 11.



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**Table 11. Primary and Secondary Outcomes in ACCORD Lipid**

| | Fenofibrate-Simvastatin (N = 2765) | | Simvastatin Monotherapy (N = 2753) | | Hazard Ratio | 95% CI | *P* value |
|---|---|---|---|---|---|---|---|
| | Events | Rate/yr | Events | Rate/yr | | | |
| Primary outcome | 291 | 2.24 | 310 | 2.41 | 0.92 | (0.79, 1.08) | 0.32 |
| Components of the primary outcome[a] | | | | | | | |
| Nonfatal MI – any | 173 | 1.32 | 186 | 1.44 | 0.91 | (0.74, 1.12) | 0.39 |
| Nonfatal stroke – any | 47 | 0.35 | 40 | 0.30 | 1.17 | (0.76, 1.78) | 0.48 |
| Death – CV cause | 99 | 0.72 | 114 | 0.83 | 0.86 | (0.66, 1.12) | 0.26 |
| Additional secondary outcomes | | | | | | | |
| Expanded macrovascular[b] outcome | 641 | 5.35 | 667 | 5.64 | 0.94 | (0.85, 1.05) | 0.30 |
| Major coronary disease event[b] | 332 | 2.58 | 353 | 2.79 | 0.92 | (0.79, 1.07) | 0.26 |
| Stroke – any | 51 | 0.38 | 48 | 0.36 | 1.05 | (0.71, 1.56) | 0.80 |
| Death – any cause | 203 | 1.47 | 221 | 1.61 | 0.91 | (0.75, 1.10) | 0.33 |
| Fatal or nonfatal CHF | 120 | 0.90 | 143 | 1.09 | 0.82 | (0.65, 1.05) | 0.10 |

a. The primary outcome was the first occurrence of any of the following outcomes: nonfatal MI, nonfatal stroke, CVD death. These individual events were secondary outcomes.

b. For definitions of these composite endpoints, refer to Section 4.1.

ACCORD Lipid confirms that routine use of fibrate-statin coadministration therapy does not significantly decrease CV events in the general diabetic patient population. However, as described previously in Section 4.2, the ACCORD Lipid results should be evaluated in the context of the evidence available from other fibrate CV outcomes trials. The following section describes results from ACCORD Lipid in patients with elevated TG and low HDL-C.

## 4.4 ACCORD Lipid Prespecified Subgroup with Dyslipidemia

The ACCORD Lipid trial prespecified a subgroup analysis of patients with simultaneous elevated TG and low HDL-C at baseline, based upon thresholds of the upper tertile of TG



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(≥ 204 mg/dL) and the lower tertile of HDL-C (≤ 34 mg/dL). The authors termed these patients the "subgroup with dyslipidemia" (N = 941). This group had higher median TG and lower mean HDL-C at baseline compared to the overall population (Table 12).

**Table 12. Demographic and Baseline Characteristics of Prespecified Subgroup with Dyslipidemia in ACCORD Lipid**

| | | Subgroup with Dyslipidemia | |
|---|---|---|---|
| **Characteristic** | **Overall Population (N = 5518)** | **Fenofibrate-Simvastatin (N = 485)** | **Simvastatin Monotherapy (N = 456)** |
| **Categorical Variable** | | **n (%)** | |
| Gender | | | |
| Female | 1694 (30.7) | 97 (20.0) | 92 (20.2) |
| Male | 3824 (69.3) | 388 (80.0) | 364 (79.8) |
| Race | | | |
| White | 3774 (68.4) | 375 (77.3) | 372 (81.6) |
| Black | 834 (15.1) | 36 (7.4) | 22 (4.8) |
| Hispanic | 407 (7.4) | 24 (4.9) | 27 (5.9) |
| Had previous CVD event | 2016 (36.5) | 195 (40.2) | 186 (40.8) |
| Statin use at baseline | 3299 (59.8) | 247 (50.9) | 230 (50.4) |
| **Numeric Variable** | | **Mean (SD)** | |
| Age, years | 62.3 (6.8) | 60.8 (6.3) | 61.6 (6.9) |
| Duration of diabetes, years (median) | 9 | 8 | 8 |
| Baseline lipid values, mg/dL | | | |
| LDL-C | 100.6 (30.7) | 96.3 (32.0) | 98.3 (32.8) |
| HDL-C | 38.1 (7.8) | 29.5 (3.8) | 29.4 (3.7) |
| TG, median (Q1, Q3) | 162 (113, 229) | 291 (238, 375) | 276 (232, 357) |
| Total-C | 175.2 (37.3) | 187.0 (38.5) | 188.9 (42.1) |

Complete results for the primary and secondary outcomes in ACCORD Lipid are shown for the subgroup with dyslipidemia in Table 13. Coadministration therapy significantly reduced the risk of the primary outcome (31% reduction, $P = 0.032$) (Figure 5), as well as the expanded macrovascular outcome (29% reduction, $P = 0.003$), major coronary disease event (37% reduction, $P = 0.004$), and CV mortality (50% reduction, $P = 0.022$) compared to simvastatin monotherapy.


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**Table 13. Primary and Secondary Outcomes in the Prespecified Subgroup with Dyslipidemia in ACCORD Lipid**

| | Fenofibrate-Simvastatin (N = 485) | | Simvastatin Monotherapy (N = 456) | | Hazard Ratio | 95% CI | *P* value |
|---|---|---|---|---|---|---|---|
| | Events | Rate/yr | Events | Rate/yr | | | |
| Primary outcome | 60 | 2.59 | 79 | 3.80 | 0.692 | (0.494, 0.969) | 0.032 |
| Components of the primary outcome[a] | | | | | | | |
| Nonfatal MI – any | 37 | 1.59 | 48 | 2.30 | 0.695 | (0.453, 1.068) | 0.097 |
| Nonfatal stroke – any | 10 | 0.42 | 10 | 0.45 | 0.910 | (0.379, 2.187) | 0.833 |
| Death – CV cause | 17 | 0.70 | 31 | 1.38 | 0.501 | (0.277, 0.906) | 0.022 |
| Additional secondary outcomes | | | | | | | |
| Expanded macrovascular[b] outcome | 130 | 6.15 | 158 | 8.58 | 0.706 | (0.560, 0.891) | 0.003 |
| Major coronary disease event[b] | 64 | 2.79 | 90 | 4.45 | 0.627 | (0.455. 0.864) | 0.004 |
| Stroke – any | 10 | 0.42 | 13 | 0.59 | 0.703 | (0.308, 1.605) | 0.403 |
| Death – any cause | 37 | 1.50 | 50 | 2.21 | 0.670 | (0.438, 1.025) | 0.065 |
| Fatal or nonfatal CHF | 33 | 1.40 | 32 | 1.48 | 0.918 | (0.564, 1.493) | 0.730 |

a. The primary outcome was the first occurrence of any of the following outcomes: nonfatal MI, nonfatal stroke, CVD death. These individual events were secondary outcomes.

b. For definitions of these composite endpoints, refer to Section 4.1.



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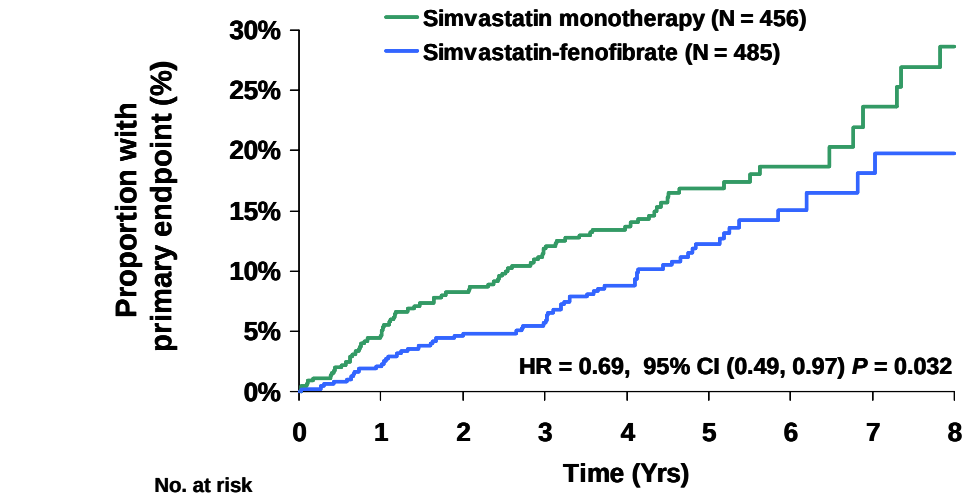
Kaplan-Meier estimates of the proportion of patients in the prespecified subgroup with dyslipidemia with a primary endpoint over time are displayed in (Figure 5).

**Figure 5. Coadministration Therapy Reduces Risk of CV Events in Prespecified Subgroup with Dysliplidemia in ACCORD Lipid**




| No. at risk | | | | | |
|---|---|---|---|---|---|
| Simvastatin monotherapy | 456 | 410 | 313 | 76 | 25 |
| Simvastatin-fenofibrate | 485 | 449 | 350 | 81 | 29 |



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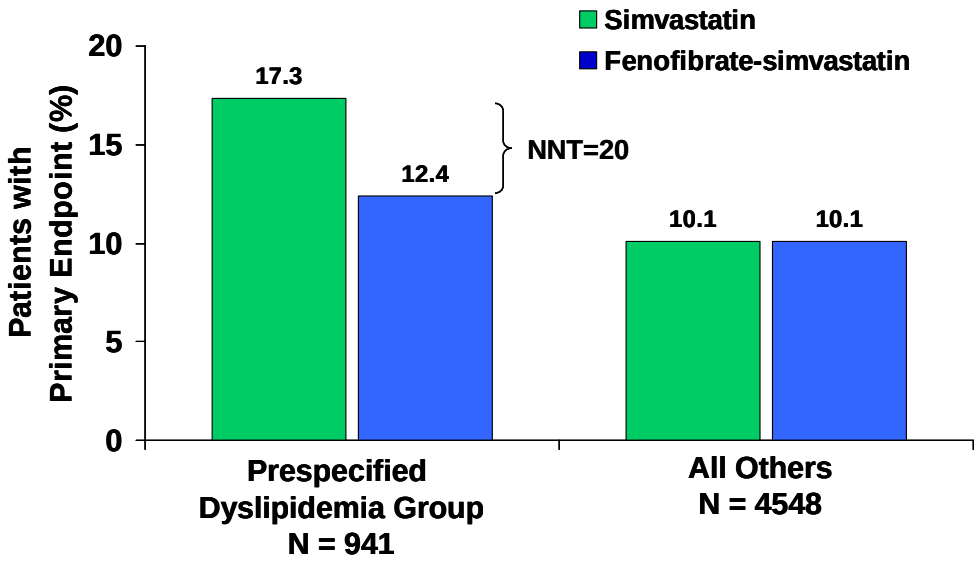
As shown in Figure 6, patients in the prespecified subgroup with dyslipidemia randomized to the simvastatin monotherapy arm were at substantially greater risk for a CV event than patients in that arm without both elevated TG and low HDL-C (17.3% versus 10.1%). In the subgroup with dyslipidemia, the 31% reduction in CV risk with coadministration therapy compared to simvastatin monotherapy corresponded to an absolute risk difference of 4.9% and a number needed-to-treat (NNT) of 20 patients for 4.7 years to prevent one CV event.

**Figure 6. Primary Outcome Events by Treatment Group in the Subgroup with Dyslipidemia and in All Other Patients in ACCORD Lipid**





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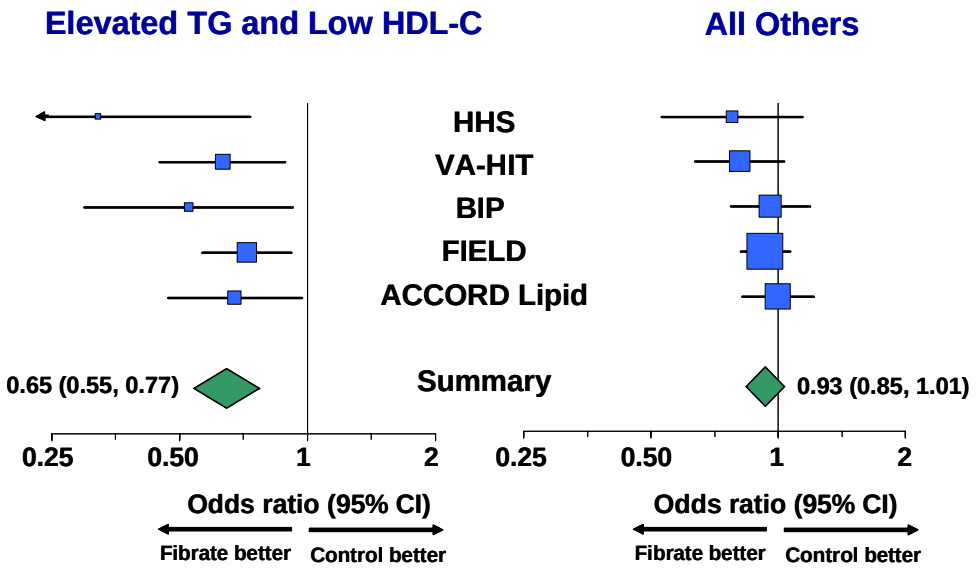
The results in the prespecified subgroup with dyslipidemia are consistent with the results from the 4 earlier fibrate outcomes trials (Figure 7, left panel). Specifically, there was a statistically significant treatment benefit in these patients in ACCORD Lipid and the magnitude of that benefit was similar to that observed in the other fibrate outcomes trials. Furthermore, results in ACCORD Lipid were also consistent with the earlier fibrate outcomes trials in that there was not a statistically significant reduction in CV events in patients without elevated TG and low HDL-C (Figure 7, right panel).

**Figure 7. ACCORD Lipid Confirms CV Benefit of Fibrate Therapy in Patients with Elevated TG and Low HDL-C**




The odds ratio of 0.65 for patients with elevated TG and low HDL-C represents a significant 35% reduction in the odds of a CV event with fibrate therapy, while the odds ratio of 0.93 in all other patients represents a nonsignificant 7% reduction in the odds of a CV event. Results of this analysis are consistent with those of similar recently published analyses.[49,50]

Thus, the ACCORD Lipid trial confirms the conclusions drawn from earlier fibrate CV outcomes trials (Section 4.2). In patients with elevated TG and low HDL-C, fibrates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consistently provide evidence of CV benefit regardless of gender, history of CV events, diabetic status, or concomitant statin therapy. In contrast, in patients without elevated TG and low HDL-C, there was a nonsignificant reduction in CV events. These conclusions are in agreement with those of the authors of the ACCORD Lipid trial publication: "We believe, therefore, that although ACCORD Lipid did not provide support for the general addition of fenofibrate to statin-treated patients with T2DM, it added significantly to the results from fibrate monotherapy trials indicative of benefit from such treatment in a significant subgroup of T2DM who present with significant dyslipidemia. In particular, ACCORD-Lipid trial, in our view, supports the addition of fenofibrate to statins in patients with optimal LDL-C levels but persistent significant hypertriglyceridemia (> 200 mg/dL) and low HDL-C levels (< 35 to 40 mg/dL)."[51]

## 4.5 Relating ACCORD Lipid Results to the Approved Trilipix Coadministration Indication

Trilipix is indicated to be coadministered 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 (Appendix C). In order to investigate how the ACCORD Lipid results relate to the approved Trilipix indication, the effect of coadministration therapy in populations most appropriate for coadministration therapy is evaluated in the following sections.

### 4.5.1 Sensitivity Analyses of the Results in the Prespecified Subgroup with Dyslipidemia in ACCORD Lipid

The National Institutes of Health granted Abbott access to a limited version of the ACCORD Lipid database after publication of the results in March 2010. Abbott used the ACCORD data to conduct sensitivity analyses of the results in the prespecified subgroup with dyslipidemia:


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| Sensitivity Analysis | Rationale for this Analysis |
|---|---|
| Subjects in the prespecified subgroup with dyslipidemia who were receiving a statin at baseline | Treatment guidelines and the Trilipix prescribing information support coadministration therapy only in patients already receiving statin therapy to achieve LDL-C goals |
| Subjects receiving a statin at baseline with TG ≥ 200 mg/dL or HDL-C < 40 mg/dL | Treatment guidelines provide TG and HDL-C thresholds for consideration of coadministration therapy that differ from those used to define the prespecified subgroup with dyslipidemia |

Each of these sensitivity analyses was also conducted among those patients who also had LDL-C < 100 mg/dL at baseline to represent a population with well-controlled LDL-C prior to the addition of fenofibrate therapy.

#### 4.5.1.1 Patients in the Prespecified Subgroup with Dyslipidemia Receiving a Statin at Baseline in ACCORD Lipid

The results for the prespecified subgroup with dyslipidemia in ACCORD Lipid demonstrate that in patients with elevated TG and low HDL-C, fenofibrate reduces the risk of CV events when coadministered with a statin, similar to the effect of fibrates in monotherapy outcomes trials. Analysis of the prespecified subgroup does not directly relate ACCORD Lipid to the Trilipix prescribing information because only 60% of patients enrolled in ACCORD Lipid were receiving a statin at baseline (study entry).[a] The Trilipix indication for coadministration therapy, consistent with treatment guidelines, specifies that patients should be receiving a statin prior to initiation of Trilipix. Therefore, Abbott conducted sensitivity analyses of the subgroup with dyslipidemia

[a] The design of ACCORD Lipid allowed, but did not require, patients to be on statin therapy prior to study participation. Baseline laboratory measurements were conducted prior to the initiation of study-provided simvastatin therapy; thus, for some patients, baseline measurements represented statin-modified lipid values, while for other patients, they represented untreated lipid values. All patients in ACCORD Lipid received 1 month of simvastatin therapy prior to initiation of randomized fenofibrate/placebo. However, lipid values were not measured at the end of this 1-month simvastatin monotherapy run-in. Therefore, for patients who were not receiving statin therapy prior to enrollment in ACCORD Lipid, it is unknown whether, after the initiation of simvastatin monotherapy, any of them had elevated TG and/or low HDL-C. Hence, the patients who were receiving a statin prior to enrollment in ACCORD Lipid provide the most relevant information to relate the study results to the Trilipix prescribing information.


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including only patients who were receiving statin therapy at baseline and the further subset of those who also had LDL-C < 100 mg/dL at baseline.

In ACCORD Lipid, 941 out of 5,518 patients (17%) were included in the subgroup with dyslipidemia, and of these, 477 were receiving statin therapy at baseline, 374 of whom had LDL-C < 100 mg/dL at baseline. In each of these subgroups, similar to the prespecified subgroup with dyslipidemia, a significant decrease in the risk of the primary outcome of CV events was observed for the coadministration of fenofibrate and simvastatin compared to simvastatin monotherapy (Table 14).

**Table 14. CV Risk Reduction in Sensitivity Analyses of the Prespecified Subgroup with Dyslipidemia in ACCORD Lipid: Patients Receiving a Statin at Baseline**

| Subgroup (Lipid parameters in mg/dL) | Mean Baseline Lipid Values, mg/dL | | | Number of CV Events (%) | | Hazard Ratio (95% CI) | *P* value |
|---|---|---|---|---|---|---|---|
| | LDL-C | TG | HDL-C | Fenofibrate-Simvastatin | Simvastatin Monotherapy | | |
| TG ≥ 204, HDL-C ≤ 34 | 97 | 326 | 29 | 60/485 (12.4%) | 79/456 (17.3%) | 0.69 (0.49, 0.97) | 0.032[a] |
| TG ≥ 204, HDL-C ≤ 34, baseline statin use | 81 | 305 | 30 | 31/247 (12.6%) | 49/230 (21.3%) | 0.55 (0.35, 0.87) | 0.010[b] |
| TG ≥ 204, HDL-C ≤ 34, baseline statin use, baseline LDL-C < 100 | 71 | 308 | 29 | 22/197 (11.2%) | 40/177 (22.6%) | 0.45 (0.27, 0.77) | 0.003[c] |

a. *P* value for treatment-by-subgroup (compared to all other patients, N = 4548) interaction = 0.057.
b. *P* value for treatment-by-subgroup (compared to all other patients, N = 5012) interaction = 0.016.
c. *P* value for treatment-by-subgroup (compared to all other patients, N = 5115) interaction = 0.005.

In the prespecified subgroup with dyslipidemia, for patients receiving a statin at baseline, the absolute risk difference for the primary endpoint was 8.8%, corresponding to an NNT of 11 patients over 4.7 years to prevent one CV event. Among those patients receiving a statin at baseline and whose LDL-C was < 100 mg/dL, the absolute risk difference was 11.4%, corresponding to an NNT of 9. These values compare favorably to the NNT of 20 in the overall prespecified subgroup with dyslipidemia.


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### 4.5.1.2 ACCORD Lipid Results in Patients Receiving a Statin at Baseline with TG of 200 mg/dL or More and/or with HDL-C Less than 40 mg/dL

The analysis of the prespecified subgroup with dyslipidemia confirms the reduction in CV risk with coadministration therapy in patients with TG ≥ 204 mg/dL and HDL-C ≤ 34 mg/dL, and the sensitivity analyses described in Section 4.5.1.1 confirm that this reduction in CV risk is also present in the subset of these patients who were receiving a statin at baseline. However, these analyses do not address whether coadministration therapy reduces CV risk in patients meeting other TG and HDL-C thresholds.

NCEP ATP III treatment guidelines identify TG ≥ 200 mg/dL as high and recommend consideration of treatment beyond LDL-C–lowering therapy for patients with TG above this threshold. For HDL-C, NCEP ATP III guidelines identify HDL-C < 40 mg/dL categorically as low, and the 2004 update to the ATP III guidelines indicates that for high-risk patients with low HDL-C, consideration can be given to combining a fibrate with an LDL-C–lowering drug.[10,11] Therefore, the sensitivity analyses described below evaluated the effect of coadministration therapy in patients who were receiving a statin at baseline and had TG ≥ 200 mg/dL and/or HDL-C < 40 mg/dL at baseline.

**Table 15. CV Risk Reduction in Patients Meeting Guideline-Based Lipid Thresholds in ACCORD Lipid**

| Subgroup (Lipid parameters in mg/dL) | Mean Baseline Lipid Values, mg/dL | | | Number of CV Events (%) | | Hazard Ratio (95% CI) | *P* value |
|---|---|---|---|---|---|---|---|
| | LDL-C | TG | HDL-C | Fenofibrate-Simvastatin | Simvastatin Monotherapy | | |
| Baseline statin use and either TG ≥ 200 or HDL-C < 40 at baseline | 86 | 205 | 35 | 119/1070 (11.1%) | 160/1115 (14.3%) | 0.76 (0.60, 0.96) | 0.021[a] |
| Baseline statin use, and baseline LDL-C < 100, and either TG ≥ 200 or HDL-C < 40 at baseline | 75 | 203 | 34 | 84/805 (10.4%) | 118/822 (14.4%) | 0.69 (0.52, 0.91) | 0.009[b] |

a. *P* value for treatment-by-subgroup (compared to all other patients, N = 3304) interaction = 0.024.

b. *P* value for treatment-by-subgroup (compared to all other patients, N = 3862) interaction = 0.017.



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In the group of patients receiving a statin at baseline with either TG ≥ 200 mg/dL or HDL-C < 40 mg/dL, the absolute risk difference for the primary endpoint was 3.2%, corresponding to an NNT of 31 patients over 4.7 years to prevent one CV event. Among those patients receiving a statin at baseline, with LDL-C < 100 mg/dL, and either TG ≥ 200 mg/dL or HDL-C < 40 mg/dL, the absolute risk difference was 3.9%, corresponding to an NNT of 26.

#### 4.5.1.3 ACCORD Lipid Results in Patients Receiving a Statin at Baseline by TG and HDL-C Thresholds

The sensitivity analyses described in the preceding sections demonstrate that coadministration therapy reduces CV risk among patients receiving a statin at baseline for various TG and HDL-C thresholds in ACCORD Lipid. The relationship between TG and HDL-C thresholds and the percentage of patients with the primary endpoint in each treatment group is illustrated in Figure 8. For patients treated with simvastatin monotherapy, the percentage of patients with the primary endpoint increased with increasing TG levels and decreasing HDL-C levels (ranging from 13% to 21%). These results illustrate that residual risk for CV events in ACCORD Lipid for patients on simvastatin monotherapy was strongly associated with the degree of TG and HDL-C abnormalities at baseline. These results are consistent with the CV risk known to be associated with elevated TG and low HDL-C, as described in Section 2.0. In contrast, the percentage of patients with the primary endpoint in the coadministration therapy group was lower and relatively uniform regardless of baseline TG and HDL-C levels (ranging from 10% to 13%), illustrating that coadministration therapy reduces the incremental residual risk associated with elevated TG and low HDL-C.


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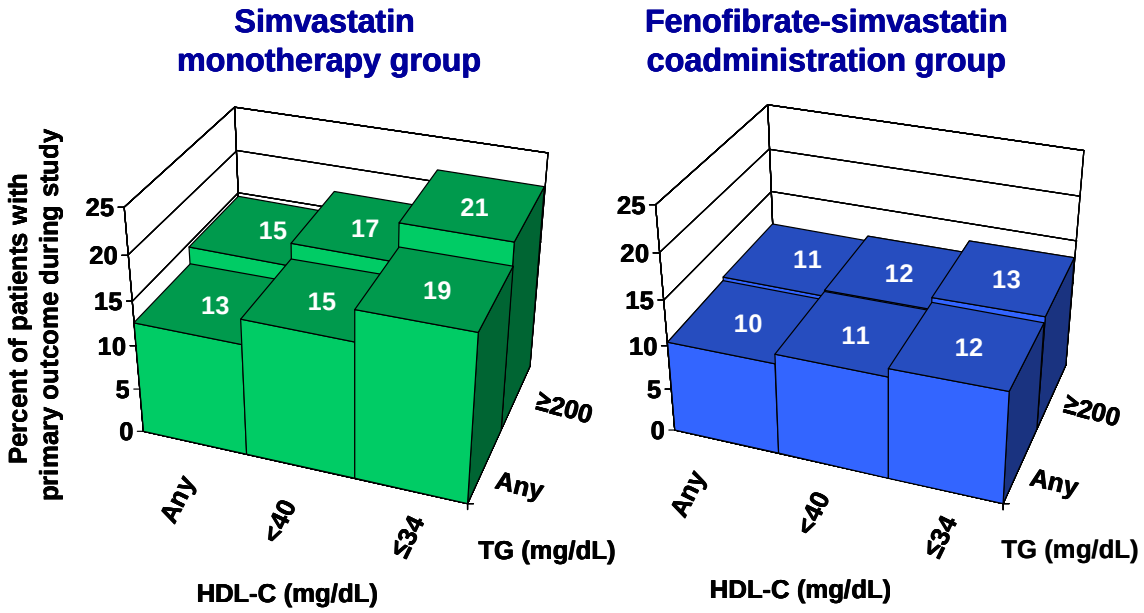
**Figure 8. Percentage of CV Events by TG and HDL-C Thresholds in Patients Receiving a Statin at Baseline in ACCORD Lipid**




For each combination of TG and HDL-C levels illustrated in Figure 8, an analysis was conducted to compare fenofibrate-simvastatin coadministration therapy to simvastatin monotherapy (Table 16). For 5 of the 6 analyses, a statistically significant difference in favor of coadministration therapy was observed (Table 16), and the estimated magnitude of reduction in CV risk provided by coadministration therapy increased with higher TG and lower HDL-C.



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**Table 16. Relative Risk of a CV Event for Coadministration Therapy Compared to Simvastatin Monotherapy by TG and HDL-C Thresholds in Patients Receiving a Statin at Baseline in ACCORD Lipid**

| | | HDL-C, mg/dL | | |
|---|---|---|---|---|
| | | **Any** | **< 40** | **≤ 34** |
| **TG, mg/dL** | **≥ 200** | N = 1000<br>**HR = 0.716**<br>*P* = 0.063 | N = 770<br>**HR = 0.659**<br>*P* = 0.032 | N = 489<br>**HR = 0.565**<br>*P* = 0.012 |
| | **Any** | N = 3299<br>**HR = 0.799**<br>*P* = 0.031 | N = 1955<br>**HR = 0.736**<br>*P* = 0.015 | N = 1064<br>**HR = 0.633**<br>*P* = 0.004 |

## Summary

In order to relate the ACCORD Lipid results to the Trilipix label and to confirm the results in the subgroup with dyslipidemia, Abbott performed sensitivity analyses on patient populations appropriate for coadministration therapy: those meeting the prespecified dyslipidemia criteria and receiving a statin at baseline, including those with LDL-C < 100 mg/dL, and those receiving a statin at baseline with thresholds for TG and HDL-C that are based on guidelines rather than the prespecified tertile criteria. In ACCORD Lipid, fenofibrate-simvastatin coadministration therapy demonstrated a statistically significant reduction in risk of CV events in these patient populations, as in the prespecified subgroup. In simvastatin-treated patients, risk of a CV event increased with increasing TG levels and decreasing HDL-C levels, consistent with the CV risk known to be associated with elevated TG and low HDL-C. In contrast, in the coadministration therapy group, event rates were consistently lower and relatively uniform, regardless of baseline TG and HDL-C levels, suggesting a mitigation of the impact of elevated TG and low HDL-C on CV risk with the addition of fenofibrate to simvastatin therapy.



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## 5.0 ACCORD Lipid Subgroup Analysis by Gender

**Highlights:**

- A significant treatment-by-gender interaction in ACCORD Lipid indicated a significant reduction in risk of CV events with coadministration therapy in men and a trend toward a potentially higher risk of CV events in women treated with coadministration therapy compared to simvastatin monotherapy, driven by a higher rate of nonfatal MI in women in the coadministration therapy group.
- In women in ACCORD Lipid, the rate of death from a CV cause was identical between the 2 treatment groups, while the all-cause mortality rate was lower with coadministration therapy compared to simvastatin monotherapy.
- The treatment-by-gender interaction in ACCORD Lipid is not substantiated by other published studies, including FIELD.
- Further investigation of the results in women in ACCORD Lipid did not reveal any explanation for the significant treatment-by-gender interaction.
- In the prespecified subgroup with dyslipidemia in ACCORD Lipid, there was not a treatment-by-gender interaction, indicating that, in this subgroup, the reduction in CV risk with coadministration therapy was not different for men and women.

A prespecified subgroup analysis based on gender in ACCORD Lipid[29] identified a statistically significant treatment-by-gender interaction ($P = 0.01$). Results in gender subgroups indicated a statistically significant treatment benefit of coadministration therapy in men and a trend toward a potentially higher risk of CV events in women treated with coadministration therapy compared to simvastatin monotherapy (Table 17).


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**Table 17. Risk of CV Events by Gender in ACCORD Lipid**

| | Fenofibrate-Simvastatin | Simvastatin Monotherapy | Hazard Ratio | 95% CI | *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 |

*P* value for treatment-by-gender interaction = 0.01.

## 5.1 Gender Analyses in ACCORD Lipid

Fewer than one-third of patients in ACCORD Lipid were female (30.7%). Statistically significant differences were observed between men and women for most demographic and baseline characteristics. Smaller proportions of women than men were taking statins (54% versus 62%, $P < 0.001$), while a higher proportion of men than women had experienced a previous CV event (41% versus 26%, $P < 0.001$). Duration of diabetes was similar in men and women.

Abbott evaluated the components of the CV endpoints in women and assessed the effect of fenofibrate-simvastatin coadministration therapy compared to simvastatin monotherapy in women with TG and HDL-C abnormalities at baseline despite statin therapy to lower LDL-C.

### 5.1.1 Primary and Secondary Outcomes by Gender in ACCORD Lipid

Results of the primary and secondary outcomes in women and men are summarized in Table 18. Although the overall rates for the primary outcome and composite secondary outcomes were higher in women receiving fenofibrate-simvastatin coadministration therapy compared to simvastatin monotherapy, the mortality rate for death from a CV cause in women was similar between the 2 treatment groups (18/851 versus 18/843 events; HR = 0.976; 95% CI: 0.507, 1.876; $P = 0.941$). In addition, women receiving coadministration therapy had a numerically lower all-cause mortality rate than women receiving simvastatin monotherapy (45/851 versus 50/843 events; HR = 0.893; 95% CI: 0.597, 1.335; $P = 0.58$).


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**Table 18. Primary and Secondary Outcomes by Gender in ACCORD Lipid**

| | Fenofibrate-Simvastatin (N = 851) | | Simvastatin Monotherapy (N = 843) | | | | |
|---|---|---|---|---|---|---|---|
| **Women** | **Events** | **Rate/yr** | **Events** | **Rate/yr** | **Hazard Ratio** | **95% CI** | ***P* value** |
| Primary outcome | 77 | 1.94 | 56 | 1.40 | 1.378 | (0.976, 1.945) | 0.069 |
| Components of the primary outcome[a] | | | | | | | |
| Nonfatal MI – any | 52 | 1.30 | 36 | 0.90 | 1.428 | (0.933, 2.184) | 0.101 |
| Nonfatal stroke – any | 11 | 0.27 | 9 | 0.22 | 1.204 | (0.499, 2.907) | 0.679 |
| Death – CV cause | 18 | 0.43 | 18 | 0.44 | 0.976 | (0.507, 1.876) | 0.941 |
| Additional secondary outcomes | | | | | | | |
| Expanded macrovascular outcome[b] | 151 | 4.03 | 136 | 3.61 | 1.094 | (0.868, 1.379) | 0.447 |
| Major coronary disease event[b] | 92 | 2.34 | 68 | 1.72 | 1.349 | (0.986, 1.845) | 0.062 |
| Stroke – any | 13 | 0.32 | 12 | 0.29 | 1.060 | (0.483, 2.323) | 0.885 |
| Death – any cause | 45 | 1.06 | 50 | 1.18 | 0.893 | (0.597, 1.335) | 0.580 |
| Fatal or nonfatal CHF | 31 | 0.77 | 38 | 0.95 | 0.785 | (0.488, 1.262) | 0.318 |
| **Men** | **(N = 1914)** | | **(N = 1910)** | | | | |
| Primary outcome | 214 | 2.37 | 254 | 2.87 | 0.824 | (0.687, 0.989) | 0.037 |
| Components of the primary outcome[a] | | | | | | | |
| Nonfatal MI – any | 121 | 1.33 | 150 | 1.69 | 0.789 | (0.621, 1.003) | 0.053 |
| Nonfatal stroke – any | 36 | 0.39 | 31 | 0.33 | 1.152 | (0.713, 1.863) | 0.563 |
| Death – CV cause | 81 | 0.86 | 96 | 1.02 | 0.838 | (0.623, 1.126) | 0.241 |
| Additional secondary outcomes | | | | | | | |
| Expanded macrovascular outcome[b] | 490 | 5.95 | 531 | 6.62 | 0.899 | (0.795, 1.016) | 0.089 |
| Major coronary disease event[b] | 240 | 2.68 | 285 | 3.27 | 0.820 | (0.690, 0.973) | 0.023 |
| Stroke – any | 38 | 0.41 | 36 | 0.39 | 1.047 | (0.664, 1.652) | 0.844 |
| Death – any cause | 158 | 1.65 | 171 | 1.80 | 0.914 | (0.737, 1.135) | 0.417 |
| Fatal or nonfatal CHF | 89 | 0.96 | 105 | 1.15 | 0.830 | (0.626, 1.101) | 0.196 |

a. The primary outcome was the first occurrence of any of the following outcomes: nonfatal MI, nonfatal stroke, CVD death. These individual events were secondary outcomes.

b. For definitions of these composite endpoints, refer to Section 4.1.



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In women, the difference between the 2 treatment groups for the primary outcome was driven by events of nonfatal MI. Fifty-two women in the coadministration therapy group had an event of nonfatal MI compared to 36 in the simvastatin monotherapy group. The higher rate of nonfatal MI in fenofibrate-treated women is unexpected as it is in distinct contrast to the observations in FIELD, where a consistent beneficial effect of fenofibrate on nonfatal MI was reported. In FIELD, treatment with fenofibrate reduced the risk of nonfatal MI in the overall population (HR = 0.76; 95% CI: 0.62, 0.94; *P* = 0.010),[46] with similar beneficial effects observed in men (HR = 0.78; 95% CI: 0.62, 1.00; *P* = 0.048) and women (HR = 0.70; 95% CI: 0.47, 1.05; *P* = 0.086). The higher nonfatal MI rate observed in women treated with coadministration therapy in ACCORD Lipid is inconsistent with these earlier results.

### 5.1.2 Analysis of the Prespecified Subgroup with Dyslipidemia by Gender in ACCORD Lipid

In the prespecified subgroup with dyslipidemia, there was no treatment-by-gender interaction (Table 19). In women in the subgroup with dyslipidemia, there was a numerically lower rate of CV events in women treated with coadministration therapy compared to women treated with simvastatin monotherapy (13.4% versus 15.2%; HR = 0.825; 95% CI: 0.379, 1.795; *P* = 0.627).

**Table 19. Risk of CV Events by Gender in the Prespecified Subgroup with Dyslipidemia in ACCORD Lipid**

| | Fenofibrate-Simvastatin | Simvastatin Monotherapy | Hazard Ratio | 95% CI | *P* value |
|---|---|---|---|---|---|
| Men | 47/388 (12.1%) | 65/364 (17.9%) | 0.659 | (0.451, 0.962) | 0.031 |
| Women | 13/97 (13.4%) | 14/92 (15.2%) | 0.825 | (0.379, 1.795) | 0.627 |

*P* value for treatment-by gender interaction = 0.524.

Primary and secondary outcomes among women in the prespecified subgroup with dyslipidemia are summarized in Table 20. There was no significant difference between coadministration therapy and simvastatin monotherapy for any individual event, with


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hazard ratios for all endpoints (except for major coronary disease event) favoring coadministration therapy.

**Table 20. Primary and Secondary Outcomes for Women in the Subgroup with Dyslipidemia in ACCORD Lipid**

| | Fenofibrate-Simvastatin (N = 97) | | Simvastatin Monotherapy (N = 92) | | | | |
|---|---|---|---|---|---|---|---|
| **Women** | **Events** | **Rate/yr** | **Events** | **Rate/yr** | **Hazard Ratio** | **95% CI** | ***P* value** |
| Primary outcome | 13 | 2.90 | 14 | 3.34 | 0.825 | (0.379, 1.795) | 0.627 |
| Components of the primary outcome[a] | | | | | | | |
| Nonfatal MI – any | 8 | 1.79 | 8 | 1.91 | 0.945 | (0.354, 2.524) | 0.910 |
| Nonfatal stroke – any | 1 | 0.22 | 2 | 0.46 | NA | NA | NA |
| Death – CV cause | 4 | 0.86 | 6 | 1.36 | 0.659 | (0.185, 2.346) | 0.520 |
| Additional secondary outcomes | | | | | | | |
| Expanded macrovascular outcome[b] | 20 | 4.65 | 25 | 6.62 | 0.664 | (0.367, 1.201) | 0.176 |
| Major coronary disease event[b] | 13 | 2.91 | 11 | 2.64 | 1.080 | (0.483, 2.417) | 0.851 |
| Stroke – any | 1 | 0.22 | 4 | 0.92 | 0.221 | (0.025, 1.989) | 0.178 |
| Death – any cause | 6 | 1.26 | 9 | 1.99 | 0.645 | (0.229, 1.817) | 0.406 |
| Fatal or nonfatal CHF | 6 | 1.34 | 7 | 1.69 | 0.791 | (0.265, 2.358) | 0.674 |

NA = not available, no model fit for outcomes with fewer than 5 events

a. The primary outcome was the first occurrence of any of the following outcomes: nonfatal MI, nonfatal stroke, CVD death. These individual events were secondary outcomes.

b. For definitions of these composite endpoints, refer to Section 4.1.

Sensitivity analyses similar to those described in Section 4.5.1 are summarized for women in Table 21. In each of these sensitivity analyses, there was no significant treatment-by-gender interaction. Although the sample sizes in some of these analyses were small, the absence of a significant interaction suggests no significant difference between men and women in the CV risk reduction provided by coadministration therapy.



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**Table 21. Risk of CV Events in Sensitivity Analyses in Women in ACCORD Lipid**

| Subgroup (Lipid parameters in mg/dL) | Number of CV Events (%) | | Hazard Ratio (95% CI) | *P* value |
|---|---|---|---|---|
| | Fenofibrate-Simvastatin | Simvastatin Monotherapy | | |
| TG ≥ 204, HDL-C ≤ 34, baseline statin use | 4/38 (10.5%) | 7/37 (18.9%) | 0.607 (0.169, 2.183) | 0.444[a] |
| TG ≥ 204, HDL-C ≤ 34, baseline statin use, baseline LDL-C < 100 | 3/28 (10.7%) | 6/26 (23.1%) | 0.451 (0.108, 1.881) | 0.275[b] |
| Baseline statin use and either TG ≥ 200 or HDL-C < 40 at baseline | 24/246 (9.8%) | 25/248 (10.1%) | 1.018 (0.579, 1.790) | 0.952[c] |
| Baseline statin use, baseline LDL-C < 100, and either TG ≥ 200 or HDL-C < 40 at baseline | 16/164 (9.8%) | 19/176 (10.8%) | 0.958 (0.490, 1.872) | 0.899[d] |

a. *P* value for treatment-by-gender interaction = 0.891.
b. *P* value for treatment-by-gender interaction = 0.945.
c. *P* value for treatment-by-gender interaction = 0.286.
d. *P* value for treatment-by-gender interaction = 0.345.

Among patients receiving a statin at baseline, the relationship between TG and HDL-C thresholds and the percentage of patients with the primary endpoint in each treatment group is illustrated for women in Figure 9 and for men in Figure 10. For both women and men, results were similar to those observed in the overall population (Figure 8); in the simvastatin group, event rates for a CV event increased with increasing baseline TG and decreasing baseline HDL-C, while in the coadministration group, event rates were relatively stable regardless of baseline TG and HDL-C, suggesting a mitigation of this risk.


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**Figure 9.** **Percentage of CV Events in Subgroups of Dyslipidemic Women Receiving a Statin at Baseline in ACCORD Lipid**

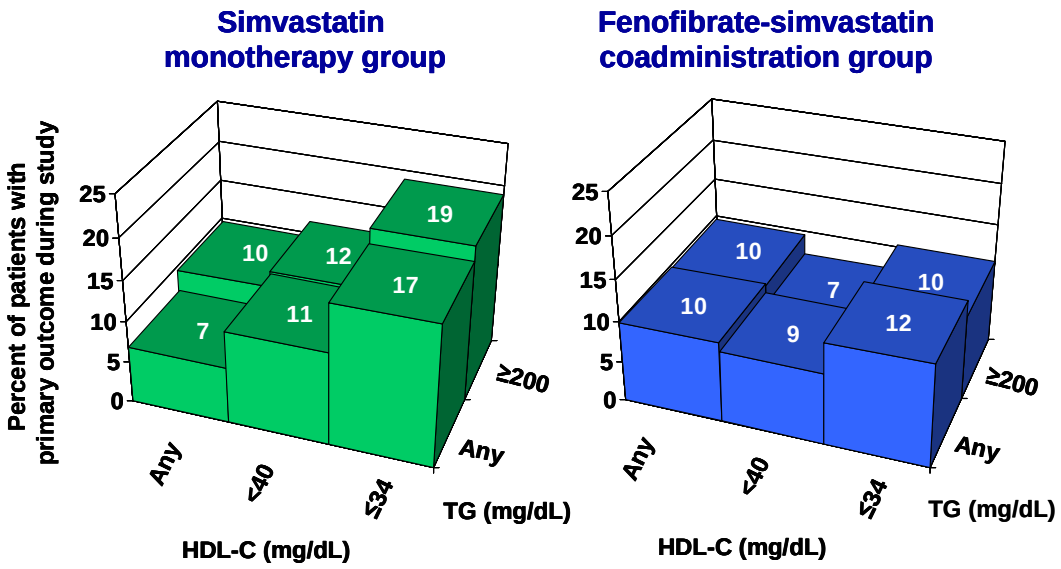
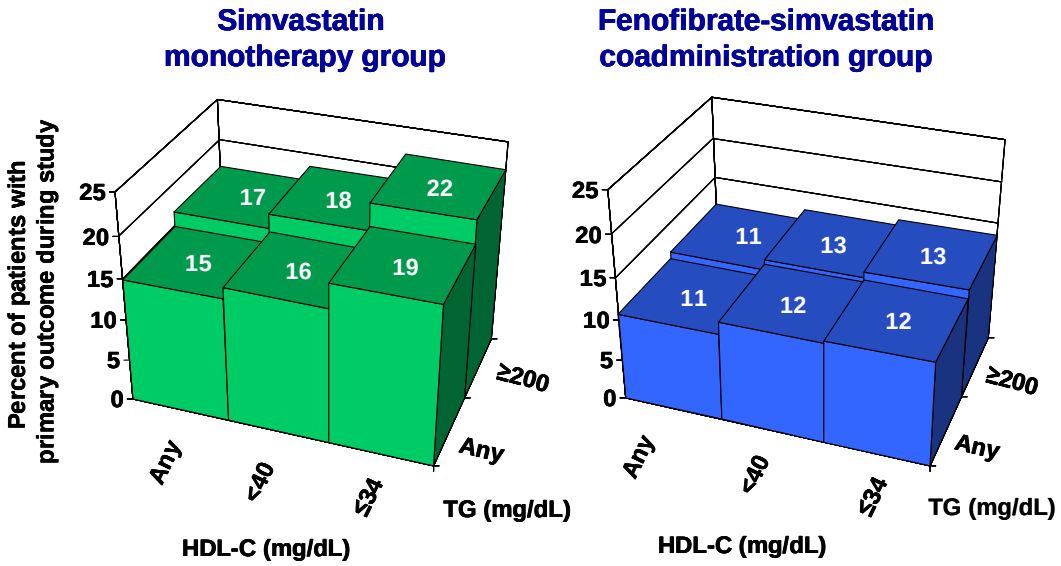



**Figure 10.** **Percentage of CV Events in Subgroups of Dyslipidemic Men Receiving a Statin at Baseline in ACCORD Lipid**



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For each combination of TG and HDL-C levels illustrated in Figure 9, an analysis was conducted to compare fenofibrate-simvastatin coadministration therapy to simvastatin monotherapy. In women receiving a statin at baseline, the estimated treatment effect of coadministration therapy improved with higher TG and lower HDL-C relative to treatment with simvastatin alone (Table 22).

**Table 22. Relative Risk of a CV Event for Coadministration Therapy Compared to Simvastatin Monotherapy by TG and HDL-C Thresholds in Women Receiving a Statin at Baseline in ACCORD Lipid**

| | | HDL-C, mg/dL | | |
|---|---|---|---|---|
| | | **Any** | **< 40** | **≤ 34** |
| **TG, mg/dL** | **≥ 200** | N = 293 | N = 163 | N = 76 |
| | | **HR = 1.034**<br>*P* = 0.931 | **HR = 0.772**<br>*P* = 0.636 | **HR = 0.604**<br>*P* = 0.442 |
| | **Any** | N = 918 | N = 364 | N = 151 |
| | | **HR = 1.461**<br>*P* = 0.107 | **HR = 0.857**<br>*P* = 0.651 | **HR = 0.681**<br>*P* = 0.381 |

Although the sample sizes in the subgroups of women are small, the results are consistent with the findings of the analysis of the dyslipidemic subgroups in the overall population. Specifically, among women receiving a statin at baseline, the estimated treatment effect of coadministration therapy compared to simvastatin monotherapy showed greater improvements with higher TG and lower HDL-C thresholds. These findings are consistent with current NCEP treatment guidelines that recommend consideration of addition of a fibrate to statin therapy in patients with elevated TG and/or low HDL-C.

### 5.1.3 Possible Explanations for the Findings in Women in ACCORD Lipid

To assess the observed differences between treatment groups in women in ACCORD Lipid, several potential explanations were explored, as described below. These include imbalances in important risk factors at baseline, differential effects of coadministration therapy compared to simvastatin monotherapy on lipid parameters or other laboratory


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variables that are associated with CV events, or a gender-specific pharmacological interaction between fenofibrate and simvastatin.

#### 5.1.3.1 Demographics and Baseline Characteristics of Women in ACCORD Lipid

Overall, demographics and baseline characteristics in women were well balanced between treatment groups (Table 23). Women randomized to coadministration therapy had a significantly lower mean age compared to those randomized to simvastatin monotherapy (61.3 versus 62.0 years, respectively; $P = 0.038$) and a trend toward higher median TG (176.0 versus 167.0 mg/dL, respectively; $P = 0.090$), but the differences were small in magnitude and were not expected to have a meaningful impact on CV outcomes.


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**Table 23. Demographic and Baseline Characteristics of Women by Treatment Group in ACCORD Lipid**

| | Fenofibrate-Simvastatin (N = 851) | Simvastatin Monotherapy (N = 843) | *P* value |
|---|---|---|---|
| **Categorical Variable** | **n (%)** | | |
| Race[a] | | | |
| White | 537 (63.1%) | 526 (62.4%) | 0.764 |
| Black | 154 (18.1%) | 164 (19.5%) | 0.474 |
| Hispanic | 89 (10.5%) | 92 (10.9%) | 0.762 |
| Had previous CV event[b] | 228 (26.8%) | 212 (25.1%) | 0.440 |
| Had previous heart failure[b] | 50 (5.9%) | 40 (4.7%) | 0.294 |
| Lipid medication at baseline | | | |
| Any statin[b] | 456 (53.6%) | 462 (54.8%) | 0.614 |
| Any lipid-lowering agent[b] | 490 (57.6%) | 498 (59.1%) | 0.533 |
| GFR | | | 0.955 |
| 30 – 49 mL/min/1.73 $m^2$ | 45 (5.3%) | 44 (5.2%) | |
| > 50 mL/min/1.73 $m^2$ | 800 (94.0%) | 792 (94.0%) | |
| Missing | 6 (0.7%) | 7 (0.8%) | |
| **Numeric Variable** | **Mean (SD)** | | |
| Age, years | 61.3 (6.6) | 62.0 (6.6) | 0.038 |
| Duration of diabetes, years (median) | 9.0 | 9.0 | 0.532 |
| Glycated hemoglobin, % | 8.4 (1.1) | 8.3 (1.1) | 0.251 |
| Serum creatinine, mg/dL | 0.8 (0.2) | 0.8 (0.2) | 0.282 |
| Baseline lipid values, mg/dL | | | |
| LDL-C | 104.5 (31.0) | 106.6 (33.2) | 0.195 |
| HDL-C | 41.2 (7.8) | 41.6 (7.7) | 0.202 |
| TG, median (Q1, Q3) | 176.0 (124, 242) | 167.0 (119, 231) | 0.090 |
| Total-C | 184.4 (38.0) | 185.8 (40.3) | 0.465 |

a. Compared to patients who were non-white, non-black, or non-Hispanic, respectively.

b. Compared to patients who did not have previous CVD event or CHF or did not use statins or did not use other lipid-lowering agents at baseline, respectively.

To investigate the impact of baseline variables on the estimated hazard ratio for coadministration therapy versus simvastatin monotherapy in women, a multivariable Cox proportional hazard regression analysis was conducted, using a stepwise variable selection procedure ($P$ = 0.15 to enter and stay in the model). In this analysis, the overall



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hazard ratio for treatment effect in women was modestly reduced after controlling for other variables included in the final model, as displayed in Table 24.

**Table 24. Association Between CV Events and Coadministration Therapy in Women After Adjustment for Important Baseline Factors in ACCORD Lipid**

| Model | Covariates Included in the Final Model | Covariates Not Included in the Final Model | HR for Treatment Group (95% CI) | *P* value |
|---|---|---|---|---|
| Prespecified primary analysis | Prespecified model: treatment group, clinical trial network, randomization to intensive glycemic therapy, previous CVD | Not applicable | 1.378 (0.976, 1.945) | 0.069 |
| Multivariable model incorporating baseline factors with $P < 0.15$ | Treatment group; clinical trial network; randomization to intensive glycemic therapy; previous CVD; baseline creatinine, TG, $HbA_{1c}$; age > 65 years; White race; previous heart failure; duration of diabetes | Baseline glucose, LDL-C, HDL-C, GFR, BMI; use of statins, metformin, insulin, or aspirin at baseline | 1.293 (0.909, 1.839) | 0.153 |

Thus, imbalances in baseline characteristics did not explain the observed results in women in ACCORD Lipid.

#### 5.1.3.2 Effect of Fenofibrate on Laboratory Variables Potentially Associated with Response in Women in ACCORD Lipid

Theoretically, the suggestion of harm observed in women treated with coadministration therapy compared to simvastatin monotherapy could arise if fenofibrate altered lipid parameters in women differently than in men, as this difference could affect CV outcomes. However, the beneficial effects of fenofibrate typically seen on TG and HDL-C were also observed in ACCORD Lipid; women treated with coadministration therapy had significantly larger reduction in TG compared to those treated with


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simvastatin monotherapy at all study visits and significantly larger increases in HDL-C through Year 3.

In some studies, fibrate-statin coadministration therapy has resulted in smaller mean decreases in LDL-C compared to statin monotherapy.[52–55] Such an observation could hypothetically result in more events in patients treated with coadministration therapy, if the attenuation of LDL-C lowering more than offsets benefits from greater HDL-C increases and greater TG decreases. However, in ACCORD Lipid, this effect was not observed. Women treated with coadministration therapy in ACCORD Lipid generally had greater mean decreases in LDL-C compared to those treated with simvastatin monotherapy. Mean percent decreases from baseline in LDL-C were 1% to 5% greater for the coadministration therapy group at all visits; differences were statistically significant at Month 4, Year 1, and Year 3. Therefore, differential changes in LDL-C are unlikely to explain the observed hazard ratio in women.

#### 5.1.3.3 Potential for Gender-Specific Pharmacologic and Pharmacokinetic Interactions Between Fenofibrate/Fenofibric Acid and Statins

Across several outcomes trials of statin monotherapies, there has been no indication of meaningful differences in treatment benefits between men and women.[2–4,7] Similarly, no meaningful differences in treatment effects of fenofibrate monotherapy have been observed between men and women.[46,47] Therefore, if the treatment-by-gender interaction observed in ACCORD Lipid were a real clinical phenomenon, it would suggest a gender-specific pharmacologic interaction between fenofibrate and simvastatin. Available laboratory data from ACCORD Lipid demonstrate that differences between the treatment arms in lipids and other laboratory parameters in women were similar to those observed in men. This finding does not support the presence of a gender-specific pharmacological interaction.

To examine potential gender-specific differences in the pharmacokinetic interaction between fenofibrate and statins, pharmacokinetic data from clinical studies investigating potential fenofibrate-statin drug interactions were analyzed separately for females and


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males. Abbott analyzed the pharmacokinetic data from 2 drug interaction studies, Study M02-514 and Study M02-525, which included pharmacokinetic data from a sufficient number of females and males for such analyses. Other fenofibrate-statin interactions studies contained too few females for statistical analyses of gender differences. Study M02-514 examined the interaction between pravastatin and fenofibrate, while Study M02-525 examined the interaction between fluvastatin and fenofibrate. The results of these analyses indicate that there were no statistically significant differences between females and males in the pharmacokinetic interaction between fenofibrate and statins ($P$ = 0.103 to 0.925).

#### 5.1.3.4 Other Possible Explanations for the Treatment Difference by Gender in ACCORD Lipid

As noted by the authors of ACCORD Lipid, 19 statistical tests of hypotheses related to primary or secondary endpoints and subgroups were conducted, giving a 62% probability that at least one of these tests would be significant at the 0.05 level due to chance alone, even if no such interaction was present in the population from which the study sample was drawn. The observed $P$ values can be evaluated more directly by applying a multiple-testing procedure in order to control the family-wise type I error rate. As shown in Table 25, the multiplicity-adjusted $P$ value for the treatment-by-gender interaction is approximately 0.20. While post hoc application of multiplicity adjustment procedures can be difficult to interpret, the consistency of the results across a range of commonly used methods suggests the possibility that the interaction may have arisen by chance.

**Table 25. Multiplicity-Adjusted *P* values for the Treatment-by-Gender Interaction in ACCORD Lipid**

| | Multiple Comparison Methodologies | | | | | |
|---|---|---|---|---|---|---|
| **Raw (nominal) *P* value** | **Bonferroni** | **Sidak** | **Holm** | **Hochberg** | **Simes-Hommel** | **Fisher Combination** |
| 0.011 | 0.209 | 0.190 | 0.209 | 0.209 | 0.209 | 0.240 |

Other factors that could have potentially influenced the outcomes observed in women include use of hormone replacement therapy, underlying thyroid dysfunction, use of


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low-dose fenofibrate, and differential management of other modifiable risk factors such as blood pressure and glycemic control. However, data on these factors in ACCORD Lipid were not available for assessment.

In summary, investigation of potential baseline imbalances, potential effects of fenofibrate-mediated changes of laboratory parameters such as LDL-C and serum creatinine, and potential gender-specific pharmacologic interventions did not suggest that any of these factors explain the observed results in women. Assessment of the multiplicity-adjusted *P* value for the treatment-by-gender interaction in ACCORD Lipid (*P* value of approximately 0.20) suggests that consideration should be given to the conclusion that the observation is a chance result.

## 5.2 Supportive Evidence of the Benefit of Fibrate Therapy in Women

The finding of a potential increased risk of CV events in women in ACCORD Lipid is not consistent with the FIELD trial.[46] As in ACCORD Lipid, gender subgroup analyses were prespecified in FIELD. The FIELD trial enrolled 3,657 women (37.3% of the total), more than twice as many women as were enrolled in ACCORD Lipid (n = 1,694). In FIELD, the treatment-by-gender interaction was not statistically significant ($P = 0.30$), and women who received fenofibrate had a lower rate of CV events than those receiving placebo (7.7% versus 9.5%; $P = 0.04$). In the FIELD trial, there was a numerically lower risk of nonfatal MI among women with fenofibrate therapy (HR = 0.70; $P = 0.086$), which contradicts the finding of an increased risk of nonfatal MI in women who received fenofibrate-simvastatin coadministration therapy in ACCORD Lipid. Further, the hazard ratio for this event was lower in women than in men (HR = 0.78; $P = 0.048$) and in the population overall (HR = 0.76; $P = 0.010$).

In a 16-year follow-up of the BIP trial, bezafibrate therapy demonstrated a 27% reduction in mortality among women compared to a 9% reduction among men.[56]


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## 5.3 Summary of the Benefit-Risk Profile of Fibrate-Statin Coadministration Therapy in Women

A treatment-by-gender interaction for the primary CV event endpoint was observed in ACCORD Lipid. Although there was a significant reduction in CV events with fenofibrate-simvastatin coadministration therapy compared to simvastatin monotherapy in men, there was a contrasting trend towards a higher risk of CV events with coadministration therapy in women. This finding is unsubstantiated by results from other fibrate studies, notably FIELD, in which the CV benefit of fibrate therapy was numerically greater in women than in men.

The primary difference among women between the coadministration therapy and statin monotherapy arms was that those treated with coadministration therapy had numerically more nonfatal MI events than those treated with simvastatin monotherapy. This finding is contrary to the observed beneficial effect of fenofibrate on nonfatal coronary events in in FIELD as well as in a meta-analysis of 18 fibrate outcomes trials.[25,46] There was no concomitant higher rate of death from CV causes in women receiving coadministration therapy and death from any cause was numerically lower in women receiving coadministration therapy than those treated with simvastatin monotherapy.

Furthermore, a higher rate of CV events was not observed in the cohorts of women who were in the subgroup with dyslipidemia. Specifically, among women with dyslipidemia who were receiving a statin at baseline and among women receiving a statin at baseline but with TG ≥ 200 mg/dL or HDL-C ≤ 40 mg/dL, the CV benefit of coadministration therapy compared to simvastatin monotherapy was consistent with the overall results in the subgroup with dyslipidemia. These findings are consistent with current treatment guidelines that recommend additional therapy in patients receiving a statin who have elevated TG and/or low HDL-C.

Analysis of the available ACCORD Lipid data for women did not identify any relevant imbalances in baseline risk factors, differential effects between treatment groups on lipid and other laboratory parameters associated with CV events, or a gender-specific


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pharmacological interaction between fenofibrate and simvastatin that could explain the disparate treatment effect of coadministration therapy in women. Thus, there is a paucity of evidence to support the biological plausibility of a treatment-by-gender interaction. A total of 19 statistical tests of the primary and secondary endpoint hypotheses and subgroups were conducted in the primary analyses in ACCORD Lipid, resulting in a 62% chance that at least one of these tests would be significant at the 0.05 level. Applying multiple-testing procedures to control the family-wise type I error rate results in a multiplicity-adjusted *P* value for the treatment-by-gender interaction in ACCORD Lipid of approximately 0.20. Therefore, consideration should be given to the conclusion that the observation is a chance result.

In summary, Abbott concludes that the benefit-risk profile of fenofibrate-statin coadministration therapy is positive in women with dyslipidemia.

## 5.4 Assessment of Subgroup Analyses

Analyses in this report focused on subgroups defined by dyslipidemia criteria and gender. Assessment of subgroup analyses must be conducted with caution because of the risk of over-interpretation of the observed results. Biological plausibility, prespecification of the subgroup, and evidence from other clinical trials should be considered, in addition to the statistical strength of the evidence.

The prespecified subgroup with dyslipidemia in ACCORD Lipid was not aligned with treatment guidelines or the Trilipix coadministration indication in that it did not require patients to have persistent elevated TG and low HDL-C while receiving statin therapy. Therefore, in sensitivity analyses of the prespecified subgroup with dyslipidemia, Abbott assessed populations appropriate for coadministration therapy according to treatment guidelines and Trilipix labeling. These included patients who had TG and/or HDL-C abnormalities despite use of statin therapy. Analysis of these patients in ACCORD Lipid indicated that fenofibrate-simvastatin coadministration therapy significantly reduced the risk of CV events, and the treatment effect was greater in patients with a higher TG and/or lower HDL-C. It is biologically plausible that these patients should benefit from


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addition of a fibrate to statin therapy, given the recognized relationships between elevated TG and/or low HDL-C and the risk of CV morbidity and mortality, and given the TG decreases and HDL-C increases induced by fibrate therapy. This biological plausibility is reinforced by results from 4 previous CV outcomes trials with fibrate therapy, each of which showed significant reductions in the risk of CV events in patients with elevated TG and low HDL-C.

In contrast, the treatment-by-gender interaction observed in ACCORD Lipid was not observed in several other CV outcomes trials of statins or fibrates, including FIELD, which enrolled more than twice as many women as ACCORD Lipid. The results in ACCORD Lipid demonstrated treatment effects favoring coadministration therapy in men but favoring simvastatin monotherapy in women, and such qualitative interactions in which treatment effects are in opposite directions are generally considered to be rare and highly implausible.[57] Abbott's investigation of the observations in women in ACCORD Lipid did not reveal any explanation for the results, and in the prespecified subgroup with dyslipidemia, there was no significant treatment-by-gender interaction.

In ACCORD Lipid, diabetic patients with a modest degree of dyslipidemia treated with coadministration therapy demonstrated a nonsignificant reduction in the risk of CV events compared to patients treated with statin monotherapy. These findings are consistent with the modest degree of baseline dyslipidemia in enrolled patients. Therefore, they do not suggest that the approved Trilipix coadministration therapy indication is inappropriate, but rather that a majority of the study population did not require coadministration therapy as recommended by treatment guidelines or the approved Trilipix indication.

The totality of evidence supports the benefit of treatment with fenofibrate in patients with elevated TG and/or low HDL-C, confirming that the approved Trilipix label accurately defines the criteria for the appropriate use of Trilipix coadministered with a statin.



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# 6.0 Additional Evidence of the CV Benefits of Fibrate Therapy in Dyslipidemic Patients

**Highlights:**

- A meta-analysis relating lipid changes to CV outcomes demonstrates that the results in ACCORD Lipid in the overall study population are explained by the modest degree of dyslipidemia at baseline and the modest changes of lipid parameters on treatment.
- The benefits of fibrate therapy are supported by results from a published meta-analysis of 18 fibrate outcomes trials.

## 6.1 Meta-Analysis to Assess the Effect of Lipid Changes on the Risk of CV Events

Abbott performed a literature-based meta-analysis to characterize the multivariate relationship between changes in LDL-C, HDL-C, and TG and risk for major CV and coronary events after treatment with statins, fibrates, or niacin. An evaluation of whether the changes in lipid parameters could explain the treatment effect or whether there is an additional effect for certain drug classes or drugs within a class unexplained by lipid changes was also explored. The meta-analysis was also used to evaluate whether, for a given change in lipid parameters, there is a difference in the benefit for males and females. Additionally, this meta-analysis was used to compare the predicted risk reduction to the observed risk reduction in ACCORD Lipid. A description of the meta-analysis can be found in Appendix A.

A broad literature search was performed using Medline® for all randomized controlled trials published in the English language that evaluated the safety and efficacy of simvastatin, atorvastatin, rosuvastatin, fluvastatin, lovastatin, cerivastatin, pravastatin, ezetimibe, fenofibrate, gemfibrozil, bezafibrate, niacin, Niaspan, and nicotinic acid. Of the 165 references identified that reported CV or coronary outcomes, a total of 45 trials


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reported major CV events and 70 trials reported major coronary events. These trials evaluated more than 200,000 subjects.

The risk reduction for major CV events between active and control arms was found to be statistically significantly dependent ($P < 0.001$) on the absolute difference in on-treatment LDL-C and TG between active and control arms and duration of trial. LDL-C and TG contributed independently to the reduction in risk. Higher baseline HDL-C values attenuated the effects of LDL-C and TG on major cardiovascular outcomes ($P < 0.001$). The risk reduction for major coronary events was estimated to be 18.5% (95% CI: 14.1, 22.7) for every 1-mmol/L reduction in LDL-C and 27.5% (95% CI: 15.7, 37.7) for every 1-mmol/L reduction in TG. The risk reduction for major cardiovascular events was estimated to be 16.5% (95% CI: 12.9, 20.0) for every 1-mmol/L reduction in LDL-C and 24.0% (95% CI: 13.0, 33.8) for every 1-mmol/L reduction in TG at a baseline HDL-C of 45 mg/dL. These results correspond to risk reductions of 4.5% (95% CI: 3.5, 5.6) for every 10-mg/dL reduction in LDL-C and 3.0% (95% CI: 1.5, 4.5) for every 10-mg/dL reduction in TG.

The average treatment duration to achieve 50% of maximal risk reduction was 6.2 months for major coronary events and 4.2 months for CV events. No significant effect of drug class or specific drug was found, suggesting that the LDL-C and TG relationships were similar across drugs and drug classes. These results suggest that the difference in benefit of statins and fibrates could be solely explained by their differences in LDL-C and TG reduction.

The predicted hazard ratio for the overall population in ACCORD Lipid, based on the reported TG and LDL-C differences between treatment groups and the baseline HDL-C in the ACCORD Lipid trial, is 0.90 (95% CI: 0.85, 0.94) for major CV outcomes and 0.91 (95% CI: 0.87, 0.95) for major coronary outcomes. Therefore, the predicted risk reduction based on the meta-analysis model that did not include the ACCORD Lipid trial (HR = 0.91) was nearly identical to the observed risk reduction in the ACCORD Lipid trial (HR = 0.92). The observed and model-predicted relative risks for each of the fibrate trials that reported coronary or CV outcomes is shown in Figure 11.


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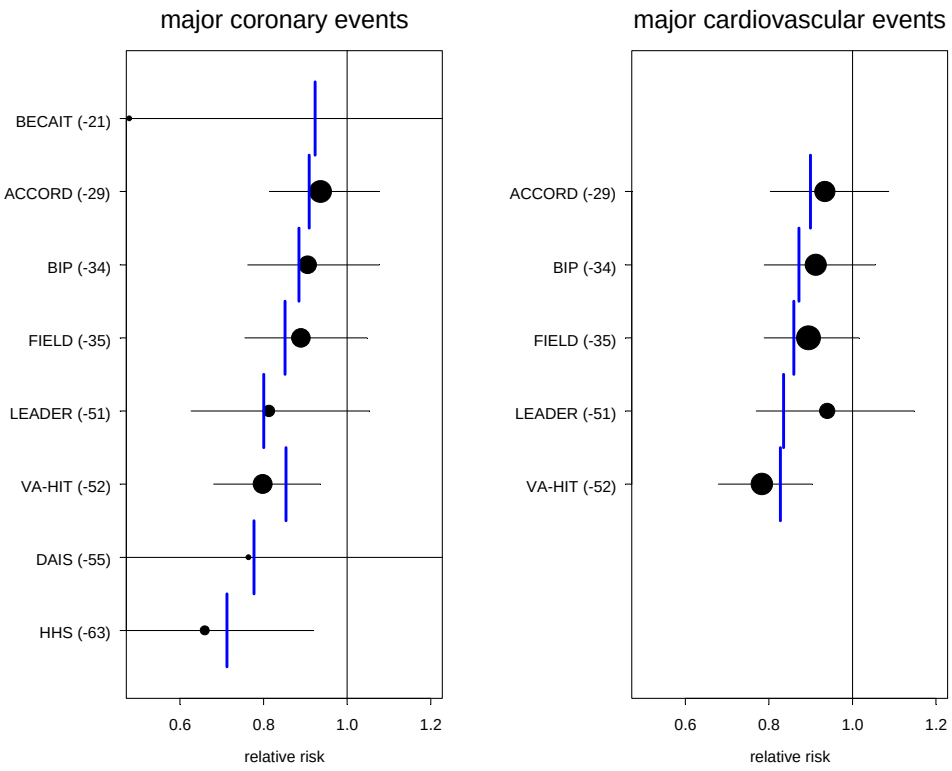
**Figure 11. Forest Plot of Observed and Model-Predicted Relative Risk for Major Coronary and Cardiovascular Events for Fibrate Trials Including ACCORD Lipid**




Numbers in parentheses are observed TG differences between treatment groups
• = observed risk, | = predicted risk

To assess the impact of the results from the ACCORD Lipid trial on the parameter estimates from the meta-analysis model, the results from ACCORD Lipid were added to the model for CV and coronary events and the meta-analysis model estimates were updated. The estimated meta-analysis model parameters including and excluding the results from the ACCORD Lipid trial for CV and coronary events were nearly identical. This suggests that the major CV or coronary outcome results from the ACCORD Lipid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trial are consistent with the results from the meta-analysis model using the large number of clinical trials previously reported in the literature.

The meta-analysis was also used to explore potential differences in outcomes between women and men. As very few individual studies reported outcomes for males and females separately, the relationship between lipid changes and risk reduction was performed on the percentage of females in each trial. The relationship between lipid changes and risk reduction for major coronary and major CV events in the meta-analysis model was not statistically significantly dependent on the percentage of females in the trial, suggesting that the risk was no different between males and females.

## 6.2 Published Fibrate Meta-Analysis of 18 Outcomes Trials

In the independent published meta-analysis of 18 randomized, placebo-controlled fibrate outcomes trials conducted by Jun et al (including FIELD and ACCORD Lipid), 5 of the 18 studies included data on CV events from a total of 19,944 participants with 2,870 events. In this analysis, fibrate therapy conferred a 10% relative risk reduction for major CVD events (95% CI: 0%, 18%; $P = 0.048$) and a 13% relative risk reduction for coronary events (95% CI: 7%, 19%; $P < 0.0001$. Fibrate therapy had no effect on stroke, all-cause mortality, CV mortality, sudden death, or nonvascular mortality.

For coronary events, the benefit of fibrate therapy was larger in trials with a higher mean baseline TG level ($P = 0.030$). In addition, a correlation between the on-treatment TG reductions and risk of coronary events was noted ($P = 0.026$), with larger risk reductions associated with larger decreases in TG as a consequence of fibrate therapy.

Furthermore, the meta-analysis identified no evidence that results of ACCORD Lipid are different from those of other fibrate trials and thus that "there is no strong rationale for expecting that fibrates might not provide some benefit."[25]



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## 6.3 Summary of Additional Evidence of the CV Benefit of Fenofibrate-Statin Coadministration Therapy

The Abbott-conducted meta-analysis relating lipid changes to CV outcomes established that CV benefit in a particular study is explained by the degree of TG and LDL-C changes in that study. The results of ACCORD Lipid were predicted by the meta-analysis, illustrating that the lack of an overall statistically significant benefit in ACCORD Lipid is due to the modest degree of dyslipidemia at baseline and modest on-treatment lipid changes. The published fibrate outcomes meta-analysis supports the finding of a CV benefit in patients receiving fibrate therapy.



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# 7.0 Microvascular Benefits of Fenofibrate Therapy

**Highlights:**

- Fenofibrates has demonstrated important microvascular benefits in the overall diabetic patient populations of ACCORD Lipid and FIELD.
- These benefits include reductions in albuminuria, retinopathy, neuropathy, and amputation.
- Results regarding albuminuria and retinopathy benefits have been published for ACCORD Lipid that confirm the benefits observed in FIELD.

Comorbidities of T2DM, such as retinopathy, renal impairment, and amputation, are life-altering and debilitating. Beyond the demonstrated benefits of fenofibrate on lipid parameters associated with CV risk and on actual CV outcomes in patients with elevated TG and low HDL-C, microvascular benefits of fenofibrate have also been demonstrated. While these effects have not been reviewed for inclusion in the Trilipix prescribing information, they are considered to be clinically significant effects of fenofibrate/fenofibric acid.

## 7.1 Reduced Albuminuria with Fenofibrate Therapy

The development of macroalbuminuria (albumin/creatinine ratio ≥ 300 mg albumin per gram of creatinine) or microalbuminuria (albumin/creatinine ratio ≥ 30 mg albumin per gram of creatinine) were prespecified endpoints in ACCORD Lipid. Fenofibrate-simvastatin coadministration therapy demonstrated a statistically significant reduction in microalbuminuria and macroalbuminuria compared to simvastatin monotherapy in ACCORD Lipid (Table 26).


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**Table 26. Incidence of Microalbuminuria and Macroalbuminuria in ACCORD Lipid**

| ACCORD Lipid | Fenofibrate-Simvastatin (N = 2765) | Simvastatin Monotherapy (N = 2753) | *P* value |
|---|---|---|---|
| Post-randomization incidence of microalbuminuria (≥ 30 mg/g creatinine)[a] | 1050 (38.2%) | 1137 (41.6%) | 0.01 |
| Post-randomization incidence of macroalbuminuria (≥ 300 mg/g creatinine) | 289 (10.5%) | 337 (12.3%) | 0.03 |

a. This category was described incorrectly as "(≥ 30 to < 300 mg/g creatinine)" in the ACCORD Lipid publication.[29]

Similar observations were made in the FIELD trial. In FIELD, the rate of progression to microalbuminuria (or from microalbuminuria to macroalbuminuria) was significantly reduced in the fenofibrate group: 2.6% more patients allocated to fenofibrate than to placebo regressed or demonstrated no progression ($P = 0.002$). In addition, a similar treatment effect was seen in urinary albumin concentration unadjusted for urinary creatinine ($P = 0.001$).[46]

Importantly, in both ACCORD Lipid and FIELD, the incidence of progression to end-stage renal failure was similar between the groups that received fibrate therapy and those that did not (see Section 8.1.3).

## 7.2 Reduced Retinopathy with Fenofibrate Therapy

The ACCORD Lipid and FIELD studies also provide data on another important prespecified microvascular endpoint, the progression of diabetic retinopathy. A total of 1,593 of ACCORD Lipid patients were enrolled in the ACCORD Eye Study. The rate of progression of diabetic retinopathy, defined as at least 3 stages on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale, photocoagulation, or vitrectomy, at 4 years was 6.5% (52 of 806 participants) in the coadministration group and 10.2% (80 of 787 participants) in the simvastatin monotherapy group (adjusted OR = 0.60; 95% CI: 0.42, 0.87; $P = 0.006$), indicating that fenofibrate slows the progression of diabetic retinopathy.[40]


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Treatment with fenofibrate reduced the requirement for laser therapy in FIELD. More placebo-treated patients (253) than fenofibrate-treated patients (178) needed one or more laser treatments for any eye disease (1.6% difference, $P = 0.0003$). This effect was observed in patients with and without retinopathy at baseline and was not correlated with plasma lipid concentrations.[58] The percentage of patients requiring first laser treatment for diabetic eye disease was significantly lower in the fenofibrate group than in the placebo group (164 [3.4%] patients receiving fenofibrate versus 238 [4.9%] patients receiving placebo; HR = 0.69; 95% CI: 0.56, 0.84; $P = 0.0002$; absolute risk reduction 1.5% [0.7 to 2.3]). In patients with preexisting retinopathy, significantly fewer patients receiving fenofibrate had a 2-step progression (worsening) of their retinopathy than did those receiving placebo (3 patients [3.1%] versus 14 patients [14.6%]; $P = 0.004$). In addition, an exploratory composite endpoint of 2-step progression of retinopathy grade by ETDRS, macular edema, or laser treatments was significantly lower in the fenofibrate group than in the placebo group (HR = 0.66; 95% CI: 0.47, 0.94; $P = 0.022$).[58]

## 7.3 Reduced Amputation with Fenofibrate Therapy

The FIELD trial also demonstrated that treatment with fenofibrate was associated with a lower risk of amputations, particularly minor amputations in patients without known large-vessel disease.[59] The risks of first amputation (45 versus 70 events; HR = 0.64; 95% CI: 0.44, 0.94; $P = 0.02$) and minor amputation events without known large-vessel disease (18 versus 34 events; HR = 0.53; 95% CI: 0.30, 0.94, $P = 0.027$) were lower for patients receiving fenofibrate than for patients receiving placebo, with no difference between groups in risk of major amputations (24 versus 26 events; HR = 0.93; 95% CI: 0.53, 1.62; $P = 0.79$).

Amputation data from ACCORD Lipid are not yet available.

## 7.4 Reduced Neuropathy with Fenofibrate Therapy

In FIELD, 5.8% of patients (564/9795) had neuropathy at baseline. After 5 years of treatment, 8.0% of placebo-treated patients had neuropathy compared to 6.6% of fenofibrate-treated patients ($P = 0.02$). There was a relative 18% reduction in new


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neuropathy with fenofibrate compared to placebo (5.3% versus 4.4%; OR = 0.82; 95% CI: 0.67, 1.01; *P* = 0.06) and a 40% greater reversal of existing neuropathy (42% versus 55%, OR = 0.60; 95% CI: 0.42, 0.88; *P* = 0.009).[60]

Neuropathy data from ACCORD Lipid are not yet available.

## 7.5 Summary of Microvascular Benefits of Fenofibrate Therapy

Fenofibrate has demonstrated important microvascular benefits in patients with diabetes in ACCORD Lipid and FIELD. These benefits include reductions in albuminuria, retinopathy, neuropathy, and amputation.



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# 8.0 Safety of Fibrate-Statin Coadministration Therapy

**Highlights:**

- The overall safety profile of fenofibrate/fenofibric acid is well defined, predictable, and consistent with approved prescribing information.
- Elevations in creatine kinase occurred at a low rate in ACCORD Lipid, FIELD, and the Trilipix clinical studies.
- In a retrospective cohort analysis, the rate of rhabdomyolysis resulting in hospitalization was higher with fenofibrate monotherapy and fenofibrate statin coadministration therapy compared to statin monotherapy, but the rate was very low and is consistent with past data.
- While increases in serum creatinine are observed in some patients treated with fenofibrate/fenofibric acid, in ACCORD Lipid and FIELD, these increases were reversible upon discontinuation of therapy and not associated with an increase in important renal events.
- Elevations in AST and ALT were observed at a low rate in ACCORD Lipid, FIELD, and the Trilipix clinical studies.
- The approved Trilipix prescribing information adequately describes the safety profile of coadministration therapy.

Results from FIELD, ACCORD Lipid, and the 3 randomized, controlled trials in the Trilipix clinical program provide a large body of data supporting the safety of fenofibrate and fibrate-statin coadministration therapy.

## 8.1 Safety Events of Interest

The well-characterized safety profile for fenofibrate/fenofibric acid is based on over 35 years of patient experience, including extensive global postmarketing experience with an exposure over the past decade of more than 32 million patient treatment-years.



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In addition, 3 large observational studies based on medical and pharmacy claims have been conducted to evaluate the safety of fibrate and statin use in the dyslipidemic population. The earliest study by Graham et al (2004) focused on evaluation of hospitalized rhabdomyolysis and included 232,940 patient treatment-years of exposure.[61] The second observational study (i3/Abbott Study 1) was conducted by i3 (now i3 Innovus) and supported by Abbott.[62] In this study, which included 885,580 patient treatment-years of exposure, incidence rates of hospitalized rhabdomyolysis, renal impairment, hepatic injury, and pancreatitis were evaluated from 2004 to 2007 with medical record adjudication of hospitalized cases. The third observational study (i3/Abbott Study 2) was a postapproval commitment for Trilipix that specifically focused on rhabdomyolysis and had a 10-year period of study from 1998 to 2007 and with follow-up through the end of 2008. It was the largest of the 3 observational studies, with 2,389,466 patient treatment-years of exposure.

Safety issues for fenofibrate/fenofibric acid include the potential for rhabdomyolysis as well as reversible increases in serum creatinine level and liver function tests and the potential for pancreatitis. These safety issues are described in the *Warning and Precautions* sections of both the TriCor® and Trilipix® labels.

### 8.1.1 Muscle Events

In FIELD, elevations in creatine kinase (CK) occurred at a very low rate in both treatment groups. For CK between 5 × upper limit of normal (ULN) and 10 × ULN, there were 7 (< 1%) instances in patients in the placebo group and 11 (< 1%) instances in patients in the fenofibrate group. For CK elevations > 10 × ULN, there were 3 (< 1%) instances in patients in the placebo group and 4 (< 1%) instances in patients in the fenofibrate group. Cases of rhabdomyolysis were reported in 1 patient receiving placebo and 3 patients receiving fenofibrate. Of note, 2 of the 3 reported events of rhabdomyolysis in fenofibrate-treated patients in FIELD were described in the context of serious complicating medical conditions, including delirium tremens and sepsis. All reported events of rhabdomyolysis were fully resolved.[46]


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The muscle safety profile for fenofibrate in ACCORD Lipid was generally similar to that observed in FIELD. In ACCORD Lipid, instances of CK elevations were generally low and not significantly different between treatment groups, as demonstrated in Table 27. Clinical reports of severe muscle aches or pain (with or without coincident elevation in CK) were also not different between treatment groups. Serious adverse events of myopathy, myositis, or rhabdomyolysis were reported in 4 (0.1%) patients receiving fenofibrate and simvastatin coadministration therapy and 3 (0.1%) patients receiving simvastatin monotherapy ($P$ = 1.000).[29]

**Table 27. Incidence of Elevations in Creatine Kinase in ACCORD Lipid**

| Population | ACCORD Lipid | Fenofibrate-Simvastatin (N = 2765) | Simvastatin Monotherapy (N = 2753) | *P* value |
|---|---|---|---|---|
| All patients | CK ever > 5 × ULN | 51 (1.9%) | 59 (2.2%) | 0.427 |
| | CK ever > 10 × ULN | 10 (0.4%) | 9 (0.3%) | 0.826 |
| Men | CK ever > 5 × ULN | 44 (2.3%) | 48 (2.5%) | 0.666 |
| | CK ever > 10 × ULN | 8 (0.4%) | 7 (0.4%) | 0.799 |
| Women | CK ever > 5 × ULN | 7 (0.8%) | 11 (1.3%) | 0.333 |
| | CK ever > 10 × ULN | 2 (0.2%) | 2 (0.2%) | 0.992 |

Note: For men, N = 1914 for fenofibrate-simvastatin and N = 1910 for simvastatin. For women, N = 851 for fenofibrate-simvastatin and N = 843 for simvastatin.

In the Trilipix clinical program, the incidence of elevations in CK was not consistently higher with coadministration therapy compared with monotherapy (Table 28).



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**Table 28. Incidence of Elevations in Creatine Kinase in the Trilipix Clinical Program**

| | Treatment Group | | | | | |
|---|---|---|---|---|---|---|
| **Subjects with** | **Fenofibric Acid (N = 490)** | **Low-dose Statin (N = 493)** | **Fenofibric Acid + Low-dose Statin (N = 490)** | **Moderate-dose Statin (N = 491)** | **Fenofibric Acid + Moderate-dose Statin (N = 489)** | **High-dose Statin (N = 245)** |
| Any CK > 5 × ULN | 0/472 | 2/484 (0.4%) | 6/481 (1.2%) | 3/480 (0.6%) | 1/472 (0.2%) | 3/238 (1.3%) |
| Any CK > 10 × ULN | 0/472 | 0/484 | 1/481 (0.2%) | 3/480 (0.6%) | 0/472 | 1/238 (0.4%) |

### 8.1.2 Rhabdomyolysis

Lipid-lowering therapies, including fibrates, statins, and their combination, have been associated with an overall risk of rhabdomyolysis, with estimates ranging from approximately 1 per 10,000 patient treatment-years in the Graham study to 1 per 34,000 patient treatment-years in i3/Abbott Study 2. The study by Graham included events that occurred with cerivastatin,[61] while the design of both i3/Abbott studies excluded events that occurred with cerivastatin. In the Graham study, only 1 event of rhabdomyolysis occurred with fenofibrate-statin coadministration therapy, and no events were reported with fenofibrate monotherapy. The overall incidence rates for rhabdomyolysis events with fibrate monotherapy, statin monotherapy, and fibrate-statin coadministration therapy combined are provided in Table 29 for the Graham study, i3/Abbott Study 1, and i3/Abbott Study 2. These rates consistently demonstrate that hospitalized rhabdomyolysis is a rare event overall.


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**Table 29. Overall Incidence Rates for Hospitalized Rhabdomyolysis in 3 Large Observational Studies**

| Study | Incidence Rate per 10,000 Patient Treatment-Years | 95% CI |
|---|---|---|
| Graham[a] | 1.03 | (0.66, 1.53) |
| Graham, excluding cerivastatin[a] | 0.62 | (0.34, 1.04) |
| i3/Abbott Study 1 | 0.25 | (0.16, 0.38) |
| i3/Abbott Study 2 | 0.29 | (0.23, 0.37) |

a. Incidence rate estimates for the study by Graham were derived from Table 1 of Graham et al.[61]

Incidence rate ratios for hospitalized rhabdomyolysis comparing statin monotherapy with fibrate-statin coadministration therapy are provided in Table 30 for the largest of these 3 studies, i3/Abbott Study 2. In this study, analyses were performed comparing statin monotherapy to 2 different coadministration therapies: fenofibrate-statin and gemfibrozil-statin.

**Table 30. Incidence Rate Ratios for Hospitalized Rhabdomyolysis in i3/Abbott Study 2**

| Study | Adjusted Incidence Rate Ratio[a] | 95% CI |
|---|---|---|
| Statin monotherapy | reference | |
| Fenofibrate-statin | 3.26 | (1.21, 8.80) |
| Gemfibrozil-statin | 11.93 | (3.96, 35.93) |

a. Adjusted for age, gender, history of diabetes, hypertension, year of cohort entry, number of prescriptions, and total cost.

Additionally, in a published assessment of the FDA Adverse Event Reporting System (AERS) database from 01 January 1998 to 31 March 2002, the reporting rate for the event of rhabdomyolysis for fenofibrate coadministered with a statin (excluding cerivastatin) was 15-fold lower than for gemfibrozil coadministered with a statin. For fenofibrate, the rate was 0.58 cases per million prescriptions, while for gemfibrozil, it was 8.6 cases per million prescriptions.[63]


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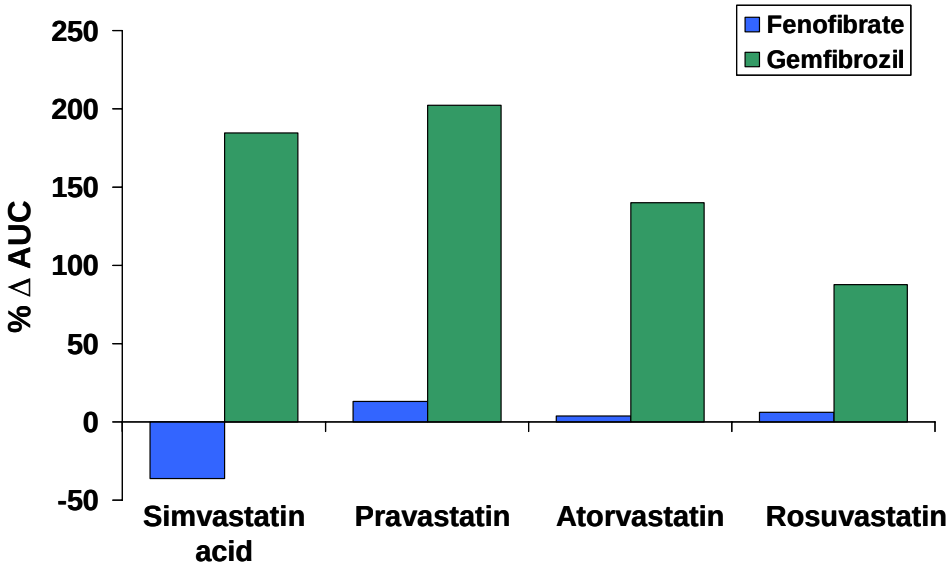
The higher rate of rhabdomyolysis with gemfibrozil is likely due to the increase in plasma concentration of statins by approximately 2-fold or more with gemfibrozil (Figure 12).[64–67] Conversely, fenofibrate does not have a clinically meaningful effect on statin concentrations.

**Figure 12. Plasma Concentration of Statins Increases with Gemfibrozil Compared to Fenofibrate**




The number needed-to-harm (NNH), calculated from i3/Abbott Study 2, was 17,987 patients, i.e., treatment of 17,987 patients for 1 year with fenofibrate-statin coadministration therapy would result in 1 additional case of rhabdomyolysis. In contrast, the NNH with gemfibrozil-statin coadministration therapy was 3,719 patients in i3/Abbott Study 2.

Taken together, these data suggest that although there is increased risk for rhabdomyolysis with fenofibrate-statin coadministration therapy compared to statin monotherapy, the absolute risk is low and it is relatively small compared to the risk with gemfibrozil-statin coadministration therapy.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The Trilipix and TriCor labels reflect the increased risk for serious muscle toxicity in elderly patients and in patients with diabetes, renal failure, or hypothyroidism. Further, Trilipix has a Medication Guide to alert prescribers and patients to the potential increased risk of rhabdomyolysis with coadministration therapy.

In a review of Abbott postmarketing safety data, reports of rhabdomyolysis or myositis have been reported at a rate of approximately 1 per 100,000 patient treatment-years. Although limitations of postmarketing data preclude derivation of incidence rates, reported cases of rhabdomyolysis generally describe patients as presenting with symptoms of muscle tenderness or weakness with subsequent recovery following discontinuation of therapy. Fewer than 5% of rhabdomyolysis reports described a requirement for dialysis, and fatal outcomes were rare and associated with additional confounding medical conditions. Accordingly, myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevations of CK levels. As stated in the current label, Trilipix and statin therapy should be discontinued if markedly elevated CK levels occur or if myopathy or myositis is diagnosed.

### 8.1.3 Renal Events

Increases in creatinine for some patients taking a fibrate have been well described.[68–71] In prespecified analysis of renal function in FIELD, serum creatinine increased with fenofibrate therapy, but returned to baseline levels within 8 weeks after cessation of fibrate therapy (Figure 13).[46,72]



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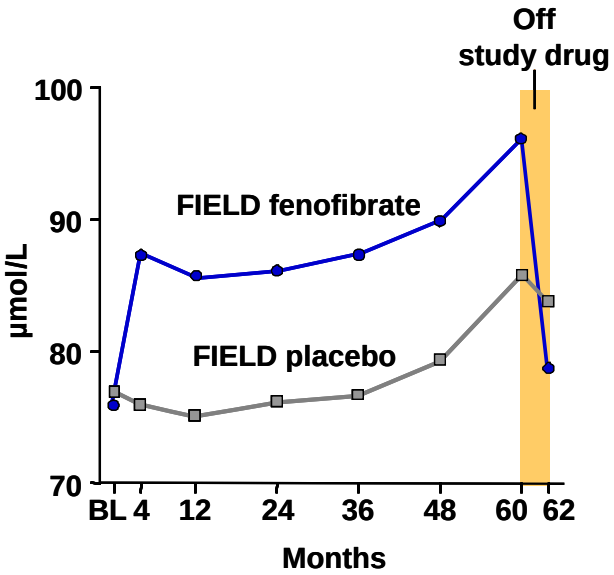
**Figure 13. Reversibility of Creatinine Changes in FIELD**




In FIELD, the number of patients with renal disease requiring hemodialysis was lower with fenofibrate compared to placebo (16 versus 21).

As expected, and consistent with the well-described effects of fenofibrate in clinical trials,[46,73] mean serum creatinine levels increased in patients treated with fenofibrate-simvastatin coadministration therapy from 0.93 to 1.10 mg/dL within the first year in ACCORD Lipid and differences between treatment groups remained relatively stable thereafter.[29] Among women, 28% treated with fenofibrate-simvastatin coadministration therapy and 19% treated with simvastatin monotherapy demonstrated serum creatinine elevations > 1.3 mg/dL ($P < 0.001$). Similarly, in men, 37% of those treated with fenofibrate-simvastatin coadministration therapy and 18% treated with simvastatin monotherapy demonstrated serum creatinine elevations > 1.5 mg/dL ($P < 0.001$). Following the initial observed increase of creatinine in patients treated with fenofibrate-simvastatin coadministration therapy, creatinine levels subsequently remained constant for the remainder of the study and there was no evidence of long-term renal damage with fenofibrate.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In an unpublished analysis of data from ACCORD Lipid, changes in creatinine following treatment discontinuation were evaluated in patients who agreed to participate in this ancillary trial of renal safety.[39] Three groups were evaluated: 1) fenofibrate cases (fenofibrate-simvastatin coadministration group): patients allocated to fenofibrate who had a ≥ 20% increase in creatinine after 3 months of treatment, 2) fenofibrate controls (fenofibrate-simvastatin coadministration group): patients allocated to fenofibrate who had a ≤ 2% increase in creatinine after 3 months of treatment, and 3) placebo controls (simvastatin monotherapy group): patients allocated to placebo irrespective of creatinine changes. Serum creatinine was measured at baseline, at Month 4 (after 3 months of randomized study-drug treatment), at the ACCORD Lipid Close-Out visit, and 6 to 8 weeks later at the Post Close-Out visit. Patients enrolled in the ancillary trial were not to receive fibrate therapy during the period between the ACCORD Lipid Close-Out and the Post Close-Out visits.

**Table 31. Serum Creatinine Changes on Fibrate Therapy and After Fibrate Cessation in ACCORD Ancillary Renal Trial**

| Time Point for Measurement of Serum Creatinine, mg/dL (SD) | ≥ 20% Increase in Creatinine After 3 Months: *Fenofibrate Cases* N = 321 | ≤ 2% Increase in Creatinine After 3 Months: *Fenofibrate Controls* N = 175 | Irrespective of Changes in Creatinine: *Placebo Controls* N = 565 |
|---|---|---|---|
| Baseline | 0.86 (0.19)*# | 0.93 (0.21) | 0.90 (0.21) |
| Month 4 | 1.17 (0.29)*# | 0.88 (0.20) | 0.90 (0.21) |
| ACCORD Lipid Close-Out | 1.13 (0.32)*# | 0.98 (0.28) | 0.98 (0.29) |
| Post Close-Out | 0.99 (0.28)# | 0.88 (0.25) | 0.99 (0.29) |

* Difference from placebo at $P \leq 0.003$.

\# Difference from fenofibrate controls at $P < 0.001$.

Mean creatinine increased by ≥ 20% after 3 months of treatment in the fenofibrate cases by definition. At the ACCORD Lipid Close-Out visit, however, mean creatinine, while still elevated, had decreased from the Month 4 value for the fenofibrate cases, but had increased slightly for the fenofibrate controls and placebo controls. By the Post Close-Out visit, the mean values had decreased for both fenofibrate cases and controls



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and were maintained at close-out levels for placebo. This ancillary trial shows the transient serum creatinine increases associated with fibrate therapy are reversible.

In ACCORD Lipid, the number of patients requiring hemodialysis or identified with end-stage renal disease was lower with fenofibrate-simvastatin coadministration compared to simvastatin monotherapy (75 versus 77). These findings were similar to those described above for the FIELD trial (16 in the fenofibrate group versus 21 in the placebo group).

In the Trilipix clinical program, the incidence of creatinine elevations was low (Table 32).

**Table 32. Incidence of Elevations in Creatinine in the Trilipix Clinical Program**

| | Treatment Group n/N (%) | | | | | |
|---|---|---|---|---|---|---|
| **Subjects with** | **Fenofibric Acid (N = 490)** | **Low-dose Statin (N = 493)** | **Fenofibric Acid + Low-dose Statin (N = 490)** | **Moderate-dose Statin (N = 491)** | **Fenofibric Acid + Moderate-dose Statin (N = 489)** | **High-dose Statin (N = 245)** |
| Any creatinine > 2 mg/dL | 4/473 (0.8%) | 2/484 (0.4%) | 6/479 (1.3%) | 0/480 | 5/472 (1.1%) | 1/238 (0.4%) |
| Creatinine increase ≥ 100% from baseline | 0/473 | 0/484 | 4/479 (0.8%) | 0/480 | 1/472 (0.2%) | 1/238 (0.4%) |

Over the 12 weeks of the randomized, controlled trials in the Trilipix clinical program, mean changes in creatinine were significantly higher with fenofibric acid–statin coadministration therapy than with statin monotherapy. On-study mean creatinine ranged from 1.02 to 1.04 mg/dL with coadministration therapy compared to a mean creatinine range of 0.90 to 0.93 mg/dL with statin monotherapy.

**Retrospective Observational Pharmacoepidemiologic Data**

i3/Abbott Study 1 evaluated the incidence of renal impairment (defined as an abrupt increase in creatinine including a doubling of baseline to at least ULN or an increase of


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≥ 2 × ULN). Consistent with previous clinical findings of serum creatinine elevations with fenofibrate, there was a 1.3-fold to 1.5-fold increased risk of renal impairment with fenofibrate alone compared to statins, with no incremental risk for coadministration. However, as in FIELD and ACCORD Lipid, i3/Abbott Study 1 did not demonstrate any increased risk of renal outcomes such as hemodialysis or requirement for renal transplantation occurring with fenofibrate therapy.

**Postmarketing Safety Data Review**

Review of Abbott postmarketing safety data has determined the overall reporting rate for cases of renal disorders to be low (0.73 per 100,000 patient treatment-years). Reports of renal failure requiring replacement including dialysis or transplantation have been rare and generally confounded by underlying renal disease or other comorbidities. The rarity of reports describing a need for renal replacement therapy suggests that the reversible increases in creatinine in patients receiving fenofibrate therapy may not confer an increased risk for significant renal injury. Nonetheless, as a precaution, the Trilipix and TriCor labels recommend that monitoring of creatinine be considered for patients at risk for renal insufficiency, such as the elderly and those with diabetes.

### 8.1.4 Hepatic Events

ACCORD Lipid adds substantial additional information with regard to the safety profile for hepatic events for fenofibrate that was demonstrated by FIELD.

In FIELD, elevations in ALT occurred at a very low rate in both treatment groups. For ALT elevations between 3 and 5 × ULN, there were 26 (< 1%) instances in patients in the placebo group and 11 (< 1%) instances in patients in the fenofibrate group. For ALT elevation > 5 × ULN, there were 12 (< 1%) instances in patients in the placebo group and 11 (< 1%) instances in patients in the fenofibrate group. Six cases of clinical hepatitis were reported in each of the fenofibrate and placebo groups.[46]

In ACCORD Lipid, instances of ALT elevations were also low and generally not significantly different between treatment groups, as demonstrated in Table 33. The


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significantly higher incidence of ALT elevations in women receiving coadministration therapy is consistent with published finding that females more commonly develop drug-related hepatotoxicity than males.[74] Consistent with observations in the Trilipix clinical program, ALT elevations were observed more commonly in women treated with coadministration therapy than in women treated with simvastatin monotherapy. There were 3 reports of a serious adverse event of hepatitis in the fenofibrate and simvastatin coadministration therapy group (0.1%) and no reports in the simvastatin monotherapy group (0.0%), $P = 0.25$.[29]

**Table 33. Incidence of ALT Elevations in ACCORD Lipid**

| Population | ACCORD Lipid | Fenofibrate-Simvastatin | Simvastatin Monotherapy | *P* value |
|---|---|---|---|---|
| All patients | ALT ever > 3 × ULN | 52 (1.9%) | 40 (1.5%) | 0.215 |
| | ALT ever > 5 × ULN | 16 (0.6%) | 6 (0.2%) | 0.033 |
| Men | ALT ever > 3 × ULN | 28 (1.5%) | 32 (1.7%) | 0.597 |
| | ALT ever > 5 × ULN | 9 (0.5%) | 5 (0.3%) | 0.286 |
| Women | ALT ever > 3 × ULN | 24 (2.9%) | 8 (1.0%) | 0.005 |
| | ALT ever > 5 × ULN | 7 (0.8%) | 1 (0.1%) | 0.035 |

Note: For men, N = 1914 for fenofibrate-simvastatin and N = 1910 for simvastatin. For women, N = 851 for fenofibrate-simvastatin and N = 843 for simvastatin.

In the Trilipix clinical program, the incidence of ALT or aspartate transaminase (AST) elevations was higher with coadministration therapy than with either fenofibric acid monotherapy or statin monotherapy (Table 34). Nevertheless, most subjects with hepatic adverse events did not have postbaseline ALT and/or AST values > 3 × ULN on 2 consecutive visits or > 5 × ULN on any occasion.



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**Table 34. Incidence of ALT and AST Elevations in the Trilipix Clinical Program**

| | Treatment Group n/N (%) | | | | | |
|---|---|---|---|---|---|---|
| **Subjects with** | **Fenofibric Acid (N = 490)** | **Low-dose Statin (N = 493)** | **Fenofibric Acid + Low-dose Statin (N = 490)** | **Moderate-dose Statin (N = 491)** | **Fenofibric Acid + Moderate-dose Statin (N = 489)** | **High-dose Statin (N = 245)** |
| Any ALT > 5 × ULN | 9/472 (1.9%) | 0/484 | 7/479 (1.5%) | 0/480 | 5/472 (1.1%) | 2/238 (0.8%) |
| ALT > 3 × ULN on 2 consecutive occasions | 9/472 (1.9%) | 0/484 | 6/479 (1.3%) | 0/480 | 6/472 (1.3%) | 2/238 (0.8%) |
| Any AST > 5 × ULN | 1/472 (0.2%) | 0/484 | 1/479 (0.2%) | 0/480 | 1/472 (0.2%) | 1/238 (0.4%) |
| AST > 3 × ULN on 2 consecutive occasions | 1/472 (0.2%) | 0/484 | 2/479 (0.4%) | 0/480 | 2/472 (0.4%) | 1/238 (0.4%) |

## Retrospective Observational Pharmacoepidemiologic Data

i3/Abbott Study 1 evaluated the incidence of hepatic injury including hospitalization for the clinical diagnoses with no obvious alternative etiology. Overall, there were very few events, with no evidence of a differential risk for hepatic injury between fenofibrate monotherapy, statin monotherapy, or coadministration therapy.

## Postmarketing Safety Data Review

In a review of Abbott postmarketing safety data, the reporting rate for cases of hepatic disorder was approximately 1.68 per 100,000 patient treatment-years. However, reports of hepatic failure resulting in death have been rare and were generally confounded by complex medical conditions. There were no reports of hepatic failure requiring transplantation. Hepatocellular, chronic active, and cholestatic hepatitis observed with fenofibrate therapy have been reported after exposures of weeks to several years. In extremely rare cases, cirrhosis has been reported in association with chronic active hepatitis.


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As noted in the current labeling for fenofibrate, regular monitoring of liver function, including serum ALT should be performed for the duration of therapy with Trilipix, and therapy discontinued if transaminase levels persist above 3 × ULN.

### 8.1.5 Pancreatitis

Pancreatitis has been reported in patients taking drugs of the fibrate class, including Trilipix. This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridemia, a direct drug effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation with obstruction of the common bile duct.

In ACCORD Lipid, there were 5 serious adverse event reports (0.2%) of pancreatitis with coadministration therapy and 4 (0.1%) with simvastatin statin monotherapy. In the FIELD study, there were 23 reports of pancreatitis (0.5%) with placebo and 40 reports (0.8%) with fenofibrate. There was a single case in the Trilipix clinical program (0.2%), reported with low-dose statin coadministered with fenofibric acid.

**Retrospective Observational Pharmacoepidemiologic Data**

i3/Abbott Study 1 determined an approximately 2.7-fold increase in risk for events of clinically confirmed cases of pancreatitis for fenofibrate alone compared to statins alone, with no incremental risk for patients receiving fenofibrate coadministered with a statin.[62]

**Postmarketing Safety Data Review**

Review of Abbott postmarketing safety data has determined the reporting rate for cases of pancreatitis to be approximately 0.58 per 100,000 patient treatment-years. Most of the reports were confounded by other conditions or concomitant medications. Reports of pancreatitis with fatal outcomes were rare. The occurrence of pancreatitis is currently represented in the *Warnings and Precautions* section of the Trilipix and TriCor labels.


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## 8.2 Morbidity and Mortality

In general, ACCORD Lipid demonstrated that coadministration therapy with fenofibrate and simvastatin was well tolerated, and there were no new safety signals identified during the course of therapy. Indeed, previously identified potential safety concerns, including thromboembolic events, and gallbladder-related events, were not found to occur at a higher rate in patients treated with fenofibrate-simvastatin coadministration therapy than in those treated with simvastatin monotherapy. In addition, all-cause mortality in ACCORD Lipid was lower in patients treated with fenofibrate-simvastatin coadministration therapy than in those treated with simvastatin monotherapy.

In the prespecified subgroup with dyslipidemia in ACCORD Lipid, the annual rate of all-cause mortality was lower in patients treated with fenofibrate and simvastatin coadministration therapy compared to simvastatin monotherapy (1.50 versus 2.21 events per 100 patient treatment-years), and the hazard ratio (0.670; 95% CI: 0.438, 1.025) numerically favored coadministration therapy. In addition, other statistically significant differences, favoring coadministration therapy over simvastatin monotherapy, were observed, such as a 37% reduction of the risk of major coronary disease events (2.79 versus 4.45 events per 100 patient treatment-years; HR = 0.627; 95% CI: 0.455, 0.864; $P = 0.004$) and a 50% reduction in the risk of death from a CV cause (0.70 versus 1.38 events per 100 patient treatment-years; HR = 0.501; 95% CI: 0.277, 0.906; $P = 0.022$).

## 8.3 Safety in Published Fibrate Meta-Analysis of 18 Outcomes Trials

In the independent meta-analysis that included over 45,000 patients by Jun et al,[25] there was no significant increase in the risk of serious drug-related adverse events, risk of rhabdomyolysis, muscle abnormalities, gastrointestinal disorders, or gallbladder disease associated with fibrate therapy. As expected, an increase in creatinine was observed in patients treated with a fibrate; however, fibrate therapy significantly reduced the risk of progression of albuminuria.


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## 8.4 Fenofibrate/Fenofibric Acid-Statin Coadministration Prescribing Patterns

Abbott conducted analyses of patient-level clinical data from Centricity Physician Office® Electronic Medical Records (EMR) to understand real-world usage of fenofibrate/fenofibric acid-statin coadministration therapy. This analysis, based on data from 01 July 2000 to 31 October 2010, showed that 89% of patients who are initiating fenofibrate or fenofibric acid in addition to existing statin therapy have TG ≥ 200 mg/dL and/or HDL-C < 40 mg/dL (Table 35) prior to initiation of fenofibrate or fenofibric acid. The annual rate was consistent over time, ranging from a low of 87% to a high of 92%.

**Table 35. Summary of Lipid Values for Patients with Fenofibrate/Fenofibric Acid Added to Their Existing Statin Therapy**

| Population | N | Median (Mean) TG, mg/dL | Median (Mean) HDL-C, mg/dL | Percentage with TG ≥ 200 mg/dL and/or HDL-C < 40 mg/dL |
|---|---|---|---|---|
| Overall | 13,401 | 303 (370) | 38 (39.4) | 88.9% |
| Men | 7,571 | 312 (387) | 35 (36.3) | 91.7% |
| Women | 6,107 | 293 (349) | 42 (43.1) | 85.4% |

Thus, prescription data indicate that for patients on statin therapy, fenofibrate/fenofibric acid is generally added in patients with elevated TG and/or low HDL-C, in accordance with treatment guidelines and also consistent with the Trilipix prescribing information. Importantly these patients can be identified by routine lipid analysis (elevated TG and/or low HDL-C) prior to and during treatment.


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## 9.0 Benefit-Risk Conclusions

Fenofibrate and fenofibric acid, considered jointly in this document because they share the same active moiety, have a substantial body of clinical trial, postmarketing safety surveillance, and epidemiological data. Other data sources such as meta-analyses and prescription utilization data aid in the understanding of the role of appropriate coadministration therapy with fenofibrate or fenofibric acid and a statin.

In each of 5 CV outcomes trials including ACCORD Lipid, fibrate therapy demonstrated a statistically significant reduction in the risk of CV events in patients with elevated TG and low HDL-C. In these trials, there was a nonsignificant reduction in CV events in those patients without elevated TG and low HDL-C. The consistency of the results across these trials demonstrates that in a population with elevated TG and low HDL-C, fibrate therapy reduces CV risk regardless of whether the population has diabetes, has had previous CV events, or is receiving concomitant statin therapy.

While coadministration therapy with fenofibrate and simvastatin did not result in a statistically significant reduction in CV risk in the overall population of ACCORD Lipid, a significant reduction in CV risk was observed in patients in the prespecified subgroup with dyslipidemia, with an NNT of 20 patients over 4.7 years. Because treatment guidelines and the Trilipix prescribing information support coadministration therapy only in patients already receiving statin therapy to achieve LDL-C goals, sensitivity analyses of the prespecified subgroup with dyslipidemia were conducted among patients who were receiving a statin at baseline. In these sensitivity analyses, coadministration therapy also demonstrated a statistically significant reduction in CV risk for patients with elevated TG, low HDL-C, or both.

In ACCORD Lipid, among patients receiving a statin at baseline, the absolute CV risk for patients randomized to receive simvastatin monotherapy increased with increasing TG and/or decreasing HDL-C. Thus, the residual CV risk among patients receiving simvastatin monotherapy was associated with the degree of TG and/or HDL-C abnormalities, consistent with epidemiological evidence associating elevated TG and/or


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low HDL-C with risk of CV events. In contrast, the percentage of patients with the primary endpoint in the coadministration therapy group was lower and relatively uniform regardless of baseline TG and HDL-C levels, illustrating that coadministration therapy reduces the incremental residual risk associated with elevated TG and low HDL-C.

A prespecified subgroup analysis identified a statistically significant treatment-by-gender interaction in ACCORD Lipid, with a statistically significant treatment benefit of coadministration therapy in men and a trend toward a potentially higher risk of CV events in women treated with coadministration therapy compared to simvastatin monotherapy. However, in the prespecified subgroup with dyslipidemia, there was not a significant treatment-by-gender interaction, suggesting that, in this subgroup, the reduction in CV risk with coadministration therapy was not different for men and women.

ACCORD Lipid provides additional data on microvascular benefits (including reductions in retinopathy and albuminuria) of fenofibrate therapy in patients with diabetes, similar to results previously reported in FIELD. These findings are considered clinically significant and may be an important factor for prescribers in the decision to select fenofibrate/fenofibric acid therapy. No other specific therapy has demonstrated these microvascular benefits that delay the progression of complications in patients with diabetes.

The risks of fenofibrate/fenofibric acid therapy have been well defined for over 35 years of clinical use, including in controlled clinical trials such as ACCORD Lipid, FIELD, and the Trilipix clinical program. Muscle adverse events, including rhabdomyolysis, have been reported with the use of fenofibrate/fenofibric acid as monotherapy and when coadministered with a statin. In a large pharmacoepidemiologic study, the incidence of hospitalized rhabdomyolysis with coadministration therapy was rare, but was higher than in patients receiving statin monotherapy. These results are consistent with previously reported findings and represent an acceptable level of risk that is markedly less than the risk with coadministration of gemfibrozil and a statin. For coadministration of fenofibrate with a statin, the NNH for rhabdomyolysis is large; one additional event would be expected for every 18,000 patient treatment-years. The risk and presenting


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symptoms of rhabdomyolysis are described in Trilipix labeling and the Medication Guide for Trilipix.

The safety results in ACCORD Lipid were reassuring and consistent with the known safety profile of fenofibrate/fenofibric acid. Adverse events in ACCORD Lipid, including transaminase elevations, reversible creatinine increases, and pancreatitis occurred at expected or lower rates with the coadministration of fenofibrate and simvastatin. An overall favorable safety profile for coadministration therapy was also observed in the Trilipix clinical program.

In summary, coadministration therapy of fenofibrate/fenofibric acid with a statin significantly reduces CV events in patients with elevated TG and/or low HDL-C. The safety profile of fenofibrate/fenofibric acid is well characterized, and the risks, which primarily include muscle, renal, and hepatic adverse events, are appropriately described in the prescribing information. Therefore, coadministration therapy of fenofibrate/fenofibric acid with a statin has a positive benefit-risk profile and offers an important therapeutic option for appropriately selected patients.


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# 10.0 Recommendations to Guide Appropriate Usage

On the basis of the data contained within this document, Abbott presents for consideration the following potential changes to the Trilipix US prescribing information designed to provide additional information to the prescriber. Abbott also notes that appropriate educational activities will be conducted to support all changes to the prescribing information.

The potential changes described below relate to the *Indications* section and the *Warnings and Precautions* section of the Trilipix US prescribing information.

1. Potential changes to *Indications* (Section 1.1):

Potential changes to the indication for the coadministration of Trilipix with a statin may involve a revision to the current wording for clarity, **or** the addition of thresholds for TG and/or HDL-C to provide additional information to the prescriber.

**a. Revision of the coadministration *Indications* statement (Section 1.1 of the Trilipix US prescribing information) for clarity:**

The following language is provided as an example of a revised indications statement to clarify the appropriate population for coadministration therapy. Language not currently contained in the *Indications* statement is underlined:

*Trilipix is indicated as an adjunct to diet in combination with a statin to reduce TG and increase HDL-C in patients with mixed dyslipidemia (elevated TG and/or low HDL-C) and CHD or a CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal.*

**Rationale:** The addition of such a parenthetical statement would clarify the appropriate population for the coadministration of Trilipix with a statin as those patients with abnormal TG and/or HDL-C at baseline, who are already on a statin with optimal control of LDL-C. This clarification is supported by the findings in


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ACCORD Lipid and FIELD, showing that patients with elevated TG and low HDL-C derived CV benefit with fenofibrate (and similarly, fenofibric acid) treatment.

**b. Addition of lipid values to the *Indications* statement in Section 1.1 of the Trilipix US prescribing information.**

As an alternative to the language provided in 1a above, the inclusion of specific TG and/or HDL-C values in the indication for the coadministration of Trilipix with a statin may provide guidance to a prescriber:

> *Trilipix is indicated as an adjunct to diet in combination with a statin to reduce TG and increase HDL-C in patients with mixed dyslipidemia (TG ≥ 200 mg/dL, and/or HDL-C < 40 mg/dL) and CHD or a CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal.*

**Rationale:** The addition of TG and/or HDL-C values appropriate for initiation of Trilipix/statin coadministration therapy (e.g., TG ≥ 200 mg/dL and/or HDL-C < 40 mg/dL) could further clarify which patients are appropriate for this therapy.

However, in ACCORD Lipid and FIELD increasing CV benefit with fenofibrate therapy was observed with worsening degrees of dyslipidemia, and may be present at values not meeting the thresholds described above. This observation is also applicable to fenofibric acid treatment. Other products in this therapeutic area do not include lipid thresholds in their indications for the treatment of dyslipidemia. Furthermore, the inclusion of defined thresholds for TG and HDL-C has the potential to limit access to coadministration treatment for patients whose values are near, but do not meet, these thresholds; in such patients prescribers may consider other factors beyond specific lipid values in determining the appropriateness of coadministration therapy. Finally, the values noted above are based on current NCEP/ATP III treatment guidelines; such treatment guidelines may become obsolete. Therefore, Abbott's preferred option is 1a.


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**2. Removal of the *Indications – Limitations of Use* statement.**

Abbott proposes deletion of the Limitations of Use statement currently included in Section 1.4 of the Trilipix US prescribing information.

**Rationale:** The results of ACCORD Lipid support the incremental benefit of the addition of fenofibrate (or fenofibric acid) to statin monotherapy in patients with elevated TG and/or low HDL-C, in terms of cardiovascular risk reduction. Abbott is not requesting an indication for cardiovascular risk reduction; however the sponsor concludes that on the basis of the ACCORD Lipid study findings, the existing Limitations of Use statement is no longer accurate.

**3. Addition of a description of the ACCORD Lipid findings to *Indications – General Considerations for Treatment* (Section 1.5), as well as to the *Warnings and Precautions – Cardiovascular Morbidity and Mortality* (Section 5.9) subsection of the Trilipix US prescribing information.**

Abbott proposes to add a description of the ACCORD Lipid study findings to the *Indications – General Considerations for Treatment* section (Section 1.5) and to *Warnings and Precautions – Mortality and Coronary Heart Disease Morbidity* (Section 5.9) in the Trilipix US prescribing information. These additions would describe the study design of ACCORD Lipid, the primary endpoint results, the results from the dyslipidemia subgroup, and the treatment-by-gender interaction finding.

Abbott is also proposing elevation of the existing *Warnings and Precautions – Mortality and Coronary Heart Disease Morbidity* language from the existing location in Section 5.9 and to Section 5.3 of the Trilipix US prescribing information.

**Rationale:** The inclusion of information from ACCORD Lipid in the Trilipix US prescribing information would provide prescribers with additional information to consider when evaluating whether the coadministration of Trilipix with a statin is appropriate for their individual patient.


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# Appendix A. Meta-Analysis to Assess the Contribution of Fenofibrate to Reduce the Risk for Major Cardiovascular Events in Patients Receiving Fenofibrate-Statin Combination Therapy



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# Abbott Laboratories (Abbott)

# Meta-Analysis to Assess the Contribution of Fenofibrate to Reduce the Risk for Major Cardiovascular Events in Patients Receiving Fenofibrate-Statin Combination Therapy



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## 1.0 Objective

The primary objective of this literature based meta-analysis was to characterize the multivariate relationship between changes in low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) and risk for major cardiovascular and coronary events after treatment with statins, fibrates or niacin. An evaluation of whether the changes in lipid parameters could explain the treatment effect or whether there is an additional effect for certain drug classes or drugs within a class unexplained by lipid changes was also explored. The meta-analysis was also used to evaluate whether for a given change in lipid parameters there is a difference in the benefit for certain patient groups such as females, patients with diabetes or prior coronary heart disease (CHD), and other differentiating characteristics. Additionally, this meta-analysis was used to compare the predicted risk reduction to the observed risk reduction in ACCORD Lipid.

## 2.0 Methods

A broad literature search limited only to clinical trial was performed using Medline for all randomized controlled trials published through May 2009 in the English language that evaluated the safety and efficacy of atorvastatin, rosuvastatin, simvastatin, fluvastatin, lovastatin, cerivastatin, pravastatin, ezetimibe, fenofibrate, gemfibrozil, bezafibrate, niacin, niaspan, and nicotinic acid. The searches yielded 2,755 references that were evaluated for inclusion in the current analysis. Randomized controlled trials that compared treatment with statins, fibrates, cholesterol absorption inhibitors, niacin, or combinations thereof with placebo, usual care or active control and that reported on major coronary or cardiovascular events were included in the meta-analysis. A total of 165 references reported cardiovascular event outcomes or all cause mortality. Of these references a total of 54 (representing 45 trials) reported major cardiovascular events and 84 (representing 70 trials) reported major coronary events, the two endpoints of interest for this meta-analysis. Only one trial that reported cardiovascular events did not report coronary events, therefore a total of 71 trials were incorporated in the meta-analysis between the two endpoints. The 70 coronary event trials evaluated 109,360 patients on



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active treatment and 105,960 patients on placebo treatment. The major coronary events analysis contains 25 more trials with 33,074 more subjects than the major cardiovascular events analysis.

The analyses were designed to characterize the relationships between lipid parameters and outcomes (major cardiovascular or major coronary events) of fenofibrates and statins in general when administered as either monotherapy or in combination with each other. The analysis described the contribution of LDL-C, HDL-C and TG lowering to reducing risk of cardiovascular and coronary outcomes. The model based meta-analysis methodology followed the general statistical principles of meta-analysis. The generalized least squares regression function (GNLS) and the nonlinear mixed effect regression function (NLME) provided in S-PLUS were used to calculate maximum likelihood estimates of the model parameters.

# 3.0 Results

## 3.1 Meta-Analysis Without ACCORD Lipid

The risk reduction (difference in log of odds-ratio) for major coronary and cardiovascular events between active and control arms was found to be statistically significantly dependent on the absolute difference in on-treatment LDL-C between active and control arm, the absolute difference in on-treatment TG between active and control arm and the treatment duration. The risk reduction for major cardiovascular events was also dependent on baseline HDL-C.

The impact of LDL-C and TG on the risk reduction was highly significant ($p < 0.001$ for each variable). Both factors were found to contribute independently to the reduction in risk; the TG effect was statistically significant in addition to the LDL-C effect and the LDL-C effect was statistically significant in addition to the TG effect. There was no significant interaction between the impact of LDL-C and TG changes suggesting the effect is additive. Higher baseline HDL-C values attenuated the effects of LDL-C and TG on major cardiovascular outcomes. The risk reduction for major coronary events was estimated to be 18.5% (95% confidence interval [CI]: 14.1 to 22.7) for every 1 mmol/L



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reduction in LDL-C (38.7 mg/dL) and 27.5% (95% CI: 15.7 to 37.7) for every 1 mmol/L reduction in TG (88.6 mg/dL). The risk reduction for major cardiovascular events was estimated to be 16.5% (95% CI: 12.9 to 20.0) for every 1 mmol/L reduction in LDL-C and 24.0% (95% CI: 13.0 to 33.8) for every 1 mmol/L reduction in TG at a baseline HDL-C of 45 mg/dL. The parameter estimates for the major cardiovascular and major coronary models were strikingly similar; the only difference was the contribution of baseline HDL-C for the major cardiovascular event model.

The impact of differences in on-treatment LDL-C, TG, and HDL-C on the relative risk for a major cardiovascular event by trial and drug class is shown in Figure 1. No significant effect of drug class or specific drug was found on the intercept of the model ($E_0$) or the slope of the LDL-C and TG relationships, suggesting that the LDL-C and TG relationships could be similar across drugs and drug classes. These results suggest that the difference in benefit of statins and fibrates could be explained by their differences in LDL-C and TG reduction.



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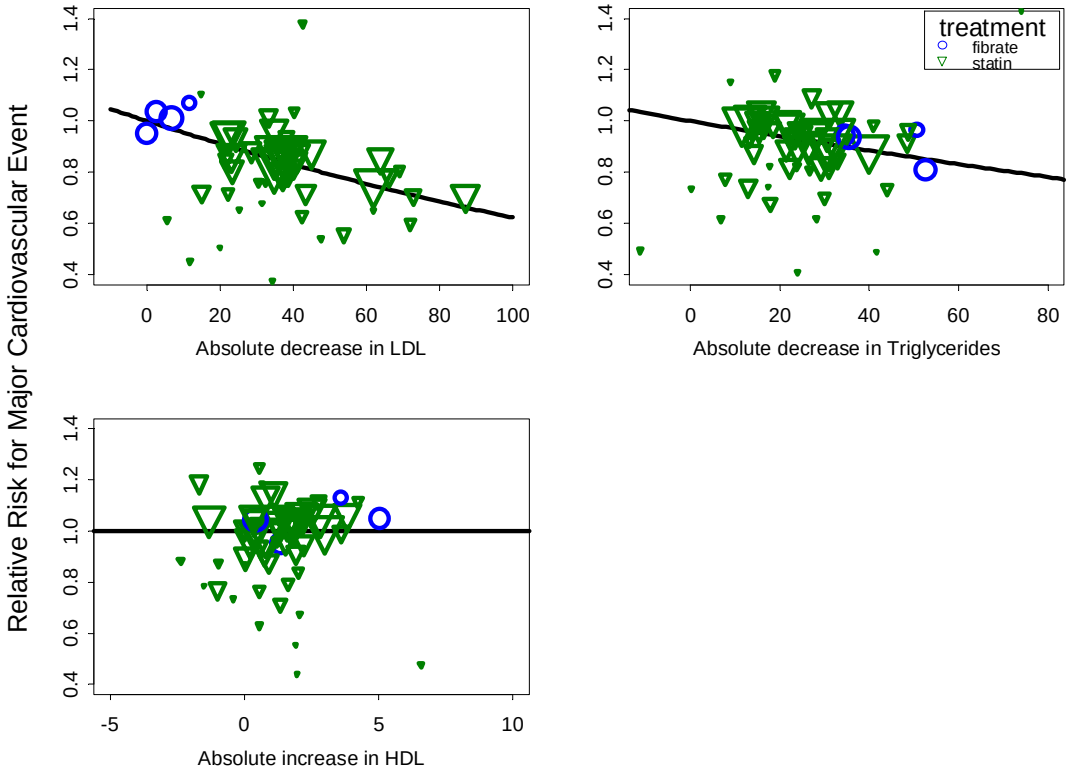
**Figure 1. Relationship Between Relative Risk for Major Cardiovascular Events and Absolute Change in Lipid Parameters**




Observed relative risk (symbol) versus model predicted contribution of LDL-C, HDL-C and TG changes to the relative risk (line) for a major cardiovascular event. Predictions are made for a 4-year treatment duration. Observations are adjusted for difference in treatment duration. The top left hand panel shows the model predictions for LDL-C reduction assuming no change in TG. The top right hand panel shows the model predictions for TG reduction assuming no change in LDL-C. The bottom left hand panel shows the model predictions for HDL-C changes assuming no change in either LDL-C or TG.

While the relationship between lipid changes and risk reduction for major coronary and major cardiovascular events in the meta-analysis model was not statistically significantly different between statins and fibrates, sensitivity analyses were undertaken to further assess whether differences between fibrates and statins had the potential to impact the conclusions of the analyses. In these sensitivity analyses, a model that used separate



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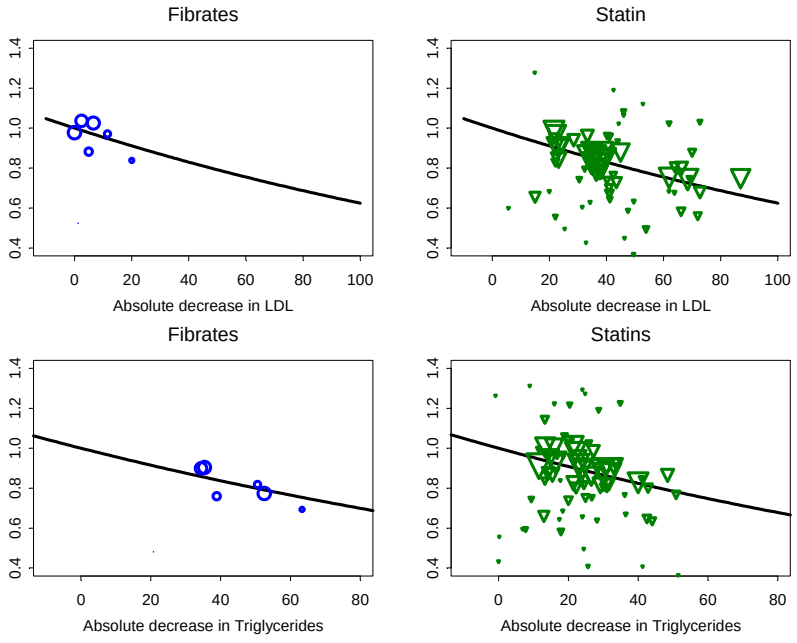
slopes for LDL-C and TG relationships for each drug class did not improve the fit of the model compared to the original model that used a single slope for all drug classes.

In a model that estimated a different slope for the TG and LDL-C effect by drug class, the slope of the TG relationship for coronary events for fibrates (p = 0.006) and statins (p = 0.005) were both significantly greater than zero suggesting that for both drug classes a statistically significant portion of the risk reduction is mediated through TG reduction. No significant difference between statins and fibrates was found on the slopes of the LDL-C and TG relationships (p = 0.33), suggesting that the lipid relationships would be similar across the drug classes. **These results suggest that the difference in benefit of statins and fibrates could be explained by their differences in LDL-C and TG reduction.** The relationships between LDL-C and TG lowering on coronary risk reduction are further depicted in Figure 2, where fibrate and statin effects are independently displayed.

**Figure 2. Relationship Between Risk of Major Coronary Event and Absolute Change in Lipid Parameters by Drug Class**



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Based on the observed reductions in TG and LDL-C associated with fibrate use, a significant risk reduction for major coronary events was found for fibrates, predominantly (~85%) of their benefit is predicted to be mediated through their TG lowering effect. For statins, the reduction in LDL-C was found to explain most (~70%) of their benefit, but the reduction in TG was found to provide a statistically and clinically significant contribution (~30%) to their overall risk reduction. **The independent effect of TG and LDL-C lowering supports the role for treatment combinations such as statins and fibrates that impact LDL-C and TG differentially.**

None of the other differences in patient characteristic across trials, including percent female/male, age, CHD, diabetes, baseline LDL-C or TG, and acute intervention significantly impacted the risk reduction due to lipid changes. This suggests that the benefit due to an absolute difference in lipid changes is independent of gender, age, diabetes status, presence of CHD, or acute intervention.

As expected, the treatment benefit was less for trials of shorter duration and greater for trials of longer duration ($p < 0.001$). The average trial duration to achieve 50% of maximal risk reduction was 0.52 years (95% CI: 0.16 to 1.6) and 0.35 years (95% CI: 0.09 to 1.3) for major coronary and cardiovascular events, respectively. This suggests that maximal risk reduction due to lipid changes is achieved within 2 years of treatment.

## 3.2 Meta-Analysis with ACCORD Lipid

The reported absolute mean differences, averaged over 6 years, in lipid parameters in the ACCORD Lipid trial of –29.2 mg/dL TG and 0.06 mg/dL LDL-C for the subjects who received fenofibrate and simvastatin compared to those receiving placebo and simvastatin, correspond to hazard ratios of 0.92 (95% CI: 0.79 to 1.07) for major coronary events and 0.92 (95% CI: 0.79 to 1.08) for major cardiovascular events. The predicted hazard ratio according to the meta-analysis model, based on the reported TG and LDL-C differences between treatment groups and the baseline HDL-C in ACCORD Lipid is 0.90 (95% CI: 0.85 to 0.94) for major cardiovascular outcomes and 0.91



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(95% CI: 0.87 to 0.95) for major coronary outcomes. **Therefore, the predicted risk reduction based on the meta-analysis model, which did not include ACCORD Lipid (0.91 hazard ratio) was nearly the same as the observed risk reduction in ACCORD Lipid (0.92 hazard ratio).**

To assess the impact of the results from ACCORD Lipid on the parameter estimates from the meta-analysis model, the results from ACCORD Lipid were added to the model for cardiovascular and coronary events and the meta-analysis model estimates were updated. The estimated meta-analysis model parameters including and excluding the results from ACCORD Lipid for cardiovascular and coronary events were nearly identical. **Therefore, the inclusion of ACCORD Lipid results in the meta-analysis model had very little to no influence on the overall parameter estimates for the change in lipids to major cardiovascular or major coronary outcomes relationship or associated variability.** This suggests that the major cardiovascular or coronary outcome results from ACCORD Lipid are consistent with the results from the meta-analysis model using the large number of clinical trials previously reported in the literature. The observed relative risk (symbol with 95% CI) and predicted relative risk (vertical lines) for major cardiovascular events for each of the fibrate trials after the model update with the ACCORD Lipid data is shown in Figure 3. The trials are sorted by their absolute difference in TG between the active and control arm. The difference in TG is shown after the trial name. The fibrate trials are well predicted by the model and a larger risk reduction is observed with larger changes in TG values.



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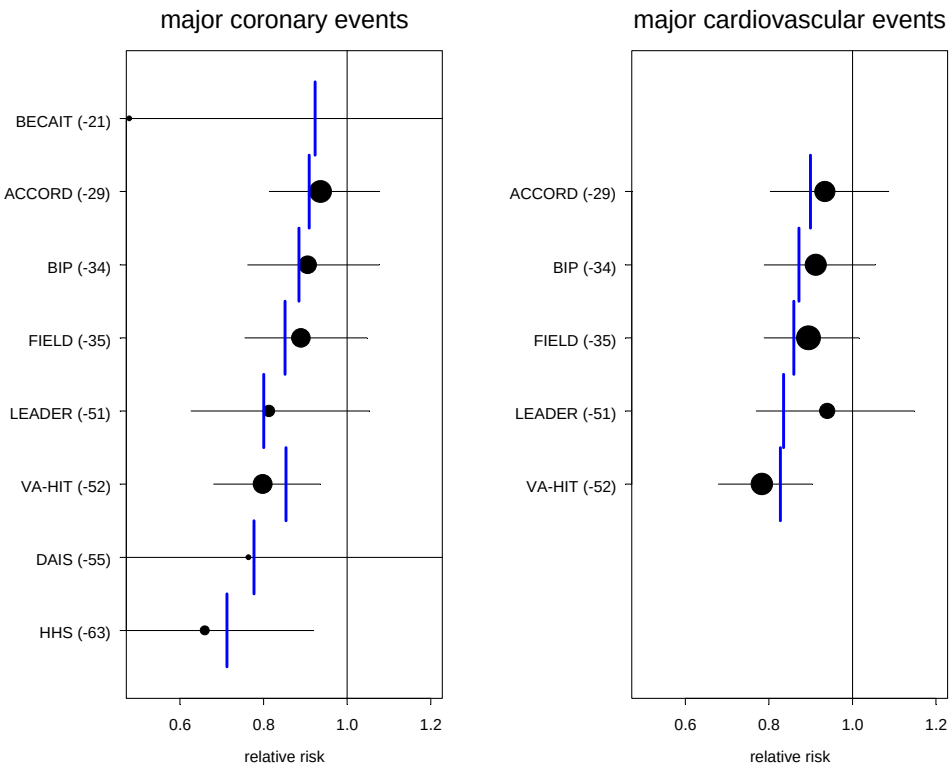
**Figure 3. Forest Plot of Observed and Model Predicted Relative Risk for Major Coronary and Cardiovascular Events for Fibrate Trials Including ACCORD Lipid**




The small risk reduction in ACCORD Lipid is explained by the small absolute TG difference observed in this study. The TG difference in ACCORD Lipid (–29.2 mg/dL) is much smaller than observed in the trials supporting the indication for the use of fenofibric acid in combination with a statin. Twelve weeks of combination therapy with a low-dose and moderate-dose statins resulted in a mean difference of –71 mg/dL and –55 mg/dL in TG, respectively, when compared to statin monotherapy. The main difference between these trials and ACCORD Lipid is the baseline lipid profile. In ACCORD Lipid, the mean TG baseline was 188 mg/dL compared to 282 mg/dL in the Trilipix clinical program. The absolute change in TG after treatment with fenofibric acid is primarily dependent on the baseline TG values. **Therefore, subjects with higher**

**baseline TG values are expected to experience a greater absolute decrease in TG with fenofibric acid treatment and a greater risk reduction for major coronary and cardiovascular events.**

## 3.3 Major Cardiovascular and Major Coronary Outcomes in Women Compared to Men Based on the Meta-Analysis Model

The meta-analysis models were also used to explore potential differences in outcomes between women and men. As very few individual studies reported outcomes for males and females, separately, the relationship between lipid changes and risk reduction was performed on the % of females in each trial. The relationship between lipid changes and risk reduction for major coronary and major cardiovascular events in the meta-analysis model was not statistically significantly dependent on the percent of females in the trial. The database contains a significant number of women with data from trials enrolling 58,964 women and 156,356 men. There is a reasonable variation in the percent females enrolled across the trials suggesting that the lack of an impact of female sex on the risk reduction per unit change in LDL-C and TG is not due to a lack of power to detect such a dependency in the meta-analysis events.

As part of a sensitivity analysis, the slopes of the relationship between lipid changes and risk for major coronary events were estimated for men and women using subgroup data, if reported, and proportion of males and females in each trial. The point estimates for the risk reduction per unit LDL-C and TG lowering are similar between men and women, but the CIs for the slopes in women include zero. When the impact of sex on the slope of the relationship between risk reduction and LDL-C or TG lowering is assumed to be similar for the two lipid variables, the slope estimates for the LDL-C and TG relationships in women are 0.050 (95% CI: 0.009 to 0.081) for every 10 mg/dL decrease in LDL-C and 0.032 (95% CI: 0.004 to 0.072) for every 10 mg/dL decrease in TG. Under these conditions the slopes for the LDL-C and TG relationships are significantly different from zero in women as well as men. Thus, a statistically significant relationship between risk for major coronary events and reduction in LDL-C and TG is found for both women and



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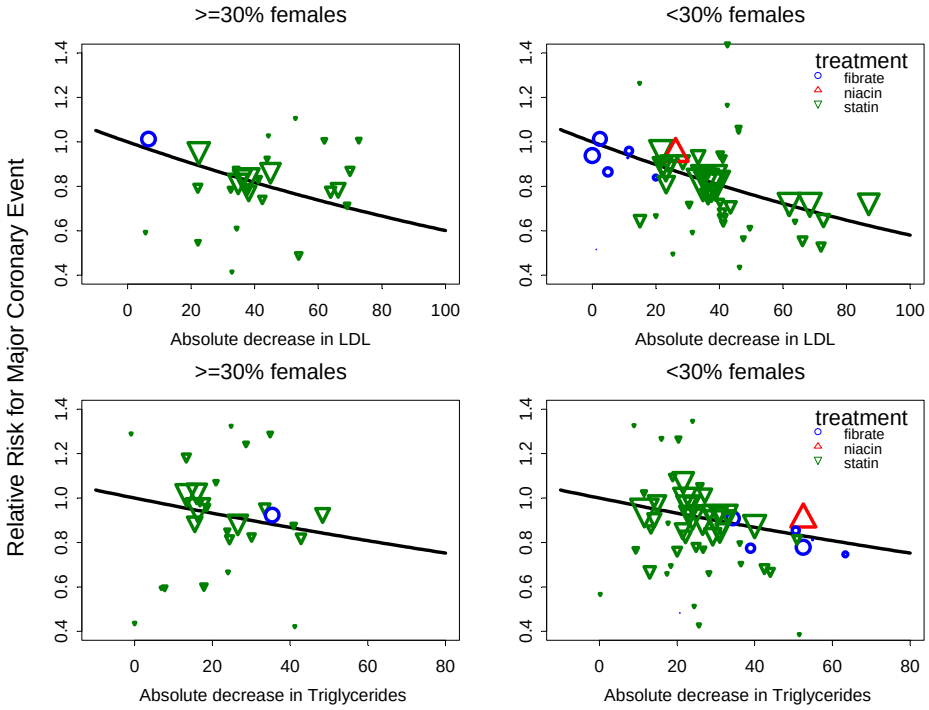
men with the slopes approximately 13% smaller in women compared to men. The estimated and observed relative risk for major coronary events versus LDL-C and TG changes stratified by trials that have fewer than 30% females and trials that have more than 30% females is shown in Figure 4.

**Figure 4. Effect of Sex on Relationship Between Coronary Risk and TG or LDL-C Changes**




Observed relative risk (symbol) versus model relative risk (line) for a major coronary event by change in LDL-C (top panel) and TG (bottom panel) catergorized by trials with > and < 30% females. Predictions are made for a 4-year treatment duration. Observations are adjusted for difference in treatment duration. The symbol size is proportional to the precision of the relative risk observed in the trial. A larger symbol indicates a more precise observation.

The meta-analysis model suggests that the cardiovascular and coronary outcome benefits were similar in males and females and were not altered in sensitivity analyses. Therefore the results of the meta-analysis model suggest that the ACCORD Lipid results in women may be an anomaly.

## 4.0 Conclusions

- The meta-analysis model indicates that fenofibrate, independent of the effects of statin, contributes to improved major cardiovascular and coronary outcomes. The meta-analysis model also demonstrates that the improved outcome due to the impact of fenofibrate treatment is similar for major cardiovascular and major coronary outcomes.
- The predicted hazard ratio according to the meta-analysis model, based on the reported TG and LDL-C differences between treatment groups and the baseline HDL-C in ACCORD Lipid and using all trials in the meta-analysis database with the exception of ACCORD Lipid, was 0.90 (95% CI: 0.85 to 0.94) or major cardiovascular outcomes and 0.91 (95% CI: 0.87 to 0.95) for major coronary outcomes. The predicted cardiovascular risk reduction based on the meta-analysis model which did not include ACCORD Lipid (0.91 hazard ratio) was nearly exactly the same as the observed risk reduction in ACCORD Lipid (0.92 hazard ratio).
- The inclusion of ACCORD Lipid results in the meta-analysis model had very little to no influence on the overall parameter estimates for the change in lipids to major cardiovascular or major coronary outcomes relationship or associated variability. This suggests that the major cardiovascular or coronary outcome results from ACCORD Lipid are consistent with the results from the meta-analysis model using the large number of clinical trials previously reported in the literature.
- The meta-analysis model suggests that the cardiovascular or coronary outcome benefits were similar between trials with a smaller proportion of female subjects versus a larger proportion of female subjects included in the analyses. This suggests that ACCORD Lipid results in women may be an anomaly.



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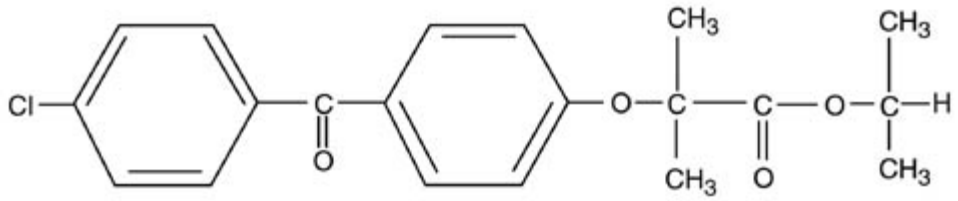
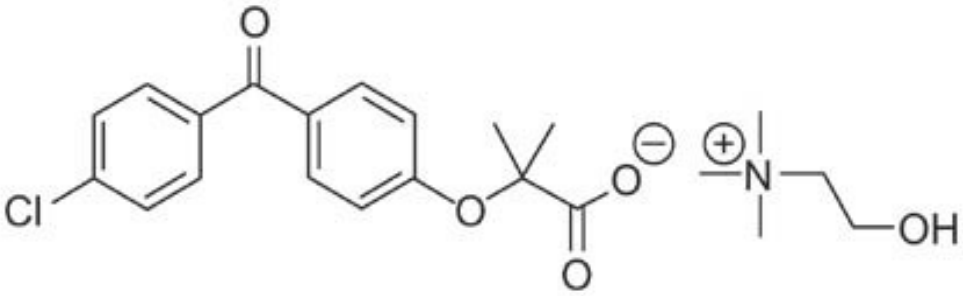
## Appendix B. Molecular Structure of Fenofibrate and Fenofibric Acid

Fenofibrate = $C_{20}H_{21}O_4Cl$




Fenofibric acid (choline salt) = $C_{22}H_{28}ClNO_5$



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## Appendix C. United States Prescribing Information for Trilipix



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**HIGHLIGHTS OF PRESCRIBING INFORMATION**

**These highlights do not include all the information needed to use Trilipix safely and effectively. See full prescribing information for Trilipix.**
**Trilipix (fenofibric acid) capsule, delayed release for oral use**
**Initial U.S. Approval: 2008**

**-------INDICATIONS AND USAGE-------**

Trilipix is a peroxisome proliferator receptor alpha (PPARα) activator indicated:

- 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 (1.1).
- As monotherapy to reduce TG in patients with severe hypertriglyceridemia (1.2).
- 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 (1.3).

Limitations of use: No incremental benefit of Trilipix on cardiovascular morbidity and mortality over and above that demonstrated for statin monotherapy has been established.

General Considerations For Treatment: Fenofibrate at a dose equivalent to 135 mg of Trilipix was not shown to reduce coronary heart disease morbidity and mortality in a large, randomized controlled trial of patients with type 2 diabetes mellitus.

**-------DOSAGE AND ADMINISTRATION-------**

- Mixed dyslipidemia: 135 mg once daily (2.2).
- Hypertriglyceridemia: 45 to 135 mg once daily (2.3).
- Renally impaired patients: 45 mg once daily (2.5).
- Maximum dose: 135 mg once daily (2.1).
- May be taken without regard to food (2.1).
- May be taken at the same time as a statin (2.2).
- Co-administration with the maximum dose of a statin has not been evaluated in clinical studies and should be avoided unless the benefits are expected to outweigh the risks (2.2).

**-------DOSAGE FORMS AND STRENGTHS-------**

Oral Delayed Release Capsules: 45 mg and 135 mg (3).

**-------CONTRAINDICATIONS-------**

- Severe renal dysfunction, including patients receiving dialysis (4, 12.3).
- Active liver disease (4, 5.3).
- Gallbladder disease (4, 5.4).
- Nursing mothers (4, 8.3).

**-------WARNINGS AND PRECAUTIONS-------**

- Myopathy and rhabdomyolysis have been reported in patients taking fenofibrate. The risks for myopathy and rhabdomyolysis are increased when fibrates are co-administered with a statin (with a significantly higher rate observed for gemfibrozil), particularly in elderly patients and patients with diabetes, renal failure, or hypothyroidism (5.1).
- Trilipix can increase serum transaminases. Liver tests should be monitored periodically (5.3).
- Trilipix can reversibly increase serum creatinine levels (5.2). Renal function should be monitored periodically in patients with renal insufficiency (8.6).
- Trilipix increases cholesterol excretion into the bile, leading to risk of cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated (5.4).
- Exercise caution in concomitant treatment with oral coumarin anticoagulants. Adjust the dosage of coumarin anticoagulant to maintain the prothrombin time/INR at the desired level to prevent bleeding complications (5.5).

**-------ADVERSE REACTIONS-------**

The most common adverse events (≥ 3% of patients receiving Trilipix or Trilipix co-administered with statins) are headache, back pain, nasopharyngitis, nausea, myalgia, diarrhea, and upper respiratory tract infection (6.1).
To report SUSPECTED ADVERSE REACTIONS, contact Abbott Laboratories at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

**-------DRUG INTERACTIONS-------**

- Coumarin Anticoagulants: (7.1).
- Bile Acid Resins: (7.2).
- Cyclosporine: (7.3).

**-------USE IN SPECIFIC POPULATIONS-------**

- Geriatric Use: Dose selection for the elderly should be made on the basis of renal function (8.5).
- Renal Impairment: Trilipix should be avoided in patients with severe renal impairment. Dose adjustment is required in patients with mild to moderate renal impairment (8.6).
- The use of Trilipix has not been evaluated in patients with hepatic impairment (8.7).

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

**Revised: 03/2011**

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# FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

### 1.1 Co-administration Therapy with Statins for the Treatment of Mixed Dyslipidemia

Trilipix is indicated as an adjunct to diet 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.

CHD risk equivalents comprise:

- Other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease);
- Diabetes;
- Multiple risk factors that confer a 10-year risk for CHD > 20%

### 1.2 Treatment of Severe Hypertriglyceridemia

Trilipix is indicated as adjunctive therapy to diet to reduce TG in patients with severe hypertriglyceridemia. Improving glycemic control in diabetic patients showing fasting chylomicronemia will usually obviate the need for pharmacological intervention. Markedly elevated levels of serum triglycerides (e.g. > 2,000 mg/dL) may increase the risk of developing pancreatitis. The effect of Trilipix therapy on reducing this risk has not been adequately studied.

### 1.3 Treatment of Primary Hyperlipidemia or Mixed Dyslipidemia

Trilipix is indicated as adjunctive therapy to diet to reduce elevated LDL-C, Total-C, TG, and Apo B, and to increase HDL-C in patients with primary hyperlipidemia or mixed dyslipidemia.

### 1.4 Important Limitations of Use

**No incremental benefit of Trilipix on cardiovascular morbidity and mortality over and above that demonstrated for statin monotherapy has been established.**

### 1.5 General Considerations for Treatment

Fenofibrate at a dose equivalent to 135 mg of Trilipix was not shown to reduce coronary heart disease morbidity and mortality in a large, randomized controlled trial of patients with type 2 diabetes mellitus.

Laboratory studies should be performed to establish that lipid levels are abnormal before instituting Trilipix therapy.

Every reasonable attempt should be made to control serum lipids with non-drug methods including appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that may be contributing to the lipid abnormalities. Medications known to


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exacerbate hypertriglyceridemia (beta-blockers, thiazides, estrogens) should be discontinued or changed if possible, and excessive alcohol intake should be addressed before triglyceride-lowering drug therapy is considered. If the decision is made to use lipid-altering drugs, the patient should be instructed that this does not reduce the importance of adhering to diet.

Drug therapy is not indicated for patients who have elevations of chylomicrons and plasma triglycerides, but who have normal levels of VLDL.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 General Considerations

**Patients should be placed on an appropriate lipid-lowering diet before receiving Trilipix as monotherapy or co-administered with a statin *[see DOSAGE AND ADMINISTRATION (2.2, 2.3 and 2.4)]*, and should continue this diet during treatment. Trilipix delayed release capsules can be taken without regard to meals. Serum lipids should be monitored periodically. The maximum dose is 135 mg once daily.**

### 2.2 Co-administration Therapy with Statins for the Treatment of Mixed Dyslipidemia

Trilipix 135 mg may be co-administered with an HMG-CoA reductase inhibitor (statin) in patients with mixed dyslipidemia. For convenience, the daily dose of Trilipix may be taken at the same time as a statin, according to the dosing recommendations for each medication. Co-administration with the maximum dose of a statin has not been evaluated in clinical studies and should be avoided unless the benefits are expected to outweigh the risks.

### 2.3 Severe Hypertriglyceridemia

The initial dose of Trilipix is 45 to 135 mg once daily. Dosage should be individualized according to patient response, and should be adjusted if necessary following repeat lipid determinations at 4 to 8 week intervals. The maximum dose is 135 mg once daily.

### 2.4 Primary Hyperlipidemia or Mixed Dyslipidemia

The dose of Trilipix is 135 mg once daily.

### 2.5 Impaired Renal Function

Treatment with Trilipix should be initiated at a dose of 45 mg once daily in patients with mild to moderate renal impairment and should only be increased after evaluation of the effects on renal function and lipid levels at this dose. The use of Trilipix should be avoided in patients with severely impaired renal function.

### 2.6 Elderly Patients

Dose selection for the elderly should be made on the basis of renal function *[see USE IN SPECIFIC POPULATIONS (8.5)]*.


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## 3 DOSAGE FORMS AND STRENGTHS

- 45 mg choline fenofibrate delayed release capsules with a reddish-brown cap imprinted in white ink the Abbott "A" logo and a yellow body imprinted in black ink the number "45".
- 135 mg choline fenofibrate delayed release capsules with a blue cap imprinted in white ink the Abbott "A" logo and a yellow body imprinted in black ink the number "135".

## 4 CONTRAINDICATIONS

Trilipix is contraindicated in:

- patients with severe renal impairment, including those receiving dialysis.
- patients with active liver disease, including those with primary biliary cirrhosis and unexplained persistent liver function abnormalities.
- patients with preexisting gallbladder disease.
- nursing mothers.
- patients with hypersensitivity to fenofibric acid, choline fenofibrate or fenofibrate *[see WARNINGS and PRECAUTIONS (5.7)]*.

When Trilipix is co-administered with a statin, refer to the *Contraindications* section of the respective statin labeling.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Skeletal Muscle

**Fibrate and statin monotherapy increase the risk of myositis or myopathy, and have been associated with rhabdomyolysis. Data from observational studies suggest that the risk for rhabdomyolysis is increased when fibrates are co-administered with a statin (with a significantly higher rate observed for gemfibrozil). Refer to the respective statin labeling for important drug-drug interactions that increase statin levels and could increase this risk. The risk for serious muscle toxicity appears to be increased in elderly patients and in patients with diabetes, renal failure, or hypothyroidism.**

Myalgia was reported in 3.3% of patients treated with Trilipix monotherapy and 3.1% to 3.5% of patients treated with Trilipix co-administered with statins compared to 4.7% to 6.1% of patients treated with statin monotherapy. Increases in creatine phosphokinase (CPK) to > 5 times upper limit of normal occurred in no patients treated with Trilipix monotherapy and 0.2% to 1.2% of patients treated with Trilipix co-administered with statins compared to 0.4% to 1.3% of patients treated with statin monotherapy.

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevations of CPK levels. Patients should promptly report unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CPK levels should be assessed in patients reporting these symptoms, and Trilipix and statin therapy should be discontinued if markedly elevated CPK levels occur or myopathy or myositis is diagnosed.


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### 5.2 Serum Creatinine

Reversible elevations in serum creatinine have been reported in patients receiving Trilipix as monotherapy or co-administered with statins as well as patients receiving fenofibrate. In the pooled analysis of three double-blind controlled studies of Trilipix administered as monotherapy or in combination with statins, increases in creatinine to > 2 mg/dL occurred in 0.8% of patients treated with Trilipix monotherapy and 1.1% to 1.3% of patients treated with Trilipix co-administered with statins compared to 0% to 0.4% of patients treated with statin monotherapy. Elevations in serum creatinine were generally stable over time with no evidence for continued increases in serum creatinine with long-term therapy and tended to return to baseline following discontinuation of treatment. The clinical significance of these observations is unknown. Monitoring renal function in patients with renal impairment taking Trilipix is suggested. Renal monitoring should be considered for patients at risk for renal insufficiency, such as the elderly and those with diabetes.

### 5.3 Liver Function

Trilipix at a dose of 135 mg once daily administered as monotherapy or co-administered with low to moderate doses of statins has been associated with increases in serum transaminases [AST (SGOT) or ALT (SGPT)]. In a pooled analysis of three double-blind controlled studies of Trilipix administered as monotherapy or in combination with statins, increases to > 3 times the upper limit of normal on two consecutive occasions in ALT and AST occurred in 1.9% and 0.2%, respectively, of patients receiving Trilipix monotherapy and in 1.3% and 0.4%, respectively, of patients receiving Trilipix co-administered with statins. Increases to > 3 times the upper limit of normal in ALT and AST occurred in no patients receiving low- to moderate-dose statin monotherapy. Increases to > 3 times the upper limit of normal in ALT and AST occurred in 0.8% and 0.4%, respectively in patients receiving high-dose statin monotherapy. In a long-term study of Trilipix co-administered with statins for up to 52 weeks, increases of > 3 times the upper limit of normal on two consecutive occasions of ALT and AST occurred in 1.2% and 0.5% of patients, respectively. When transaminase determinations were followed either after discontinuation of treatment or during continued treatment, a return to normal limits was usually observed. Increases in ALT and/or AST were not accompanied by increases in bilirubin or clinically significant increases in alkaline phosphatase.

In a pooled analysis of 10 placebo-controlled trials of fenofibrate, increases to > 3 times the upper limit of normal in ALT occurred in 5.3% of patients taking fenofibrate versus 1.1% of patients treated with placebo. The incidence of increases in transaminases observed with fenofibrate therapy may be dose related. In an 8-week dose-ranging study of fenofibrate in hypertriglyceridemia, the incidence of ALT or AST elevations ≥ 3 times the upper limit of normal was 13% in patients receiving dosages equivalent to 90 mg to 135 mg Trilipix once daily and was 0% in those receiving dosages equivalent to 45 mg Trilipix once daily or less, or placebo. Hepatocellular, chronic active, and cholestatic hepatitis observed with fenofibrate therapy have been reported after exposures of weeks to several years. In extremely rare cases, cirrhosis has been reported in association with chronic active hepatitis.

Regular monitoring of liver function, including serum ALT (SGPT) should be performed for the duration of therapy with Trilipix, and therapy discontinued if enzyme levels persist above 3 times the upper limit of normal.


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### 5.4 Cholelithiasis

Trilipix, like fenofibrate, clofibrate, and gemfibrozil, may increase cholesterol excretion into the bile, potentially leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Trilipix therapy should be discontinued if gallstones are found.

### 5.5 Concomitant Oral Anticoagulants

Caution should be exercised when Trilipix is given in conjunction with oral coumarin anticoagulants. Trilipix may potentiate the anticoagulant effects of these agents resulting in prolongation of the prothrombin time/INR. Frequent monitoring of prothrombin time/INR and dose adjustment of the oral anticoagulant are recommended until the prothrombin time/INR has stabilized in order to prevent bleeding complications.

### 5.6 Pancreatitis

Pancreatitis has been reported in patients taking drugs of the fibrate class, including Trilipix. This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridemia, a direct drug effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation with obstruction of the common bile duct.

### 5.7 Hypersensitivity Reactions

Acute hypersensitivity reactions including severe skin rashes requiring patient hospitalization and treatment with steroids have occurred very rarely during treatment with fenofibrate, including rare spontaneous reports of Stevens-Johnson Syndrome and toxic epidermal necrolysis.

### 5.8 Hematological Changes

Mild to moderate hemoglobin, hematocrit, and white blood cell decreases have been observed in patients following initiation of Trilipix and fenofibrate therapy. Extremely rare spontaneous reports of thrombocytopenia and agranulocytosis have been received with fenofibrate therapy.

### 5.9 Mortality and Coronary Heart Disease Morbidity

The effect of Trilipix on coronary heart disease morbidity and mortality and non-cardiovascular mortality has not been established. Because of similarities between Trilipix and fenofibrate, clofibrate, and gemfibrozil, the findings in the following large randomized, placebo-controlled clinical studies with these fibrate drugs may also apply to Trilipix.

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study was a 5-year randomized, placebo-controlled study of 9795 patients with type 2 diabetes mellitus treated with fenofibrate. Fenofibrate demonstrated a non-significant 11% relative reduction in the primary outcome of coronary heart disease events (hazard ratio [HR] 0.89, 95% CI 0.75-1.05, $p = 0.16$) and a significant 11% reduction in the secondary outcome of total cardiovascular disease events (HR 0.89 [0.80-0.99], $p = 0.04$). There was a non-significant 11% (HR 1.11 [0.95, 1.29], $p = 0.18$) and 19% (HR 1.19 [0.90, 1.57], $p = 0.22$) increase in total and coronary heart disease mortality, respectively, with fenofibrate as compared to placebo.


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In the Coronary Drug Project, a large study of post-myocardial infarction patients treated for 5 years with clofibrate, there was no difference in mortality seen between the clofibrate group and the placebo group. There was, however, a difference in the rate of cholelithiasis and cholecystitis requiring surgery between the two groups (3.0% vs. 1.8%).

In a study conducted by the World Health Organization (WHO), 5000 subjects without known coronary artery disease were treated with placebo or clofibrate for 5 years and followed for an additional one year. There was a statistically significant, higher age-adjusted all-cause mortality in the clofibrate group compared with the placebo group (5.70% vs. 3.96%, p = < 0.01). Excess mortality was due to a 33% increase in non-cardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. This appeared to confirm the higher risk of gallbladder disease seen in clofibrate-treated patients studied in the Coronary Drug Project.

The Helsinki Heart Study was a large (N = 4081) study of middle-aged men without a history of coronary artery disease. Subjects received either placebo or gemfibrozil for 5 years, with a 3.5 year open extension afterward. Total mortality was numerically higher in the gemfibrozil randomization group but did not achieve statistical significance (p = 0.19, 95% confidence interval for relative risk G:P = 0.91-1.64). Although cancer deaths trended higher in the gemfibrozil group (p = 0.11), cancers (excluding basal cell carcinoma) were diagnosed with equal frequency in both study groups. Due to the limited size of the study, the relative risk of death from any cause was not shown to be different than that seen in the 9 year follow-up data from WHO study (RR = 1.29). A secondary prevention component of the Helsinki Heart Study enrolled middle-aged men excluded from the primary prevention study because of known or suspected coronary heart disease. Subjects received gemfibrozil or placebo for 5 years. Although cardiac deaths trended higher in the gemfibrozil group, this was not statistically significant (hazard ratio 2.2, 95% confidence interval: 0.94-5.05).

### 5.10 Venothromboembolic Disease

In the FIELD trial, pulmonary embolus (PE) and deep vein thrombosis (DVT) were observed at higher rates in the fenofibrate- than the placebo-treated group. Of 9,795 patients enrolled in FIELD, there were 4,900 in the placebo group and 4,895 in the fenofibrate group. For DVT, there were 48 events (1%) in the placebo group and 67 (1%) in the fenofibrate group (p = 0.074); and for PE, there were 32 (0.7%) events in the placebo group and 53 (1%) in the fenofibrate group (p = 0.022).

In the Coronary Drug Project, a higher proportion of the clofibrate group experienced definite or suspected fatal or nonfatal PE or thrombophlebitis than the placebo group (5.2% vs. 3.3% at five years; p < 0.01).

## 6 ADVERSE REACTIONS

### 6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse event rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug.

Trilipix (fenofibric acid)


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Monotherapy

Treatment-emergent adverse events reported in 3% or more of patients treated with Trilipix during the randomized controlled trials are listed in Table 1 below.

Co-Administration Therapy with Statins (Double-blind Controlled Trials)

Treatment-emergent adverse events reported in 3% or more of patients treated with Trilipix co-administered with statins during the randomized controlled trials are listed in Table 1 below.

Table 1.Treatment-Emergent Adverse Events Reported in ≥ 3% of Patients Receiving Trilipix or Trilipix Co-Administered with a Statin During Double-Blind Controlled Studies [Number (%)]

| Adverse Event | Trilipix (N = 490) | Low-Dose Statin (N = 493) | Trilipix + Low-Dose Statin (N = 490) | Moderate-Dose Statin (N = 491) | Trilipix + Moderate-Dose Statin (N = 489) | High-Dose Statin (N = 245) |
|---|---|---|---|---|---|---|
| **Gastrointestinal Disorders** | | | | | | |
| Constipation | 16 (3.3) | 11 (2.2) | 16 (3.3) | 13 (2.6) | 15 (3.1) | 6 (2.4) |
| Diarrhea | 19 (3.9) | 16 (3.2) | 15 (3.1) | 24 (4.9) | 18 (3.7) | 17 (6.9) |
| Dyspepsia | 18 (3.7) | 13 (2.6) | 13 (2.7) | 17 (3.5) | 23 (4.7) | 6 (2.4) |
| Nausea | 21 (4.3) | 18 (3.7) | 17 (3.5) | 22 (4.5) | 27 (5.5) | 10 (4.1) |
| **General Disorders and Administration Site Conditions** | | | | | | |
| Fatigue | 10 (2.0) | 13 (2.6) | 13 (2.7) | 13 (2.6) | 16 (3.3) | 5 (2.0) |
| Pain | 17 (3.5) | 9 (1.8) | 16 (3.3) | 8 (1.6) | 7 (1.4) | 8 (3.3) |
| **Infections and Infestations** | | | | | | |
| Nasopharyngitis | 17 (3.5) | 29 (5.9) | 23 (4.7) | 16 (3.3) | 21 (4.3) | 9 (3.7) |
| Sinusitis | 16 (3.3) | 4 (0.8) | 14 (2.9) | 8 (1.6) | 17 (3.5) | 4 (1.6) |
| Upper Respiratory Tract Infection | 26 (5.3) | 13 (2.6) | 18 (3.7) | 23 (4.7) | 23 (4.7) | 7 (2.9) |
| **Investigations** | | | | | | |
| ALT Increased | 6 (1.2) | 2 (0.4) | 15 (3.1) | 2 (0.4) | 12 (2.5) | 4 (1.6) |
| **Musculoskeletal and Connective Tissue Disorders** | | | | | | |
| Arthralgia | 19 (3.9) | 22 (4.5) | 21 (4.3) | 21 (4.3) | 17 (3.5) | 12 (4.9) |
| Back Pain | 31 (6.3) | 31 (6.3) | 30 (6.1) | 32 (6.5) | 20 (4.1) | 8 (3.3) |
| Muscle Spasms | 8 (1.6) | 18 (3.7) | 12 (2.4) | 24 (4.9) | 15 (3.1) | 6 (2.4) |
| Myalgia | 16 (3.3) | 24 (4.9) | 17 (3.5) | 23 (4.7) | 15 (3.1) | 15 (6.1) |
| Pain in Extremity | 22 (4.5) | 24 (4.9) | 14 (2.9) | 21 (4.3) | 13 (2.7) | 9 (3.7) |
| **Nervous System Disorders** | | | | | | |
| Dizziness | 20 (4.1) | 8 (1.6) | 19 (3.9) | 11 (2.2) | 16 (3.3) | 2 (0.8) |
| Headache | 62 (12.7) | 64 (13.0) | 64 (13.1) | 82 (16.7) | 58 (11.9) | 32 (13.1) |

Low-dose statin = rosuvastatin 10 mg, simvastatin 20 mg, or atorvastatin 20 mg
Moderate-dose statin = rosuvastatin 20 mg, simvastatin 40 mg, or atorvastatin 40 mg
High-dose statin = rosuvastatin 40 mg, simvastatin 80 mg, or atorvastatin 80 mg

Co-Administration Therapy with Statins (Long-Term Exposure for up to 64 Weeks)

Patients successfully completing any one of the three double-blind, controlled studies were eligible to participate in a 52-week long-term extension study where they received Trilipix co-administered with the moderate dose statin. A total of 2201 patients received at least one dose of Trilipix co-administered with a statin in the double-blind controlled study or the long-term extension study for up to a total of 64 weeks of


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treatment. Additional treatment-emergent adverse events (not listed in Table 1 above) reported in 3% or more of patients receiving Trilipix co-administered with a statin in either the double-blind controlled studies or the long-term extension study are provided below.

*Infections and Infestations*
Bronchitis, influenza, and urinary tract infection.

*Investigations*
AST increased, blood CPK increased, and hepatic enzyme increased.

*Musculoskeletal and Connective Tissue Disorders*
Musculoskeletal pain.

*Psychiatric Disorders*
Insomnia.

*Respiratory, Thoracic, and Mediastinal Disorders*
Cough and pharyngolaryngeal pain.

*Vascular Disorders*
Hypertension.

Fenofibrate

Fenofibric acid is the active metabolite of fenofibrate. Adverse events reported by 2% or more of patients treated with fenofibrate and greater than placebo during double-blind, placebo-controlled trials are listed in Table 2. Adverse events led to discontinuation of treatment in 5.0% of patients treated with fenofibrate and in 3.0% treated with placebo. Increases in liver tests were the most frequent events, causing discontinuation of fenofibrate treatment in 1.6% of patients in double-blind trials.

Table 2. Adverse Events Reported by 2% or More of Patients Treated with Fenofibrate and Greater than Placebo During the Double-Blind, Placebo-Controlled Trials

| **BODY SYSTEM**<br>**Adverse Event** | **Fenofibrate***<br>**(N = 439)** | **Placebo**<br>**(N = 365)** |
|---|---|---|
| BODY AS A WHOLE | | |
| Abdominal Pain | 4.6% | 4.4% |
| Back Pain | 3.4% | 2.5% |
| Headache | 3.2% | 2.7% |
| DIGESTIVE | | |
| Nausea | 2.3% | 1.9% |
| Constipation | 2.1% | 1.4% |
| INVESTIGATIONS | | |
| Abnormal Liver Tests | 7.5% | 1.4% |
| Increased AST | 3.4% | 0.5% |
| Increased ALT | 3.0% | 1.6% |
| Increased Creatine Phosphokinase | 3.0% | 1.4% |


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| | | |
|---|---|---|
| RESPIRATORY | | |
| Respiratory Disorder | 6.2% | 5.5% |
| Rhinitis | 2.3% | 1.1% |

* Dosage equivalent to 135 mg Trilipix

The following adverse events have been identified during postapproval use of fenofibrate: myalgia, rhabdomyolysis, increased creatine phosphokinase, pancreatitis, increased alanine aminotransaminase, increased aspartate aminotransaminase, renal failure, muscle spasms, acute renal failure, hepatitis, cirrhosis, nausea, abdominal pain, anemia, headache, arthralgia, and asthenia. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a casual relationship to drug exposure.

## 7 DRUG INTERACTIONS

### 7.1 Oral Anticoagulants

Caution should be exercised when oral coumarin anticoagulants are given in conjunction with Trilipix *[see WARNINGS AND PRECAUTIONS (5.5)]*.

### 7.2 Bile Acid Resins

Since bile acid resins may bind other drugs given concurrently, patients should take Trilipix at least 1 hour before or 4-6 hours after a bile acid resin to avoid impeding its absorption.

### 7.3 Cyclosporine

Because cyclosporine can produce nephrotoxicity with decreases in creatinine clearance and rises in serum creatinine, and because renal excretion is the primary elimination route of drugs of the fibrate class including Trilipix, there is a risk that an interaction will lead to decline of renal function. The benefits and risks of using Trilipix with immunosuppressants and other potentially nephrotoxic agents should be carefully considered, and the lowest effective dose employed.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category: C

The safety of Trilipix in pregnant women has not been established. There are no adequate and well controlled studies of Trilipix in pregnant women. Trilipix should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

When Trilipix is administered with a statin in a woman of childbearing potential, refer to pregnancy category and product labeling for the statin *[see Precautions, Pregnancy]*. All statins are contraindicated in pregnant women.

In pregnant rats given oral dietary doses of 14, 127, and 361 mg/kg/day from gestation day 6-15 during the period of organogenesis, adverse developmental findings were not observed at 14 mg/kg/day (less than 1


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times the maximum recommended human dose [MRHD], based on body surface area comparisons; $mg/m^2$). At higher multiples of human doses evidence of maternal toxicity was observed.

In pregnant rabbits given oral gavage doses of 15, 150, and 300 mg/kg/day from gestation day 6-18 during the period of organogenesis and allowed to deliver, aborted litters were observed at 150 mg/kg/day (10 times the MRHD, based on body surface area comparisons; $mg/m^2$). No developmental findings were observed at 15 mg/kg/day (at less than 1 times the MRHD, based on body surface area comparisons; $mg/m^2$).

In pregnant rats given oral dietary doses of 15, 75, and 300 mg/kg/day from gestation day 15 through lactation day 21 (weaning), maternal toxicity was observed at less than 1 times the MRHD, based on body surface area comparisons; $mg/m^2$.

### 8.3 Nursing Mothers

Trilipix should not be used in nursing mothers. A decision should be made whether to discontinue nursing or to discontinue the drug.

### 8.4 Pediatric Use

The safety and effectiveness of Trilipix monotherapy or co-administration with a statin in pediatric patients have not been established.

### 8.5 Geriatric Use

Trilipix is substantially excreted by the kidney as fenofibric acid and fenofibric acid glucuronide, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Since elderly patients have a higher incidence of renal impairment, the dose selection for the elderly should be made on the basis of renal function *[see CLINICAL PHARMACOLOGY (12.3)]*. Consider monitoring renal function in elderly patients taking Trilipix.

### 8.6 Renal Impairment

The use of Trilipix should be avoided in patients who have severe renal impairment. Dose reduction is required in patients with mild to moderate renal impairment *[see CLINICAL PHARMACOLOGY (12.3) and DOSAGE AND ADMINISTRATION (2.5)]*. Monitoring renal function in patients with renal impairment is recommended.

### 8.7 Hepatic Impairment

The use of Trilipix has not been evaluated in subjects with hepatic impairment *[see CONTRAINDICATIONS (4) and CLINICAL PHARMACOLOGY (12.3)]*.

## 10 OVERDOSAGE

There is no specific treatment for overdose with Trilipix. General supportive care of the patient is indicated, including monitoring of vital signs and observation of clinical status, should an overdose occur. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage; usual precautions should be


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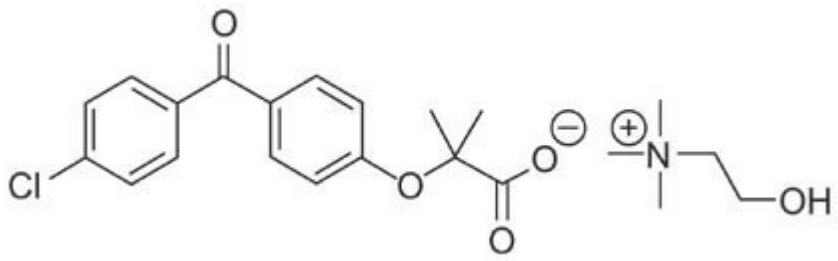
observed to maintain the airway. Because Trilipix is highly bound to plasma proteins, hemodialysis should not be considered.

## 11 DESCRIPTION

Trilipix (fenofibric acid) is a lipid regulating agent available as delayed release capsules for oral administration. Each delayed release capsule contains choline fenofibrate, equivalent to 45 mg or 135 mg of fenofibric acid. The chemical name for choline fenofibrate is ethanaminium, 2-hydroxy-N,N,N-trimethyl, 2-{4-(4-chlorobenzoyl)phenoxy] -2-methylpropanoate (1:1) with the following structural formula:




The empirical formula is $C_{22}H_{28}ClNO_5$ and the molecular weight is 421.91. Choline fenofibrate is freely soluble in water. The melting point is approximately 210°C. Choline fenofibrate is a white to yellow powder, which is stable under ordinary conditions.

Each delayed release capsule contains enteric coated mini-tablets comprised of choline fenofibrate and the following inactive ingredients: hypromellose, povidone, water, hydroxylpropyl cellulose, colloidal silicon dioxide, sodium stearyl fumarate, methacrylic acid copolymer, talc, triethyl citrate. The capsule shell of the 45 mg capsule contains the following inactive ingredients: gelatin, titanium dioxide, yellow iron oxide, black iron oxide, and red iron oxide. The capsule shell of the 135 mg capsule contains the following inactive ingredients: gelatin, titanium dioxide, yellow iron oxide, and FD&C Blue #2.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The active moiety of Trilipix is fenofibric acid. The pharmacological effects of fenofibric acid in both animals and humans have been extensively studied through oral administration of fenofibrate.

The lipid-modifying effects of fenofibric acid seen in clinical practice have been explained *in vivo* in transgenic mice and *in vitro* in human hepatocyte cultures by the activation of peroxisome proliferator activated receptor α (PPARα). Through this mechanism, fenofibric acid increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of Apo CIII (an inhibitor of lipoprotein lipase activity).

The resulting decrease in TG produces an alteration in the size and composition of LDL from small, dense particles (which are thought to be atherogenic due to their susceptibility to oxidation), to large buoyant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particles. These larger particles have a greater affinity for cholesterol receptors and are catabolized rapidly. Activation of PPARα also induces an increase in the synthesis of HDL-C and Apo AI and AII.

**12.2 Pharmacodynamics**

Elevated levels of Total-C, LDL-C, and Apo B, and decreased levels of HDL-C and its transport complex, Apo AI and Apo AII, are risk factors for human atherosclerosis. Epidemiologic studies have established that cardiovascular morbidity and mortality vary directly with the levels of Total-C, 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.

**12.3 Pharmacokinetics**

Trilipix contains fenofibric acid, which is the only circulating pharmacologically active moiety in plasma after oral administration of Trilipix. Fenofibric acid is also the circulating pharmacologically active moiety in plasma after oral administration of fenofibrate, the ester of fenofibric acid.

Plasma concentrations of fenofibric acid after administration of one 135 mg Trilipix delayed release capsule are equivalent to those after one 200 mg capsule of micronized fenofibrate administered under fed conditions.

*Absorption*
Fenofibric acid is well absorbed throughout the gastrointestinal tract. The absolute bioavailability of fenofibric acid is approximately 81%.

Peak plasma levels of fenofibric acid occur within 4 to 5 hours after a single dose administration of Trilipix capsule under fasting conditions.

Fenofibric acid exposure in plasma, as measured by $C_{max}$ and AUC, is not significantly different when a single 135 mg dose of Trilipix is administered under fasting or nonfasting conditions.

*Distribution*
Upon multiple dosing of Trilipix, fenofibric acid levels reach steady state within 8 days. Plasma concentrations of fenofibric acid at steady state are approximately slightly more than double those following a single dose. Serum protein binding is approximately 99% in normal and dyslipidemic subjects.

*Metabolism*
Fenofibric acid is primarily conjugated with glucuronic acid and then excreted in urine. A small amount of fenofibric acid is reduced at the carbonyl moiety to a benzhydrol metabolite which is, in turn, conjugated with glucuronic acid and excreted in urine.

*In vivo* metabolism data after fenofibrate administration indicate that fenofibric acid does not undergo oxidative metabolism (e.g., cytochrome P450) to a significant extent.


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*Excretion*

After absorption, Trilipix is primarily excreted in the urine in the form of fenofibric acid and fenofibric acid glucuronide.

Fenofibric acid is eliminated with a half-life of approximately 20 hours, allowing once daily administration of Trilipix.

*Specific Populations*

Geriatrics

In five elderly volunteers 77 to 87 years of age, the oral clearance of fenofibric acid following a single oral dose of fenofibrate was 1.2 L/h, which compares to 1.1 L/h in young adults. This indicates that an equivalent dose of Trilipix can be used in elderly subjects with normal renal function, without increasing accumulation of the drug or metabolites *[see USE IN SPECIFIC POPULATIONS (8.5)]*.

Pediatrics

Trilipix has not been investigated in adequate and well-controlled trials in pediatric patients.

Gender

No pharmacokinetic difference between males and females has been observed for Trilipix.

Race

The influence of race on the pharmacokinetics of Trilipix has not been studied.

Renal Impairment

The pharmacokinetics of fenofibric acid was examined in patients with mild, moderate, and severe renal impairment. Patients with severe renal impairment (creatinine clearance [CrCl] < 30 mL/min showed a 2.7-fold increase in exposure for fenofibric acid and increased accumulation of fenofibric acid during chronic dosing compared to that of healthy subjects. Patients with mild to moderate renal impairment (CrCl 30-80 mL/min) had similar exposure but an increase in the half-life for fenofibric acid compared to that of healthy subjects. Based on these findings, the use of Trilipix should be avoided in patients who have severe renal impairment and dose reduction is required in patients having mild to moderate renal impairment.

Hepatic Impairment

No pharmacokinetic studies have been conducted in patients with hepatic impairment.

*Drug-drug Interactions*

*In vitro* studies using human liver microsomes indicate that fenofibric acid is not an inhibitor of cytochrome (CYP) P450 isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2. It is a weak inhibitor of CYP2C8, CYP2C19, and CYP2A6, and mild-to-moderate inhibitor of CYP2C9 at therapeutic concentrations.

Comparison of atorvastatin exposures when atorvastatin (80 mg QD for 10 days) is given in combination with fenofibric acid (Trilipix 135 mg QD for 10 days) and ezetimibe (10 mg QD for 10 days) versus when atorvastatin is given in combination with ezetimibe only (ezetimibe 10 mg QD and atorvastatin, 80 mg QD for 10 days): The $C_{max}$ decreased by 1% for atorvastatin and ortho-hydroxy-atorvastatin and increased by 2% for



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parahydroxy-atorvastatin. The AUC decreased 6% and 9% for atorvastatin and orthohydroxy-atorvastatin, respectively, and did not change for para-hydroxy-atorvastatin.

Comparison of ezetimibe exposures when ezetimibe (10 mg QD for 10 days) is given in combination with fenofibric acid (Trilipix 135 mg QD for 10 days) and atorvastatin (80 mg QD for 10 days) versus when ezetimibe is given in combination with atorvastatin only (ezetimibe 10 mg QD and atorvastatin, 80 mg QD for 10 days): The $C_{max}$ increased by 26% and 7% for total and free ezetimibe, respectively. The AUC increased by 27% and 12% for total and free ezetimibe, respectively.

Table 3 describes the effects of co-administered drugs on fenofibric acid systemic exposure. Table 4 describes the effects of co-administered fenofibric acid on other drugs.

Table 3. Effects of Co-Administered Drugs on Fenofibric Acid Systemic Exposure from Trilipix or Fenofibrate Administration

| Co-Administered Drug | Dosage Regimen of Co-Administered Drug | Dosage Regimen of Trilipix or Fenofibrate | Changes in Fenofibric Acid Exposure | |
|---|---|---|---|---|
| | | | AUC | $C_{max}$ |
| *Lipid-lowering agents* | | | | |
| Rosuvastatin | 40 mg QD for 10 days | Trilipix 135 mg QD for 10 days | ↓2% | ↓2% |
| Atorvastatin | 20 mg QD for 10 days | Fenofibrate 160 mg[1] QD for 10 days | ↓2% | ↓4% |
| Atorvastatin + ezetimibe | Atorvastatin, 80 mg QD and ezetimibe, 10 mg QD for 10 days | Trilipix 135 mg QD for 10 days | ↑5% | ↑5% |
| Pravastatin | 40 mg as a single dose | Fenofibrate 3 x 67 mg[2] as a single dose | ↓1% | ↓2% |
| Fluvastatin | 40 mg as a single dose | Fenofibrate 160 mg[1] as a single dose | ↓2% | ↓10% |
| Simvastatin | 80 mg QD for 7 days | Fenofibrate 160 mg[1] QD for 7 days | ↓5% | ↓11% |
| *Anti-diabetic agents* | | | | |
| Glimepiride | 1 mg as a single dose | Fenofibrate 145 mg[1] QD for 10 days | ↑1% | ↓1% |
| Metformin | 850 mg TID for 10 days | Fenofibrate 54 mg[1] TID for 10 days | ↓9% | ↓6% |
| Rosiglitazone | 8 mg QD for 5 days | Fenofibrate 145 mg[1] QD for 14 days | ↑10% | ↑3% |
| *Gastrointestinal agents* | | | | |
| Omeprazole | 40 mg QD for 5 days | Trilipix 135 mg as a single dose fasting | ↑6% | ↑17% |
| Omeprazole | 40 mg QD for 5 days | Trilipix 135 mg as a single dose with food | ↑4% | ↓2% |

[1] TriCor (fenofibrate) oral tablet
[2] TriCor (fenofibrate) oral micronized capsule

Table 4. Effects of Trilipix or Fenofibrate Co-Administration on Systemic Exposure of Other Drugs

| Dosage Regimen of Trilipix or Fenofibrate | Dosage Regimen of Co-Administered Drug | Change in Co-Administered Drug Exposure | | |
|---|---|---|---|---|
| | | Analyte | AUC | $C_{max}$ |


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| | | | | |
|---|---|---|---|---|
| *Lipid-lowering agents* | | | | |
| Trilipix 135 mg QD for 10 days | Rosuvastatin, 40 mg QD for 10 days | Rosuvastatin | ↑6% | ↑20% |
| Fenofibrate 160 mg[1] QD for 10 days | Atorvastatin, 20 mg QD for 10 days | Atorvastatin | ↓17% | 0% |
| Fenofibrate 3 x 67 mg[2] as a single dose | Pravastatin, 40 mg as a single dose | Pravastatin | ↑13% | ↑13% |
| | | 3α-Hydroxyl-iso-pravastatin | ↑26% | ↑29% |
| Fenofibrate 160 mg[1] as a single dose | Fluvastatin, 40 mg as a single dose | (+)-3R, 5S-Fluvastatin | ↑15% | ↑16% |
| Fenofibrate 160 mg[1] QD for 7 days | Simvastatin, 80 mg QD for 7 days | Simvastatin acid | ↓36% | ↓11% |
| | | Simvastatin | ↓11% | ↓17% |
| | | Active HMG-CoA Inhibitors | ↓12% | ↓1% |
| | | Total HMG-CoA Inhibitors | ↓8% | ↓10% |
| *Anti-diabetic agents* | | | | |
| Fenofibrate 145 mg[1] QD for 10 days | Glimepiride, 1 mg as a single dose | Glimepiride | ↑35% | ↑18% |
| Fenofibrate 54 mg[1] TID for 10 days | Metformin, 850 mg TID for 10 days | Metformin | ↑3% | ↑6% |
| Fenofibrate 145 mg[1] QD for 14 days | Rosiglitazone, 8 mg QD for 5 days | Rosiglitazone | ↑6% | ↓1% |

[1] TriCor (fenofibrate) oral tablet
[2] TriCor (fenofibrate) oral micronized capsule

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Trilipix (fenofibric acid)

No carcinogenicity and fertility studies have been conducted with choline fenofibrate or fenofibric acid. However, because fenofibrate is rapidly converted to its active metabolite, fenofibric acid, either during or immediately following absorption both in animals and humans, studies conducted with fenofibrate are relevant for the assessment of the toxicity profile of fenofibric acid. A similar toxicity spectrum is expected after treatment with either Trilipix or fenofibrate.

Fenofibrate

Two dietary carcinogenicity studies have been conducted in rats with fenofibrate. In the first 24-month study, rats were dosed with fenofibrate at 10, 45, and 200 mg/kg/day, approximately 0.3, 1, and 6 times the maximum recommended human dose (MRHD), based on body surface area comparisons (mg/m$^2$). At a dose of 200 mg/kg/day (6 times the MRHD), the incidence of liver carcinomas was significantly increased in both sexes. A statistically significant increase in pancreatic carcinomas was observed in males at 1 and 6 times the MRHD; an increase in pancreatic adenomas and benign testicular interstitial cell tumors was observed at 6 times the MRHD in males.

A 117-week carcinogenicity study was conducted in rats comparing three drugs: fenofibrate 10 and 60 mg/kg/day (0.3 and 2 times the MRHD), clofibrate (400 mg/kg/day; 2 times the human dose), and gemfibrozil (250 mg/kg/day; 2 times the human dose, based on mg/m$^2$ surface area). Fenofibrate increased pancreatic acinar adenomas in both sexes and testicular interstitial cell tumors in males at 2 times the MRHD. Clofibrate increased hepatocellular carcinoma and pancreatic acinar adenomas in males and hepatic neoplastic nodules in


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females. Gemfibrozil increased hepatic neoplastic nodules in males and females, while all three drugs increased testicular interstitial cell tumors in males.

In an 80-week study in mice, fenofibrate 10, 45, and 200 mg/kg/day (approximately 0.2, 1, and 3 times the MRHD on the basis of mg/m$^2$ surface area) significantly increased the liver carcinomas in both sexes at 3 times the MRHD. In a second 93-week study at 10, 60, and 200 mg/kg/day, fenofibrate significantly increased the liver carcinomas in male and female mice at 3 times the MRHD.

Electron microscopy studies have demonstrated peroxisomal proliferation following fenofibrate administration to the rat. An adequate study to test for peroxisome proliferation in humans has not been done, but changes in peroxisome morphology and numbers have been observed in humans after treatment with other members of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Fenofibrate has been demonstrated to be devoid of mutagenic potential in the following tests: Ames, and micronucleus *in vivo*/rat. In addition, fenofibric acid, has been demonstrated to be devoid of mutagenic potential in the following tests: Ames, mouse lymphoma, chromosomal aberration and sister chromatid exchange in human lymphocytes, and unscheduled DNA synthesis in primary rat hepatocytes.

In a fertility study, rats were given oral dietary doses of fenofibrate. Males received doses for 61 days prior to mating and females for 15 days prior to mating through weaning, which resulted in no adverse effect on fertility at doses up to 300 mg/kg/day (~10 times the MRHD, based on mg/m$^2$ surface area comparisons).

## 14 CLINICAL STUDIES

### 14.1 Co-Administration Therapy with Statins

Efficacy and safety of Trilipix co-administered with statins were assessed in three 12-week, double-blind, controlled Phase 3 studies and one 52-week, long-term, open-label extension study in 2698 patients with mixed dyslipidemia. Patients were required to meet the following fasting lipid entry criteria: TG ≥ 150 mg/dL, and HDL-C < 40 mg/dL (males) and < 50 mg/dL (females), and LDL-C ≥ 130 mg/dL. The three multicenter, randomized, double-blind, controlled studies had similar designs, differing primarily in the statin used for combination therapy/monotherapy. Each study compared the effects of 135 mg Trilipix co-administered with either a low dose or a moderate dose of statin with Trilipix monotherapy and statin monotherapy at the corresponding dose on CHD lipid risk factors. A smaller group of patients received a high dose of statin monotherapy. In study 1, patients received Trilipix co-administered with 10 mg or 20 mg rosuvastatin. In study 2, patients received Trilipix co-administered with 20 mg or 40 mg simvastatin. In study 3, patients received Trilipix co-administered with 20 mg or 40 mg atorvastatin.

Patients were enrolled for a total of approximately 22 weeks, consisting of a 6-week diet run-in/washout period, a 12-week treatment period, and a 30-day safety follow up period. Patients who completed the 12-week treatment period were eligible to participate in the 52-week long-term extension study. Of the 2698 randomized and treated subjects in the controlled studies, 51.6% were female and 48.4% were male; 92.6% of all subjects were White, 4.7% were Black, and 2.8% were of other races. Hispanics comprised 9.9% of the study population. Mean age was 54.9 years.


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The primary efficacy endpoints for all three studies were mean percent changes from baseline to final value in HDL-C, TG, and LDL-C. For each statin dose co-administered with Trilipix, there were three primary comparisons. For HDL-C and TG, Trilipix co-administered with each statin dose was compared with statin monotherapy at the corresponding dose. For LDL-C, Trilipix co-administered with each statin dose was compared with Trilipix monotherapy. In order to declare combination therapy successful for a particular statin dose, all three primary comparisons were required to demonstrate superiority of the combination therapy over the corresponding monotherapy. The primary efficacy results were consistent in the three studies and were confirmed by the pooled analysis of the three studies. The results from the individual studies and the pooled analysis demonstrated that Trilipix co-administered with low-dose statins and moderate-dose statins was superior to the corresponding monotherapy. Statistically significant differences were observed for all three primary efficacy comparisons for both doses of combination therapy in all three double-blind, controlled studies as well as the pooled analysis.

In the pooled analysis, Trilipix co-administered with both low-dose statins and moderate-dose statins resulted in mean percent increases (18.1% and 17.5%) in HDL-C and mean percent decreases (-43.9% and -42.0%) in TG that were significantly greater than the corresponding dose of statin monotherapy (7.4% and 8.7% for HDL-C; -16.8% and -23.7% for TG). In addition, both doses of combination therapy resulted in mean percent decreases (-33.1% and -34.6%) in LDL-C that were significantly greater than Trilipix monotherapy (-5.1%). The results of the pooled analysis are described in Table 5.

Table 5.Mean Percent Change from Baseline to the Final Value in HDL-C, TG, and LDL-C (Pooled Double-Blind, Controlled Studies)

| | **Trilipix** | **Low-Dose Statin** | **Trilipix + Low-Dose Statin** | **Between-group Δ (p-value)** | **Moderate-Dose Statin** | **Trilipix + Moderate-Dose Statin** | **Between-group Δ (p-value)** | **High-Dose Statin** |
|---|---|---|---|---|---|---|---|---|
| **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 |
| Mean % Δ | 16.3% | 7.4% | 18.1% | 10.7%[a] (< 0.001) | 8.7% | 17.5% | 8.8%[a] (< 0.001) | 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 |
| Mean % Δ | -31.0% | -16.8% | -43.9% | -27.2%[a] (< 0.001) | -23.7% | -42.0% | -18.3%[a] (< 0.001) | -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 |
| Mean % Δ | -5.1% | -33.9% | -33.1% | -28.0%[b] (< 0.001) | -40.6% | -34.6% | -29.5%[b] (< 0.001) | -47.1% |

[a] Combination therapy vs. corresponding statin monotherapy
[b] Combination therapy vs. Trilipix monotherapy
Low-dose statin = rosuvastatin 10 mg, simvastatin 20 mg, or atorvastatin 20 mg
Moderate-dose statin = rosuvastatin 20 mg, simvastatin 40 mg, or atorvastatin 40 mg
High-dose statin = rosuvastatin 40 mg, simvastatin 80 mg, or atorvastatin 80 mg
BL = Baseline
% Δ = Percent change from baseline to final value


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Secondary efficacy endpoints in all three double-blind, controlled studies were percent changes in non-HDL-C (Trilipix co-administered with statin compared to Trilipix monotherapy and corresponding statin monotherapy), and percent changes in VLDL-C, Total-C, and Apo B (Trilipix co-administered with statin compared to corresponding statin monotherapy). Co-administration of Trilipix with statins resulted in the following changes in secondary parameters (Table 6).

Table 6. Percent Change from Baseline to the Final Value in Non-HDL-C, VLDL-C, Total-C, and Apo B (Pooled Double-Blind, Controlled Studies)

| Secondary Endpoints | Trilipix | Low-Dose Statin | Trilipix + Low-Dose Statin | Between-group Δ | Moderate-Dose Statin | Trilipix + Moderate-Dose Statin | Between-group Δ | High-Dose Statin |
|---|---|---|---|---|---|---|---|---|
| **Non HDL-C (mg/dL)** | (N = 420) | (N = 454) | (N = 422) | | (N = 431) | (N = 420) | | (N = 217) |
| BL mean | 222.5 | 217.6 | 219.9 | | 222.4 | 218.9 | | 220.2 |
| Mean % Δ | -17.3% | -34.9% | -40.4% | -23.1%[a]<br>-5.5%[b] | -42.4% | -42.0% | -24.8%[a]<br>0.4%[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 |
| Mean % Δ | -34.2% | -32.1% | -50.0% | -18.0%[b] | -38.9% | -51.2% | -12.3%[b] | -42.1% |
| **Total-C (mg/dL)** | (N = 459) | (N = 477) | (N = 469) | | (N = 472) | (N = 462) | | (N = 235) |
| BL mean | 260.9 | 257.0 | 258.6 | | 261.3 | 257.3 | | 258.8 |
| Mean % Δ | -12.4% | -28.7% | -31.5% | -2.8%[b] | -34.7% | -33.3% | 1.4%[b] | -39.5% |
| **Apo B (mg/dL)** | (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 |
| Mean % Δ | -15.6% | -31.1% | -36.3% | -5.2%[b] | -36.9% | -36.7% | 0.2%[b] | -42.4% |

[a] Trilipix + statin vs. Trilipix monotherapy
[b] Trilipix + statin vs. corresponding statin monotherapy
Low-dose statin = rosuvastatin 10 mg, simvastatin 20 mg, or atorvastatin 20 mg
Moderate-dose statin = rosuvastatin 20 mg, simvastatin 40 mg, or atorvastatin 40 mg
High-dose statin = rosuvastatin 40 mg, simvastatin 80 mg, or atorvastatin 80 mg
BL = Baseline
% Δ = Percent change from baseline to final value

A total of 1895 patients who completed 12 weeks of treatment in the double-blind, controlled studies were treated in the 52-week, long-term extension study. Patients received Trilipix co-administered with the moderate-dose of the statin that had been used in the double-blind, controlled study in which they were enrolled. Whether combination therapy was initiated during the double-blind, controlled studies or introduced during the long-term extension study, the treatment effect of combination therapy was observed within four weeks, and was sustained over the duration of treatment in the long-term study. A total of 568 patients completed 52 weeks of treatment with Trilipix co-administered with statins. Mean 52-week values and mean percent change from baseline (at time of enrollment in randomized controlled trials) were 91.7 mg/dL (-38.2%) for LDL-C, 47.3 mg/dL (+24.0%) for HDL-C, 135.5 mg/dL (-47.6%) for TG, 117.9 mg/dL (-45.7%)


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for non-HDL-C, 26.2 mg/dL (-53.1%) for VLDL-C, 165.2 mg/dL (-35.4%) for Total-C, and 81.4 mg/dL (-43.6%) for Apo B.

### 14.2 Hypertriglyceridemia

The effects of fenofibrate on serum triglycerides were studied in two randomized, double-blind, placebo-controlled clinical trials of 147 hypertriglyceridemic patients. Patients were treated for eight weeks under protocols that differed only in that one entered patients with baseline TG levels of 500 to 1500 mg/dL, and the other TG levels of 350 to 500 mg/dL. In patients with hypertriglyceridemia and normal cholesterolemia with or without hyperchylomicronemia, treatment with fenofibrate at dosages equivalent to 135 mg once daily of Trilipix decreased primarily VLDL-TG and VLDL-C. Treatment of patients with elevated TG often results in an increase of LDL-C (Table 7).

Table 7. Effects of Fenofibrate in Patients With Hypertriglyceridemia

| **Study 1** | **Placebo** | | | | **Fenofibrate** | | | |
|---|---|---|---|---|---|---|---|---|
| **Baseline TG levels 350 to 499 mg/dL** | **N** | **Baseline Mean (mg/dL)** | **Endpoint Mean (mg/dL)** | **Mean % Change** | **N** | **Baseline Mean (mg/dL)** | **Endpoint Mean (mg/dL)** | **Mean % Change** |
| Triglycerides | 28 | 449 | 450 | -0.5 | 27 | 432 | 223 | -46.2* |
| VLDL Triglycerides | 19 | 367 | 350 | 2.7 | 19 | 350 | 178 | -44.1* |
| Total Cholesterol | 28 | 255 | 261 | 2.8 | 27 | 252 | 227 | -9.1* |
| HDL Cholesterol | 28 | 35 | 36 | 4 | 27 | 34 | 40 | 19.6* |
| LDL Cholesterol | 28 | 120 | 129 | 12 | 27 | 128 | 137 | 14.5 |
| VLDL Cholesterol | 27 | 99 | 99 | 5.8 | 27 | 92 | 46 | -44.7* |
| **Study 2** | **Placebo** | | | | **Fenofibrate** | | | |
| **Baseline TG levels 500 to 1500 mg/dL** | **N** | **Baseline Mean (mg/dL)** | **Endpoint Mean (mg/dL)** | **Mean % Change** | **N** | **Baseline Mean (mg/dL)** | **Endpoint Mean (mg/dL)** | **Mean % Change** |
| Triglycerides | 44 | 710 | 750 | 7.2 | 48 | 726 | 308 | -54.5* |
| VLDL Triglycerides | 29 | 537 | 571 | 18.7 | 33 | 543 | 205 | -50.6* |
| Total Cholesterol | 44 | 272 | 271 | 0.4 | 48 | 261 | 223 | -13.8* |
| HDL Cholesterol | 44 | 27 | 28 | 5.0 | 48 | 30 | 36 | 22.9* |
| LDL Cholesterol | 42 | 100 | 90 | -4.2 | 45 | 103 | 131 | 45.0* |
| VLDL Cholesterol | 42 | 137 | 142 | 11.0 | 45 | 126 | 54 | -49.4* |

* = $p < 0.05$ vs. Placebo

### 14.3 Primary Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia

The effects of fenofibrate at a dose equivalent to Trilipix 135 mg once daily were assessed from four randomized, placebo-controlled, double-blind, parallel-group studies including patients with the following mean baseline lipid values: Total-C 306.9 mg/dL; LDL-C 213.8 mg/dL; HDL-C 52.3 mg/dL; and triglycerides 191.0 mg/dL. Fenofibrate therapy lowered LDL-C, Total-C, and the LDL-C/HDL-C ratio. Fenofibrate therapy also lowered triglycerides and raised HDL-C (Table 8).

Table 8. Mean Percent Change in Lipid Parameters at End of Treatment†

| **Treatment Group** | **Total-C (mg/dL)** | **LDL-C (mg/dL)** | **HDL-C (mg/dL)** | **TG (mg/dL)** |
|---|---|---|---|---|
| **Pooled Cohort** | | | | |
| Mean baseline lipid values (n = 646) | 306.9 | 213.8 | 52.3 | 191.0 |


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| | | | | |
|---|---|---|---|---|
| All Fenofibrate (n = 361) | -18.7%* | -20.6%* | +11.0%* | -28.9%* |
| Placebo (n = 285) | -0.4% | -2.2% | +0.7% | +7.7% |
| **Baseline LDL-C > 160 mg/dL and TG < 150 mg/dL** | | | | |
| Mean baseline lipid values (n = 334) | 307.7 | 227.7 | 58.1 | 101.7 |
| All Fenofibrate (n = 193) | -22.4%* | -31.4%* | +9.8%* | -23.5%* |
| Placebo (n = 141) | +0.2% | -2.2% | +2.6% | +11.7% |
| **Baseline LDL-C > 160 mg/dL and TG ≥ 150 mg/dL** | | | | |
| Mean baseline lipid values (n = 242) | 312.8 | 219.8 | 46.7 | 231.9 |
| All Fenofibrate (n = 126) | -16.8%* | -20.1%* | +14.6%* | -35.9%* |
| Placebo (n = 116) | -3.0% | -6.6% | +2.3% | +0.9% |

† Duration of study treatment was 3 to 6 months
* p = < 0.05 vs. Placebo

In a subset of the subjects, measurements of Apo B were conducted. Fenofibrate treatment significantly reduced Apo B from baseline to endpoint as compared with placebo (-25.1% vs. 2.4%, $p < 0.0001$, n = 213 and 143, respectively).

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Trilipix (fenofibric acid) delayed release capsules are supplied in two dose strengths as follows:

- Trilipix 45 mg fenofibric acid delayed release capsules have a reddish-brown cap imprinted in white ink the Abbott “A” logo and a yellow body imprinted in black ink the number “45”. Each hard gelatin capsule contains enteric coated white to off white bi-convex round mini-tablets. The delayed release capsules are available in bottles of 90 (NDC 0074-9642-90).
- Trilipix 135 mg fenofibric acid delayed release capsules have a blue cap imprinted in white ink the Abbott “A” logo and a yellow body imprinted in black ink the number “135”. Each hard gelatin capsule contains enteric coated white to off white bi-convex round mini-tablets. The delayed release capsules are available in bottles of 90 (NDC 0074-9189-90).

Storage and Handling

Store Trilipix 45 and 135 mg delayed release capsules at 25°C (77°F); excursions permitted to 15°-30°C (59° to 86°F) [See USP controlled room temperature]. Keep out of the reach of children. Protect from moisture.

## 17 PATIENT COUNSELING INFORMATION

See Medication Guide

### 17.1 Patient Counseling

Patients should be advised:

- of the potential benefits and risks of Trilipix.
- to read the Medication Guide before starting Trilipix therapy and to reread it each time the prescription is renewed.


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- of medications that should not be taken in combination with Trilipix.
- to continue to follow an appropriate lipid-modifying diet while taking Trilipix.
- to take Trilipix once daily, without regard to food, at the prescribed dose, swallowing each capsule whole. If Trilipix is co-administered with a statin, they may be taken together.
- to return for routine monitoring.
- to inform their physician of all medications, supplements, and herbal preparations they are taking and any change to their medical condition. Patients should also be advised to inform their physicians prescribing a new medication that they are taking Trilipix.
- to inform their physician of any muscle pain, tenderness, or weakness; onset of abdominal pain; or any other new symptoms.

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**MEDICATION GUIDE**

**MEDICATION GUIDE**

**Trilipix**

(try-lip-iks)

(fenofibric acid, delayed release capsules)

Read this Medication Guide before you start taking Trilipix and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

**What is the most important information I should know about Trilipix?**

Trilipix can be used with other cholesterol-lowering medicines called statins. Statins include:

- atorvastatin (Lipitor, Caduet)
- fluvastatin (Lescol, Lescol XL)
- lovastatin (Altoprev, Mevacor, Advicor)
- pitavastatin (Livalo)
- pravastatin (Pravachol)
- rosuvastatin (Crestor)
- simvastatin (Zocor, Simcor, Vytorin)



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Statins can cause muscle pain, tenderness or weakness, which may be symptoms of a rare but serious muscle condition called rhabdomyolysis. In some cases rhabdomyolysis can cause kidney damage and death. The risk of rhabdomyolysis may be higher when Trilipix is given with statins. If you take a statin, tell your healthcare provider.

Other medicines or large amounts of grapefruit juice (more than a quart) may raise the levels of statins in your body, and could then raise the risk of muscle problems. Tell your healthcare provider if you are taking any medicines listed below.

- Heart medicine
- Stomach medicine
- Antibiotic
- Anti-fungal
- Cholesterol-lowering medicine
- Hormones
- HIV/AIDS medicine
- Antidepressant
- Immunosuppressant
- Anti-seizure medicine

Ask your healthcare provider or pharmacist for a list of these medicines, if you are not sure.

Tell your healthcare provider if you drink grapefruit juice.

**What is Trilipix?**

Trilipix is a prescription medicine used to treat cholesterol in the blood by lowering the total amount of triglycerides and LDL (bad) cholesterol, and increasing the HDL (good) cholesterol. You should be on a low fat and low cholesterol diet while you take Trilipix.

The safety and effectiveness of Trilipix in children is not known.

**Who should not take Trilipix?**

**Do not take Trilipix if you:**

- are allergic to fenofibric acid, or any of the ingredients in Trilipix. See the end of this Medication Guide for a list of all the ingredients in Trilipix.
- have severe kidney disease.
- have liver disease.


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- have gallbladder disease.
- are a nursing mother.

**Talk to your healthcare provider before you take Trilipix if you have any of these conditions.**

**What should I tell my healthcare provider before taking Trilipix?**

**Before taking Trilipix, tell your healthcare provider about all your medical conditions, including if you:**

- are allergic to any medicines.
- have ever had kidney problems.
- have ever had liver problems.
- have ever had gallbladder problems.
- are pregnant or if you plan to become pregnant. It is not known if Trilipix will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if Trilipix passes into your breast milk. You and your healthcare provider should decide if you will take Trilipix or breastfeed. You should not do both.

**Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements.**

Using Trilipix with certain other medicines can affect the way these medicines work and other medicines may affect how Trilipix works. In some cases, using Trilipix with other medicines can cause serious side effects.

Know all the medicines you take. Keep a list of them and show it to your healthcare provider when you get a new medicine.

**It is especially important to tell your healthcare provider if you take any of the medicines mentioned in, "What is the most important information I should know about Trilipix?" or any of the medicines listed below:**

- **anticoagulants**, also known as blood thinners (warfarin, Coumadin)
- **bile acid resins**
- **cyclosporine**

Ask your healthcare provider if you are not sure if your medicine is one of these.

**How should I take Trilipix?**

- You should be on a low fat and low cholesterol diet while you take Trilipix.
- Take Trilipix one time each day as prescribed by your healthcare provider.


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- Take Trilipix with or without food.
- Swallow Trilipix capsules whole. Do not break, crush, dissolve, or chew Trilipix capsules before swallowing. If you cannot swallow Trilipix capsules whole, tell your healthcare provider, you may need a different medicine.
- If you take a medicine called a statin, you can take Trilipix and your statin at the same time of day.
- If you miss a dose of Trilipix, take it as soon as you remember. If it is almost time for your next dose, just skip the missed dose. Take the next dose at your regular time. If you are not sure about your dosing, call your healthcare provider. **Do not take more than one dose of Trilipix a day unless your healthcare provider tells you to.**
- If you take too much Trilipix, contact your healthcare provider or your local emergency department.
- Do not change your dose or stop Trilipix unless your healthcare provider tells you to.
- Your healthcare provider may do blood tests before you start taking Trilipix and during treatment. See your healthcare provider regularly to check your cholesterol and triglyceride levels and to check for side effects.

**What are the possible side effects with Trilipix?**

**Trilipix may cause serious side effects, including:**

- **muscle pain, tenderness, or weakness.** See "What is the most important information that I should know about Trilipix?"
- **tiredness and fever.**
- **abdominal pain, nausea, or vomiting.** These may be signs of inflammation (swelling) of the gallbladder or pancreas.

**Call your healthcare provider right away if you have any of these serious side effects.**

The most common side effects with Trilipix include:

- headache
- heartburn (indigestion)
- nausea
- muscle aches
- increases in muscle or liver enzymes that are measured by blood tests

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of Trilipix. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.


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**How do I store Trilipix?**

- Store Trilipix between 59° to 86° F (15° to 30° C).
- Protect Trilipix from moisture.

**Keep Trilipix and all medicines out of the reach of children.**

**General information about the safe and effective use of Trilipix**

Medicines are sometimes prescribed for conditions that are not mentioned in the Medication Guide. Do not use Trilipix for a condition for which it was not prescribed. Do not give Trilipix to other people, even if they have the same condition you have. It may harm them.

This Medication Guide summarizes the most important information about Trilipix. If you would like more information, talk to your healthcare provider. You can also ask your pharmacist or healthcare provider for information that is written for health professionals.

For more information go to www.Trilipix.com or call 1-800-633-9110.

**What are the ingredients in Trilipix?**

**Active Ingredient:** Fenofibric acid

**Inactive Ingredients:** Hypromellose, povidone, water, hydroxylpropyl cellulose, colloidal silicon dioxide, sodium stearyl fumarate, methacrylic acid copolymer, talc, triethyl citrate, gelatin, titanium dioxide, and yellow iron oxide. Additionally, the 45 mg capsule shell contains black iron oxide and red iron oxide, and the 135 mg capsule shell contains FD&C Blue #2.

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Rev. 09/2010 Abbott Laboratories

This Medication Guide has been approved by the U.S. Food and Drug Administration.



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## Appendix D. Additional Results from the Trilipix Clinical Program

**Brief Summary of Statistical Methods Used in the Trilipix Clinical Program**

For all efficacy variables, only patients with both a baseline and at least 1 postbaseline value for the parameter of interest were included in the analyses for that parameter. Last observation carried forward was used to impute values for subjects missing a postbaseline visit value. Only postbaseline values were carried forward.

For all efficacy variables except hsCRP, the mean percent changes from baseline to Week 12 were compared between the combination therapy arms and each corresponding monotherapy arm using contrast statements within an ANCOVA with baseline lipid value (lipid parameter corresponding to the outcome variable being modeled) as a covariate and with effects for treatment group, diabetic status (diabetic, non-diabetic), screening TG (≤ 250 mg/dL, > 250 mg/dL), and the interaction of diabetic status by screening TG. Data from all 6 treatment arms were included in the ANCOVA. The primary treatment group comparisons were performed including data from all 6 treatment arms in the ANCOVA. Similar analyses were performed within subgroups based on diabetic status and gender. However, for the subgroups based on diabetic status, the model only included the baseline lipid value (lipid parameter corresponding to the outcome variable being modeled) as a covariate and effects for treatment group and screening TG (≤ 250 mg/dL, > 250 mg/dL).

For hsCRP, a Cochran-Mantel-Haenszel mean score test using diabetic status (diabetic, non-diabetic) and screening TG (≤ 250 mg/dL, > 250 mg/dL) as stratification factors (i.e., Van Elteren test) was performed to compare the percent changes from baseline to Week 12 between the combination therapy arms and each corresponding monotherapy arm.


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## Results from the Trilipix Clinical Study Conducted with Simvastatin

### Demographic and Baseline Characteristics for Patients in the Trilipix Clinical Study with Simvastatin

| | Treatment Group n (%) | | | | | |
|---|---|---|---|---|---|---|
| **Demographic Characteristic** | **Fenofibric Acid (N = 119)** | **Low-dose Simvastatin (N = 119)** | **Fenofibric Acid + Low-dose Simvastatin (N = 119)** | **Moderate-dose Simvastatin (N = 116)** | **Fenofibric Acid + Moderate-dose Simvastatin (N = 118)** | **High-dose Simvastatin (N = 59)** |
| Sex | | | | | | |
| Female | 68 (57.1) | 56 (47.1) | 59 (49.6) | 61 (52.6) | 57 (48.3) | 31 (52.5) |
| Male | 51 (42.9) | 63 (52.9) | 60 (50.4) | 55 (47.4) | 61 (51.7) | 28 (47.5) |
| Race | | | | | | |
| White | 116 (97.5) | 110 (92.4) | 108 (90.8) | 112 (96.6) | 109 (92.4) | 55 (93.2) |
| Black | 1 (0.8) | 5 (4.2) | 4 (3.4) | 2 (1.7) | 5 (4.2) | 1 (1.7) |
| Other[a] | 2 (1.6) | 4 (3.4) | 7 (5.9) | 2 (1.7) | 4 (3.4) | 3 (5.1) |
| Ethnicity | | | | | | |
| Hispanic | 13 (10.9) | 11 (9.2) | 11 (9.2) | 16 (13.8) | 13 (11.0) | 6 (10.2) |
| No ethnicity | 106 (89.1) | 108 (90.8) | 108 (90.8) | 100 (86.2) | 105 (89.0) | 53 (89.8) |
| Age group, years | | | | | | |
| < 65 | 98 (82.4) | 104 (87.4) | 101 (84.9) | 104 (89.7) | 96 (81.4) | 48 (81.4) |
| ≥ 65 | 21 (17.6) | 15 (12.6) | 18 (15.1) | 12 (10.3) | 22 (18.6) | 11 (18.6) |
| Mean body weight (SD), kg | | | | | | |
| Males | 98.3 (21.4) | 94.2 (20.0) | 95.9 (17.0) | 98.6 (19.3) | 95.3 (17.7) | 96.2 (12.4) |
| Females | 81.7 (19.2) | 83.6 (20.5) | 85.7 (18.5) | 82.1 (17.3) | 87.4 (19.0) | 86.7 (21.3) |
| Diabetic history | | | | | | |
| With T2DM | 28 (23.5) | 26 (21.8) | 26 (21.8) | 26 (22.4) | 29 (24.6) | 14 (23.7) |
| Mean lipid parameters (SD), mg/dL | | | | | | |
| LDL-C | 159.2 (34.7) | 153.9 (38.6) | 156.7 (43.0) | 160.6 (35.1) | 157.1 (31.5) | 153.8 (30.5) |
| TG | 300.2 (195.3) | 280.3 (131.0) | 292.1 (160.6) | 290.5 (167.1) | 272.7 (125.8) | 258.1 (132.1) |
| HDL-C | 38.4 (7.0) | 38.3 (6.3) | 37.5 (7.2) | 38.5 (7.4) | 38.5 (8.2) | 39.4 (6.8) |

T2DM = type 2 diabetes mellitus.

a. "Other" race includes Indian/Alaskan, Asian, and other.



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## Prespecified Primary Endpoint in the Trilipix Clinical Study with Simvastatin

| | Treatment Group | | | | | |
|---|---|---|---|---|---|---|
| **Parameter** | **Fenofibric Acid (N = 119)** | **Low-dose Simvastatin (N = 119)** | **Fenofibric Acid + Low-dose Simvastatin (N = 119)** | **Moderate-dose Simvastatin (N = 116)** | **Fenofibric Acid + Moderate-dose Simvastatin (N = 118)** | **High-dose Simvastatin[a] (N = 59)** |
| Mean HDL-C, mg/dL | | | | | | |
| Baseline | 38.2 | 38.4 | 37.2 | 38.5 | 38.5 | 39.5 |
| Final | 44.1 | 40.8 | 43.9 | 41.3 | 45.0 | 41.5 |
| % Change | +16.2% | +7.2% | +17.8%* | +8.5% | +18.9%* | +6.8% |
| Mean TG, mg/dL | | | | | | |
| Baseline | 300.9 | 281.2 | 295.6 | 284.4 | 274.1 | 257.4 |
| Final | 181.4 | 223.1 | 164.4 | 202.3 | 147.0 | 192.9 |
| % Change | –31.7% | –14.2% | –37.4%* | –22.4% | –42.7%* | –20.2% |
| Mean LDL-C, mg/dL | | | | | | |
| Baseline | 156.5 | 153.2 | 157.9 | 163.3 | 155.9 | 155.4 |
| Final | 147.1 | 117.5 | 116.6 | 108.1 | 113.3 | 92.7 |
| % Change | –4.0% | –22.4% | –24.0%[&] | –31.7% | –25.3%[&] | –40.8% |

a. No statistical comparisons were made between the high-dose simvastatin arm and other treatment arms.

* Statistically significant difference between coadministration therapy and simvastatin monotherapy at $P \leq 0.05$.

& Statistically significant difference between coadministration therapy and fenofibric acid monotherapy at $P \leq 0.05$.

Note: Only subjects with both a baseline and at least 1 postbaseline value are included in the analyses.



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## Prespecified Secondary Endpoints in the Trilipix Clinical Study with Simvastatin

| | Treatment Group | | | | | |
|---|---|---|---|---|---|---|
| **Parameter** | **Fenofibric Acid (N = 119)** | **Low-dose Simvastatin (N = 119)** | **Fenofibric Acid + Low-dose Simvastatin (N = 119)** | **Moderate-dose Simvastatin (N = 116)** | **Fenofibric Acid + Moderate-dose Simvastatin (N = 118)** | **High-dose Simvastatin[a] (N = 59)** |
| Mean non-HDL-C, mg/dL | | | | | | |
| Baseline | 223.9 | 217.4 | 223.6 | 225.3 | 213.8 | 213.9 |
| Final | 183.7 | 163.6 | 151.3 | 143.3 | 139.5 | 128.9 |
| % Change | –17.3% | –24.4% | –30.7%*& | –35.9% | –35.0%& | –40.6% |
| Mean VLDL-C, mg/dL | | | | | | |
| Baseline | 67.2 | 64.3 | 68.2 | 64.4 | 59.9 | 59.4 |
| Final | 36.3 | 45.3 | 34.1 | 36.6 | 26.5 | 36.6 |
| % Change | –36.9% | –19.2% | –38.9%* | –35.7% | –51.1%* | –30.0% |
| Mean total cholesterol, mg/dL | | | | | | |
| Baseline | 262.6 | 254.9 | 261.5 | 263.3 | 252.8 | 252.4 |
| Final | 227.8 | 203.7 | 194.8 | 182.8 | 184.7 | 169.4 |
| % Change | –12.4% | –19.8% | –23.9% | –30.0% | –27.1% | –33.6% |
| Mean Apo B, mg/dL | | | | | | |
| Baseline | 150.0 | 144.3 | 149.4 | 149.8 | 142.7 | 143.8 |
| Final | 121.7 | 110.7 | 102.9 | 99.7 | 98.2 | 89.2 |
| % Change | –17.6% | –22.9% | –29.5% | –32.7% | –31.2% | –38.9% |
| Median hsCRP, mg/L | | | | | | |
| Baseline | 3.54 | 2.79 | 3.10 | 2.81 | 2.69 | 2.37 |
| % Change | –15.8% | –11.4% | –26.8% | –14.8% | –32.1% | –19.8% |

a. No statistical comparisons were made between the high-dose simvastatin arm and other treatment arms.

* Statistically significant difference between coadministration therapy and simvastatin monotherapy at $P \leq 0.05$.

& Statistically significant difference between coadministration therapy and fenofibric acid monotherapy at $P \leq 0.05$.

Note: Only subjects with both a baseline and at least 1 postbaseline value are included in the analyses.



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## Prespecified Primary Endpoint from Trilipix Clinical Study with Simvastatin in Subgroups

| | Treatment Group | | | | | |
|---|---|---|---|---|---|---|
| **Parameter** | **Fenofibric Acid** | **Low-dose Simvastatin** | **Fenofibric Acid + Low-dose Simvastatin** | **Moderate-dose Simvastatin** | **Fenofibric Acid + Moderate-dose Simvastatin** | **High-dose Simvastatin[a]** |
| **Females** | N = 68 | N = 56 | N = 59 | N = 61 | N = 57 | N = 31 |
| Mean HDL-C, mg/dL | | | | | | |
| Baseline | 41.2 | 41.7 | 41.0 | 42.4 | 43.0 | 42.1 |
| Final | 48.2 | 44.2 | 48.7 | 45.2 | 51.2 | 45.1 |
| % Change | +17.5% | +7.1% | +18.8%* | +8.4% | +22.8%* | +8.9% |
| Mean TG, mg/dL | | | | | | |
| Baseline | 265.2 | 270.0 | 308.4 | 269.0 | 263.7 | 260.0 |
| Final | 176.5 | 227.8 | 151.2 | 204.2 | 138.7 | 195.5 |
| % Change | –31.7% | –12.2% | –41.7%* | –20.3% | –45.9%* | –20.9% |
| Mean LDL-C, mg/dL | | | | | | |
| Baseline | 162.1 | 154.8 | 168.0 | 168.6 | 156.2 | 156.1 |
| Final | 139.0 | 117.1 | 113.1 | 108.4 | 107.2 | 93.4 |
| % Change | –13.7% | –23.8% | –29.7%[&] | –34.1% | –30.3%[&] | –40.5% |
| **Males** | N = 51 | N = 63 | N = 60 | N = 55 | N = 61 | N = 28 |
| Mean HDL-C, mg/dL | | | | | | |
| Baseline | 34.4 | 35.4 | 33.6 | 34.3 | 34.4 | 36.5 |
| Final | 38.8 | 37.7 | 39.4 | 37.0 | 39.2 | 37.5 |
| % Change | +13.3% | +8.2% | +16.2%* | +8.1% | +15.4%* | +5.6% |
| Mean TG, mg/dL | | | | | | |
| Baseline | 349.9 | 290.7 | 281.1 | 304.5 | 282.8 | 257.4 |
| Final | 187.6 | 218.6 | 177.4 | 199.9 | 154.3 | 189.5 |
| % Change | –31.8% | –16.3% | –32.9%* | –24.9% | –40.1%* | –19.8% |
| Mean LDL-C, mg/L | | | | | | |
| Baseline | 148.6 | 151.5 | 147.7 | 158.3 | 155.4 | 154.8 |
| Final | 157.8 | 117.6 | 119.5 | 108.3 | 118.5 | 92.1 |
| % Change | +8.7% | –20.9% | –19.0%[&] | –29.6% | –20.5%[&] | –40.8% |

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## Prespecified Primary Endpoint from Trilipix Clinical Study with Simvastatin in Subgroups (Continued)

| | Treatment Group | | | | | |
|---|---|---|---|---|---|---|
| **Parameter** | **Fenofibric Acid** | **Low-dose Simvastatin** | **Fenofibric Acid + Low-dose Simvastatin** | **Moderate-dose Simvastatin** | **Fenofibric Acid + Moderate-dose Simvastatin** | **High-dose Simvastatin[a]** |
| **T2DM** | N = 28 | N = 26 | N = 26 | N = 26 | N = 29 | N = 14 |
| Mean HDL-C, mg/dL | | | | | | |
| Baseline | 36.6 | 39.1 | 38.6 | 39.7 | 39.0 | 38.4 |
| Final | 42.2 | 40.0 | 44.2 | 43.0 | 44.8 | 38.5 |
| % Change | +14.7% | +2.9% | +15.2%* | +9.1% | +16.5% | +2.4% |
| Mean TG, mg/dL | | | | | | |
| Baseline | 335.8 | 272.6 | 288.3 | 304.0 | 267.0 | 238.9 |
| Final | 192.8 | 251.3 | 156.7 | 213.5 | 141.0 | 180.6 |
| % Change | –31.3% | –3.8% | –40.4%* | –28.5% | –44.8%* | –23.1% |
| Mean LDL-C, mg/dL | | | | | | |
| Baseline | 161.8 | 156.0 | 154.8 | 158.2 | 157.1 | 142.7 |
| Final | 149.4 | 120.9 | 103.4 | 108.7 | 118.1 | 80.5 |
| % Change | –2.0% | –20.7% | –32.4%& | –30.9% | –22.9%& | –47.0% |
| **Non-T2DM** | N = 91 | N = 93 | N = 93 | N = 90 | N = 89 | N = 45 |
| Mean HDL-C, mg/dL | | | | | | |
| Baseline | 38.5 | 37.9 | 36.5 | 37.9 | 38.2 | 39.5 |
| Final | 45.0 | 41.3 | 44.1 | 41.1 | 45.4 | 42.7 |
| % Change | +18.2% | +9.7% | +19.8%* | +9.6% | +21.0%* | +9.5% |
| Mean TG, mg/dL | | | | | | |
| Baseline | 287.2 | 281.0 | 295.1 | 275.9 | 273.4 | 260.7 |
| Final | 174.7 | 212.3 | 163.5 | 195.9 | 145.8 | 193.5 |
| % Change | –32.6% | –17.3% | –36.7%* | –21.3% | –42.4%* | –19.5% |
| Mean LDL-C, mg/L | | | | | | |
| Baseline | 156.0 | 153.6 | 160.0 | 165.8 | 156.7 | 160.2 |
| Final | 147.8 | 118.2 | 122.1 | 109.5 | 113.3 | 97.7 |
| % Change | –3.6% | –21.9% | –20.5%& | –30.9% | –25.1%& | –38.2% |

a. No statistical comparisons were made between the high-dose simvastatin arm and other treatment arms.

* Statistically significant difference between coadministration therapy and simvastatin monotherapy at $P \leq 0.05$.

& Statistically significant difference between coadministration therapy and fenofibric acid monotherapy at $P \leq 0.05$.

Notes: Only subjects with both a baseline and at least 1 postbaseline value are included in the analyses. Diabetic status was determined from subject's medical history.



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## Prespecified Secondary Endpoints Results from from Trilipix Clinical Study with Simvastatin in Subgroups

| | Treatment Group | | | | | |
|---|---|---|---|---|---|---|
| **Parameter** | **Fenofibric Acid** | **Low-dose Simvastatin** | **Fenofibric Acid + Low-dose Simvastatin** | **Moderate-dose Simvastatin** | **Fenofibric Acid + Moderate-dose Simvastatin** | **High-dose Simvastatin[a]** |
| **Females** | N = 68 | N = 56 | N = 59 | N = 61 | N = 57 | N = 31 |
| Mean non–HDL-C, mg/dL | | | | | | |
| Baseline | 225.3 | 215.9 | 238.0 | 226.5 | 214.9 | 218.7 |
| Final | 174.5 | 164.1 | 144.4 | 144.5 | 131.9 | 131.6 |
| % Change | –22.3% | –24.1% | –36.5%*[&] | –36.1% | –39.4%[&] | –40.1% |
| Mean VLDL-C, mg/dL | | | | | | |
| Baseline | 62.9 | 61.3 | 73.9 | 61.9 | 59.1 | 62.3 |
| Final | 34.9 | 47.6 | 31.3 | 37.9 | 25.4 | 37.8 |
| % Change | –37.3% | –13.5% | –41.2%* | –31.6% | –53.9%* | –27.1% |
| Mean total cholesterol, mg/dL | | | | | | |
| Baseline | 267.2 | 255.8 | 278.1 | 269.2 | 257.5 | 259.1 |
| Final | 223.3 | 207.8 | 193.5 | 188.5 | 184.4 | 173.7 |
| % Change | –16.0% | –19.1% | –27.5%* | –29.6% | –28.9% | –33.5% |
| Mean Apo B, mg/dL | | | | | | |
| Baseline | 151.5 | 142.4 | 155.5 | 150.8 | 142.1 | 144.9 |
| Final | 115.7 | 112.3 | 100.4 | 100.2 | 92.1 | 87.9 |
| % Change | –23.1% | –21.0% | –32.7%* | –32.6% | –35.5% | –39.8% |
| Median hsCRP, mg/L | | | | | | |
| Baseline | 3.55 | 3.73 | 4.97 | 3.89 | 4.28 | 3.37 |
| % Change | –17.1% | –13.4% | –30.2%* | –13.3% | –35.2% | –22.6% |

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## Prespecified Secondary Endpoints from Trilipix Clinical Study with Simvastatin in Subgroups (Continued)

| | Treatment Group | | | | | |
|---|---|---|---|---|---|---|
| **Parameter** | **Fenofibric Acid** | **Low-dose Simvastatin** | **Fenofibric Acid + Low-dose Simvastatin** | **Moderate-dose Simvastatin** | **Fenofibric Acid + Moderate-dose Simvastatin** | **High-dose Simvastatin[a]** |
| **Males** | N = 51 | N = 63 | N = 60 | N = 55 | N = 61 | N = 28 |
| Mean non–HDL-C, mg/dL | | | | | | |
| Baseline | 220.9 | 218.1 | 209.2 | 226.0 | 212.4 | 209.1 |
| Final | 195.6 | 162.8 | 157.1 | 142.5 | 146.1 | 125.8 |
| % Change | –11.0% | –24.8% | –24.9%[&] | –36.1% | –30.9%[&] | –41.1% |
| Mean VLDL-C, mg/dL | | | | | | |
| Baseline | 72.5 | 66.5 | 61.7 | 68.6 | 60.5 | 57.0 |
| Final | 37.8 | 43.3 | 36.9 | 34.8 | 27.5 | 35.0 |
| % Change | –37.1% | –24.6% | –37.7% | –40.6% | –48.5% | –34.4% |
| Mean total cholesterol, mg/dL | | | | | | |
| Baseline | 255.1 | 253.4 | 243.1 | 258.8 | 248.5 | 246.3 |
| Final | 233.9 | 199.7 | 195.6 | 177.0 | 184.9 | 164.7 |
| % Change | –7.8% | –20.6% | –19.6% | –31.0% | –25.3%* | –33.8% |
| Mean Apo B, mg/dL | | | | | | |
| Baseline | 147.7 | 145.7 | 142.5 | 150.1 | 143.1 | 143.2 |
| Final | 129.7 | 109.1 | 105.2 | 99.0 | 103.3 | 90.5 |
| % Change | –10.4% | –24.8% | –25.8% | –33.5% | –27.5%* | –38.3% |
| Median hsCRP, mg/L | | | | | | |
| Baseline | 3.40 | 2.25 | 1.85 | 1.70 | 2.02 | 1.96 |
| % Change | –5.9% | –9.6% | –12.1% | –21.4% | –27.7% | –12.0% |

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## Prespecified Secondary Endpoints from Trilipix Clinical Study with Simvastatin in Subgroups (Continued)

| | Treatment Group | | | | | |
|---|---|---|---|---|---|---|
| **Parameter** | **Fenofibric Acid** | **Low-dose Simvastatin** | **Fenofibric Acid + Low-dose Simvastatin** | **Moderate-dose Simvastatin** | **Fenofibric Acid + Moderate-dose Simvastatin** | **High-dose Simvastatin[a]** |
| **T2DM** | N = 28 | N = 26 | N = 26 | N = 26 | N = 29 | N = 14 |
| Mean non–HDL-C, mg/dL | | | | | | |
| Baseline | 228.0 | 221.3 | 220.3 | 222.6 | 215.9 | 200.8 |
| Final | 188.0 | 171.8 | 131.6 | 145.3 | 145.3 | 117.8 |
| % Change | –16.5% | –21.6% | –39.4%*[&] | –34.8% | –32.7%[&] | –42.9% |
| Mean VLDL-C, mg/dL | | | | | | |
| Baseline | 66.6 | 66.3 | 65.5 | 69.7 | 59.7 | 58.0 |
| Final | 38.6 | 49.9 | 28.2 | 39.6 | 27.3 | 34.8 |
| % Change | –28.2% | –20.1% | –47.4%* | –40.3% | –52.3% | –37.3% |
| Mean total cholesterol, mg/dL | | | | | | |
| Baseline | 263.9 | 260.0 | 258.7 | 260.5 | 256.9 | 236.2 |
| Final | 231.4 | 211.7 | 175.7 | 182.4 | 189.6 | 150.4 |
| % Change | –11.2% | –17.9% | –31.2%* | –30.1% | –25.8% | –38.2% |
| Mean Apo B, mg/dL | | | | | | |
| Baseline | 157.8 | 146.7 | 151.7 | 146.6 | 148.1 | 128.4 |
| Final | 128.3 | 114.1 | 96.3 | 99.2 | 101.5 | 77.7 |
| % Change | –17.1% | –22.2% | –35.4%* | –32.3% | –30.7% | –42.4% |
| Median hsCRP, mg/L | | | | | | |
| Baseline | 3.75 | 3.73 | 3.39 | 3.80 | 5.77 | 5.96 |
| % Change | –20.3% | –8.2% | –26.5% | –12.5% | –36.8% | –13.8% |

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## Prespecified Secondary Endpoints from Trilipix Clinical Study with Simvastatin in Subgroups (Continued)

| | Treatment Group | | | | | |
|---|---|---|---|---|---|---|
| **Parameter** | **Fenofibric Acid** | **Low-dose Simvastatin** | **Fenofibric Acid + Low-dose Simvastatin** | **Moderate-dose Simvastatin** | **Fenofibric Acid + Moderate-dose Simvastatin** | **High-dose Simvastatin[a]** |
| **Non-T2DM** | N = 91 | N = 93 | N = 93 | N = 90 | N = 89 | N = 45 |
| Mean non–HDL-C, mg/dL | | | | | | |
| Baseline | 223.4 | 217.2 | 225.4 | 227.1 | 213.9 | 218.3 |
| Final | 183.5 | 162.6 | 158.7 | 144.0 | 138.8 | 133.1 |
| % Change | –17.1% | –24.6% | –27.4%& | –35.6% | –35.2%& | –39.4% |
| Mean VLDL-C, mg/dL | | | | | | |
| Baseline | 67.1 | 63.5 | 68.7 | 62.5 | 59.6 | 59.5 |
| Final | 35.4 | 43.9 | 35.6 | 35.4 | 26.0 | 36.7 |
| % Change | –39.4% | –18.5% | –36.0* | –34.0 | –50.4%* | –27.5% |
| Mean total cholesterol, mg/dL | | | | | | |
| Baseline | 263.0 | 254.2 | 263.1 | 264.9 | 252.3 | 258.1 |
| Final | 228.6 | 203.5 | 202.3 | 184.9 | 185.1 | 177.1 |
| % Change | –12.0% | –19.6% | –21.0% | –29.2% | –26.7% | –31.4% |
| Mean Apo B, mg/dL | | | | | | |
| Baseline | 146.8 | 143.0 | 148.1 | 150.0 | 140.3 | 147.5 |
| Final | 119.9 | 110.2 | 105.2 | 100.1 | 97.4 | 92.8 |
| % Change | –17.2% | –22.4% | –27.1%* | –32.1% | –30.8% | –37.1% |
| Median hsCRP, mg/L | | | | | | |
| Baseline | 3.41 | 2.73 | 2.95 | 2.58 | 2.40 | 2.22 |
| % Change | –13.0% | –11.8% | –27.7% | –15.6% | –27.7% | –21.7% |

a. No statistical comparisons were made between the high-dose simvastatin arm and other treatment arms.

* Statistically significant difference between coadministration therapy and simvastatin monotherapy at $P \leq 0.05$.

& Statistically significant difference between coadministration therapy and fenofibric acid monotherapy at $P \leq 0.05$.

Notes: Only subjects with both a baseline and at least 1 postbaseline value are included in the analyses. Diabetic status was determined from subject's medical history.



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