



Clinical research

Efficacy and safety of the coadministration of ezetimibe with fenofibrate in patients with mixed hyperlipidaemia

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KEYWORDS

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Ezetimibe;
Fenofibrate;
Lipoproteins;
LDL particle size

Aims To examine the efficacy and safety of coadministered ezetimibe (EZE) with fenofibrate (FENO) in patients with mixed hyperlipidaemia.

Methods and results This was a multicentre, randomized, double-blind, placebo-controlled, parallel arm trial in patients with mixed hyperlipidaemia [LDL-cholesterol (LDL-C), 3.4–5.7 mmol/L (2.6–4.7 mmol/L for patients with type 2 diabetes); triglycerides (TG), 2.3–5.7 mmol/L] and no history of coronary heart disease (CHD), CHD-equivalent disease (except for type 2 diabetes), or CHD risk score >20%. A total of 625 patients was randomized in a 1:3:3:3 ratio to one of four daily treatments for 12 weeks: placebo; EZE 10 mg; FENO 160 mg; FENO 160 mg plus EZE 10 mg (FENO + EZE). The primary endpoint compared the LDL-C lowering efficacy of FENO + EZE vs. FENO alone. LDL-C, non-HDL-cholesterol (non-HDL-C), and apolipoprotein B were significantly ($P < 0.001$) reduced with FENO + EZE when compared with FENO or EZE alone. TG levels were significantly decreased and HDL-C was significantly increased with FENO + EZE and FENO treatments when compared with placebo ($P < 0.001$). Coadministration therapy reduced LDL-C by 20.4%, non-HDL-C by 30.4%, TG by 44.0%, and increased HDL-C by 19.0%. At baseline, >70% of all patients exhibited the small, dense LDL pattern B profile. A greater proportion of patients on FENO + EZE and FENO alone treatments shifted from a more atherogenic LDL size pattern to a larger, more buoyant, and less atherogenic LDL size pattern at study endpoint than those on placebo or EZE. All three active therapies were well tolerated.

Conclusion Coadministration of EZE with FENO provided a complementary efficacy therapy that improves the atherogenic lipid profile of patients with mixed hyperlipidaemia.

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Introduction

Mixed or combined hyperlipidaemia is a common metabolic disorder characterized by both hypercholesterolaemia and hypertriglyceridaemia.¹ Specifically, patients with mixed hyperlipidaemia have elevated LDL-cholesterol (LDL-C) and triglycerides (TG), a preponderance of small, dense LDL particles, and reduced HDL-cholesterol (HDL-C). Each of these metabolic perturbations is associated with increased risk for cardiovascular disease. Moreover, the profile of high TG and low HDL-C is typically found in patients with metabolic syndrome and diabetes.² Beyond lowering LDL-C, the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) recommends non-HDL-C as a secondary treatment target for patients with elevated TG.²

Although dietary modification and increased physical activity have demonstrated lipid-modifying benefits, these behavioural changes have limited capacity to correct more severe lipid abnormalities. The NCEP ATP III guidelines recommend combining drug therapies to achieve the lipid goals for patients with mixed hyperlipidaemia.² Lowering LDL-C is the initial target of treatment followed by treatments that improve the other lipid abnormalities associated with mixed hyperlipidaemia. Statins are the most commonly used therapy to treat elevated total cholesterol (TC) and LDL-C and are effective in reducing the risk of cardiovascular events. Although statins also improve TG and HDL-C, fibrates are more effective in treating elevated TG and reduced HDL-C levels. Fibrates regulate the transcription of genes that affect lipid and lipoprotein metabolism including genes for fatty acid uptake and transport and lipoprotein lipases.³ Fibrates also tend to decrease LDL-C by 5–20%, but may elevate LDL-C in patients with moderate to severe hypertriglyceridaemia (TG > 4.0 mmol/L) via increased lipolysis of TG-rich, VLDL.^{3–5} Statins and fibrates have complementary mechanisms and can be coadministered to patients with mixed hyperlipidaemia.^{6,7} However, safety concerns are increased with higher doses and/or certain combinations of statins and fibrates, particularly gemfibrozil.^{6–8} Finally, some patients are intolerant or non-responsive to statin and/or fibrate therapies or may not achieve treatment goals with this coadministration therapy.

Ezetimibe (EZE), a cholesterol absorption inhibitor, prevents the absorption of dietary and biliary cholesterol without affecting the absorption of TG or fat-soluble vitamins.^{9,10} Treatment with EZE reduced LDL-C by 15–25% with modest favourable effects on TG and HDL-C in patients with primary hypercholesterolaemia.^{10–12} EZE is not an inhibitor or an inducer of cytochrome P450 isoenzymes, a characteristic that should make the incidence of potential drug interactions lower.¹³ Thus, concomitant treatment with EZE and fibrates may provide a complementary and alternative treatment for mixed hyperlipidaemia without some of the safety concerns associated with coadministration of statins and fibrates. In a Phase I study, 2 week coadministration of EZE and micronized fenofibrate (FENO) produced marked reductions in LDL-C and TG and appeared to be well tolerated in healthy

patients with elevated LDL-C.¹⁴ Although limited clinical data are available addressing EZE and FENO coadministration, the efficacy and safety of this combined pharmacotherapy were examined in patients with mixed hyperlipidaemia.

Methods

Patients

All patients provided written informed consent before enrolment. Eligible patients were men and women 18 through 75 years of age with mixed hyperlipidaemia and no coronary heart disease (CHD), CHD-equivalent disease (except for type 2 diabetes), or 10 year CHD risk > 20%. Additionally, patients were excluded from participation for any of the following: homozygous familial hypercholesterolaemia; type I or V hyperlipidaemia; treatment with LDL apheresis; congestive heart failure (New York Heart Association Class III or IV); uncontrolled cardiac arrhythmia; unstable hypertension; pancreatitis; inadequately controlled diabetes (glycosylated haemoglobin, HbA1c > 8.5%); gallbladder, renal (serum creatinine > 133 μ mol/L or 1.5 mg/dL), or active liver disease; uncontrolled endocrine or metabolic disease known to influence serum lipids or lipoproteins; pregnancy or lactation; and contraindicated medications that cannot be discontinued. Lipid eligibility criteria were assessed after a 6 week period that included placebo run-in phase and a washout of previous lipid-modifying therapies (8 weeks for fibrates). Patients were also instructed to consume a lipid-altering diet during this period. After successful completion of this period, patients were randomized if LDL-C was 3.4–5.7 mmol/L (130–220 mg/dL) inclusive, TG 2.3–5.7 mmol/L (200–500 mg/dL) inclusive, and aspartate transferase (AST), alanine transferase (ALT), and creatine phosphokinase (CK) were less than 1.5 times upper limit of normal (\times ULN). Patients with type 2 diabetes were limited to those with LDL-C of 2.6–4.7 mmol/L (100–180 mg/dL) inclusive after washout period.

Study design

The study was an international, multicentre, randomized, double-blind, placebo-controlled, parallel design. The protocol was reviewed and approved by each institution and conducted according to Good Clinical Practice guidelines. After the placebo run-in/washout period, eligible patients were randomized in a 1:3:3:3 ratio to one of four daily treatments for 12 weeks: placebo; EZE 10 mg; FENO 160 mg; coadministration of FENO 160 mg plus EZE 10 mg (FENO + EZE) using a computer generated randomization schedule. All doses were administered orally with the evening meal. Patients also remained on the lipid-altering diet throughout the treatment period. Patients completing the 12 week base study were offered enrolment into a 48 week extension study, which will be the subject of a future communication.

Efficacy endpoints

The primary efficacy endpoint was per cent change in LDL-C from baseline to study endpoint after treatment with FENO + EZE vs. FENO alone. The baseline value is defined as the average of the measurements obtained 1 week before randomization and the day of randomization. The endpoint value is defined as the last post-baseline measurement during the 12 week double-blind

period. Secondary efficacy endpoints included per cent change in other lipid and lipoprotein parameters (TC, TG and non-HDL-C, HDL-C, apolipoprotein [apo] B, and apo A-I) from baseline to study endpoint. The proportion of patients shifting from a more atherogenic LDL size pattern to a less atherogenic LDL size pattern after treatment was tabulated for each treatment group. Tertiary endpoints were per cent change from baseline to study endpoint in non-lipid parameters, high sensitivity C-reactive protein (hsCRP), and fibrinogen.

Safety endpoints

Safety and tolerability were assessed by clinical and statistical reviews of all safety parameters, including adverse experiences (AEs), laboratory values, and vital signs. All AEs were rated by the investigators as definitely not, probably not, possibly, probably, or definitely related to treatment. AEs of clinical interest included patients experiencing: consecutive elevations of CK $>10\times$ ULN without muscle symptoms or $>5\times$ ULN with muscle symptoms; myopathy (muscle symptoms accompanied by CK $>10\times$ ULN); elevated hepatic transaminases (consecutive $>3\times$ ULN elevations in ALT and/or AST); and gallbladder/biliary, hepatic, gastrointestinal, and allergy/rash related AEs. Changes in serum creatinine concentrations were monitored throughout the study. Patients were also monitored for severe hypertriglyceridaemia during the active treatment period. For any values >6.8 mmol/L (600 mg/dL) during the blinded treatment period, the central laboratory was instructed to send an alert to the clinical site as 'TG >600 mg/dL'. The site was instructed to have the patient back for a redraw. If the TG level was still >6.8 mmol/L, then the patient was discontinued due to lack of efficacy. Compliance was assessed by tablet count at each visit.

Blood collection and lipid analysis

Blood samples were collected after a 12 h fast at Weeks -6 and -1, at randomization, and at Weeks 6 and 12. Complete lipid profiles and non-lipid parameters were measured in plasma at baseline and Week 12. These variables included direct LDL-C, TG, HDL-C, TC, non-HDL-C, apo B, apo A-I, LDL particle size pattern, hsCRP, and fibrinogen. LDL-C was measured directly with preparative ultracentrifugation. TC and TG were determined enzymatically. HDL-C was quantified enzymatically after selective removal of apo B-containing lipoproteins by heparin and by manganese chloride precipitation. Non-HDL-C was calculated by subtracting HDL-C from TC. Apo B and apo A-I were determined by fixed-rate nephelometry. LDL peak particle size was assessed with segmented gradient gel electrophoresis (S₃GGE™ - Berkeley Heartlab Inc., Burlingame, CA, USA). Some patients were missing LDL peak particle size, which was used to determine LDL size pattern (pattern A, I, or B). HsCRP and fibrinogen were quantified by immunonephelometry. All clinical laboratory analyses were performed at the central laboratory and technicians were blinded to treatment allocation (Medical Research Laboratory, Highland Heights, KY, USA and Zaventem, Belgium). Moreover, patients and investigators were blinded to the efficacy endpoints and to the randomized treatment.

Statistical analysis

For the efficacy variables, the analysis methods for 2×2 factorial design were not fully employed because the primary focus of the study was comparison of FENO + EZE coadministration group to FENO monotherapy for a select number of prespecified efficacy endpoints rather than examination of all possible

between-treatment relationships. The presence of other treatment groups was justified by our safety hypothesis (i.e. examination of safety and tolerability of the coadministration treatment group relative to both monotherapies and placebo). The primary analysis was a modified intention-to-treat approach, which includes all randomized patients who have baseline values, taken at least one dose of study medication, and at least one post-baseline measurement. An analysis of covariance (ANCOVA) model with terms for treatment (placebo, EZE, FENO, FENO + EZE) and baseline TG values was used to compare each efficacy endpoint among treatment groups. A test of treatment-by-baseline TG interaction was performed for each variable analysed to assess the validity of ANCOVA model assumptions. However, all within-treatment and between-treatment estimates were based on the model without this interaction term.

On the basis of a sample size of $n = 500$ [150 per active treatment group (groups = 3) and 50 for the placebo group] and a significance level of 0.05 (two-sided), and assuming that the SD for the per cent change in LDL-C was 14.1%, the study had 90% power to detect at least a 5.3% difference in per cent LDL-C reduction between coadministered FENO + EZE vs. FENO monotherapy (primary efficacy endpoint). Multiplicity adjustment using an ordered step-down approach was applied to the key secondary efficacy comparisons: LDL-C, comparing EZE + FENO vs. EZE; TG and HDL-C, comparing EZE + FENO vs. FENO.

For data that were not normally distributed, a nonparametric test (ANCOVA model based on Tukey's normalized ranks) was used for inferential testing of between-treatment differences. As moderately elevated TG levels may influence the LDL-C response to fibrate therapy and the treatment-by-baseline TG interaction term was significant in the ANCOVA model, a stratified analysis was also performed focusing on LDL-C response between patients with baseline TG above and below the median. Per cent change data were expressed as mean or median per cent change (95% CI) for each parameter. Other pre-defined subgroup analyses examined the effect of age (<65 or ≥ 65 years), gender, race, baseline lipid values above and below certain cut points (LDL-C <4.1 or ≥ 4.1 mmol/L; HDL-C <1.0 or ≥ 1.0 mmol/L), type 2 diabetes status, and metabolic syndrome status as defined by NCEP ATP III (except type 2 diabetes excluded) on LDL-C responses to treatments. The proportion of patients achieving CHD risk-specific, NCEP ATP III targets for LDL-C and non-HDL-C was also compared among groups. Baseline LDL particle size patterns and change in pattern from baseline, both expressed as per cent frequency, were also tabulated for all groups.

All randomized patients were included in the safety assessment. The safety and tolerability analyses focused on the proportion of patients experiencing either a consecutive measurements of CK ($>10\times$ ULN or $>5\times$ ULN with muscle symptoms), consecutive elevations in AST and/or ALT ($>3\times$ ULN), myopathy (muscle symptoms with CK $>10\times$ ULN), or elevations in serum creatinine ≥ 133 μ mol/L (1.5 mg/dL). These safety endpoints and also proportion of patients having gallbladder/biliary adverse events were compared using Fisher's exact test between FENO + EZE vs. other treatment groups. Changes from baseline in CK, AST, ALT, and serum creatinine were also assessed among treatment groups.

Results

Patients

Of 1675 patients screened, 625 met the eligibility criteria and were randomized (Table 1). Of the 625 randomized

Table 1 Overall disposition of patients

	Placebo	EZE 10 mg	FENO 160 mg	FENO 160 mg/EZE 10 mg
Randomized, <i>n</i>	64	187	189	185
Completed, <i>n</i>	63	175	177	172
Discontinued, <i>n</i> (%)	1 (1.6)	12 (6.4)	12 (6.3)	13 (7.0)
AEs, <i>n</i>	0	4	5	4
Treatment-related AEs, <i>n</i>	0	0	4	3
Lack of efficacy ^a , <i>n</i>	0	1	0	0
Other ^b , <i>n</i>	1	8	3	6

^aLack of efficacy = plasma TG levels >6.8 mmol/L, consecutive.

^bOther includes discontinuation because of patient lost to follow up, moved, consent withdrawal, and protocol deviation.

patients, 427 (68.3%) were not on a lipid-altering treatment and the remaining 198 patients (31.7%), all of whom required washout of previous lipid-lowering treatment(s), were mainly on a statin ($n = 131$) and/or a fibrate ($n = 73$). Approximately 16% ($n = 98$) patients had type 2 diabetes and 57% ($n = 354$) met the NCEP ATP III criteria (2) for metabolic syndrome (without type 2 diabetes). Treatment groups were generally well matched with respect to baseline demographics and characteristics, except the FENO + EZE and FENO alone groups tended to have more women and less patients with type 2 diabetes. There were no clinically meaningful differences in baseline lipid and non-lipid parameters among treatment groups (Table 2). Among the 625 patients randomized into the study, 619 were included in the modified intention-to-treat population for the LDL-C and other efficacy analyses, whereas all 625 contributed data for the safety analyses. Following randomization, 38 patients (6%) discontinued treatment because of either AEs or other events (Table 1). Rates of discontinuations were comparable among the three active treatment groups (6–7%). Treatment compliance was good, with a majority (>86%) of patients taking >90% of the total doses in each treatment group.

Efficacy

Coadministration of FENO + EZE resulted in a significantly ($P < 0.001$) greater reduction in LDL-C than with FENO or EZE alone (Figure 1). Treatment with EZE lowered LDL-C more than FENO ($P < 0.001$). Because the interaction term for baseline TG by treatment was significant, LDL-C responses to treatments were examined further by stratifying patients above and below the median baseline TG level (3.1 mmol/L). Mean (\pm SD) LDL-C level was 4.3 (± 0.7) mmol/L for patients with baseline TG ≤ 3.1 mmol/L and 4.0 (± 0.7) mmol/L for those with baseline TG >3.1 mmol/L. In the cohort with TG ≤ 3.1 mmol/L, the LDL-C reductions were numerically larger than in the total cohort, and the combination of FENO + EZE was more effective than each monotherapy (Figure 2). However, in the cohort with TG >3.1 mmol/L, the LDL-C response was lower than that seen with the entire cohort, particularly for FENO alone, which produced virtually no change in LDL-C. For the elevated TG group, coadministration was superior to FENO alone in

lowering LDL-C, but it was not significantly better than EZE alone (Figure 2).

LDL-C responses were generally consistent across the following subgroups: age, race, body mass index (BMI), and metabolic syndrome status. Effect of FENO and FENO + EZE seemed to be blunted in males compared with females, in patients with reduced baseline LDL-C (<4.1 mmol/L) or HDL-C (<1.0 mmol/L) and in patients with type 2 diabetes. These particular subgroups tended to have higher median baseline TG levels, which may account for LDL-C responses.

Similar to the LDL-C results, the effect of coadministration appeared to be additive for TC, non-HDL-C, and apo B. These parameters were significantly ($P < 0.001$) reduced in the FENO + EZE group compared with the FENO or EZE alone group (Table 3). The treatment-induced reductions in non-HDL-C were not influenced by baseline TG levels (data not shown). The lipid-lowering effects of EZE or FENO alone on TC, non-HDL-C, and apo B were significant ($P < 0.001$) compared with placebo. FENO monotherapy significantly lowered ($P = 0.009$) apo B more than EZE alone.

LDL-C and non-HDL-C goal attainment was greater with coadministration than with either single treatment (Figure 3). However, baseline TG levels seemed to have a similar impact on LDL-C goal attainment as noted with per cent LDL-C reductions (i.e. no apparent difference between coadministration and EZE alone in patients with TG >3.1 mmol/L). The effect of treatments on non-HDL-C goal attainment was consistent across baseline TG strata.

HDL-C and apo A-I were significantly increased with coadministration of FENO + EZE and FENO alone ($P < 0.001$), but the difference between these groups was not significant (Table 3). Both FENO + EZE and FENO alone treatments provided comparable median per cent reductions in TG. A slightly larger and significant ($P = 0.021$) reduction in per cent median TG was noted with coadministration compared with FENO alone (Table 3). Per cent reductions in median hsCRP and fibrinogen were similar in the FENO + EZE and FENO alone groups. The changes in these parameters with coadministration appeared to be dependent on FENO, because EZE alone did not influence the results with HDL-C, apo A-I, TG, hsCRP, and fibrinogen in patients with mixed hyperlipidaemia.

Table 2 Baseline characteristics of patients with mixed hyperlipidaemia by treatment groups

Variables ^a	Placebo (n = 64)	EZE 10 mg (n = 187)	FENO 160 mg (n = 189)	FENO 160 mg/EZE 10 mg (n = 185)
Age (years)	54.5 ± 10.8	53.5 ± 9.2	52.5 ± 10.6	55.2 ± 9.8
Weight (kg)	84.0 ± 16.7	82.6 ± 16.4	82.1 ± 15.9	81.7 ± 16.1
BMI (kg/m ²)	29.7 ± 4.9	29.3 ± 4.5	29.3 ± 4.5	29.6 ± 4.8
Men (%)	62.5	62.6	55.0	48.6
History				
Diabetes (%)	18.8	18.8	12.2	15.1
Metabolic syndrome (%) ^b	57.1	54.6	58.5	57.8
LDL-C (mmol/L)	4.2 ± 0.7	4.1 ± 0.7	4.3 ± 0.7	4.2 ± 0.7
TC (mmol/L)	6.7 ± 0.8	6.7 ± 0.8	6.9 ± 0.9	6.8 ± 0.9
HDL-C (mmol/L)	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.3	1.1 ± 0.2
TG (mmol/L) ^c	2.9 ± 0.9	3.1 ± 1.2	3.2 ± 1.0	3.1 ± 1.1
Non-HDL-C (mmol/L)	5.6 ± 0.7	5.6 ± 0.8	5.8 ± 0.8	5.7 ± 0.8
Apo B (g/L)	1.7 ± 0.2	1.7 ± 0.3	1.7 ± 0.2	1.7 ± 0.2
Apo A-I (g/L)	1.5 ± 0.3	1.5 ± 0.2	1.5 ± 0.3	1.5 ± 0.3
HsCRP (mg/L) ^c	2.1 ± 3.0	2.5 ± 3.7	3.3 ± 4.3	2.5 ± 2.9
Fibrinogen (µmol/L) ^c	11.7 ± 3.7	11.8 ± 2.8	11.5 ± 3.0	12.0 ± 2.8

^aData are presented as mean ± SD or frequency unless otherwise indicated.

^bPatients were diagnosed with metabolic syndrome according to NCEP ATP III criteria (2).

^cMedian ± SD for median.

To convert cholesterol from mmol/L to mg/dL, divide by 0.0259; to convert TG from mmol/L to mg/dL, divide by 0.0113; to convert fibrinogen from µmol/L to mg/dL, divide by 0.0294.

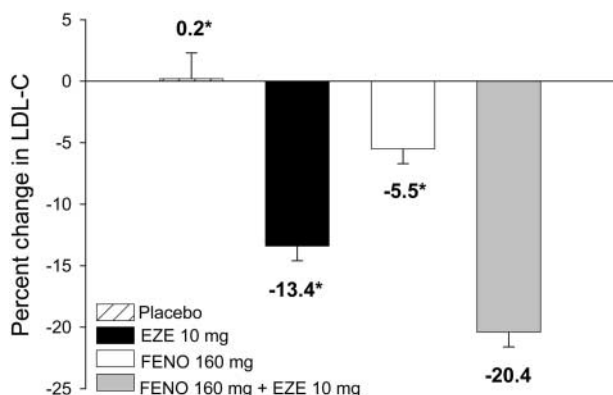


Figure 1 Least square mean per cent change (SE) in LDL-C from baseline to study endpoint. Reductions in LDL-C were greater in the FENO + EZE group compared with the other treatment groups (**P* < 0.001 compared with FENO + EZE).

At baseline, >70% of patients had the small, dense LDL size pattern B in all treatment groups (Table 4). Treatment with FENO + EZE and FENO alone resulted in a majority of patients shifting to a larger, more buoyant, LDL size pattern compared with EZE alone and placebo. There was a modestly greater shift from a more dense to a more buoyant LDL size pattern for patients in the EZE group (22.4%) vs. those in the placebo group (11.9%) at study endpoint. Furthermore, <2% of patients in the coadministration and FENO alone groups changed from a more buoyant pattern to a more dense, atherogenic pattern at study endpoint.

Safety and tolerability

The incidence of AEs was similar in all treatment groups (Table 5). Treatment-related AEs were slightly higher in

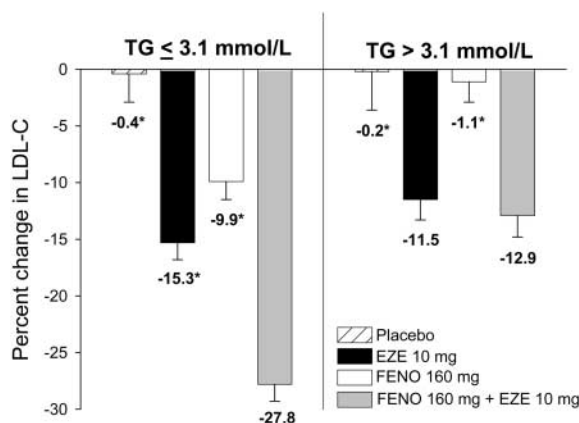


Figure 2 Least square mean per cent change (SE) in LDL-C from baseline to study endpoint for patients with baseline TG ≤ or >3.1 mmol/L (median). Significantly greater reductions in LDL-C (**P* < 0.001 for FENO + EZE compared with FENO) were observed within both TG subgroup.

the coadministration and FENO alone groups compared with the EZE alone and placebo groups. A similar trend was noted for discontinuations because of treatment-related AEs. There were no treatment-related serious AEs in this study.

No cases of elevated CK more than 10-fold, myopathy, rhabdomyolysis, or pancreatitis were reported in this 12 week study (Table 5). The incidence of gastrointestinal or musculoskeletal disorders was generally similar among treatment groups. The incidence of myalgia was similar in all treatment groups with 2 (3.1%), 3 (1.6%), 2 (1.1%), and 3 (1.6%) in the placebo, EZE, FENO, and FENO + EZE treatment groups, respectively. There were four cases of consecutive more than three-fold elevations

Table 3 Per cent change from baseline to study endpoint in lipid, apo, and non-lipid parameters

Variables ^a	Placebo (n = 61)	EZE 10 mg (n = 173)	FENO 160 mg (n = 179)	FENO 160 mg/EZE 10 mg (n = 175)
TC	0.2 (a) (-2.6, 3.0)	-11.8 (b) (-13.5, -10.2)	-10.8 (b) (-12.4, -9.2)	-22.4 (c) (-24.0, -20.8)
HDL-C	3.2 (a) (-0.9, 7.3)	3.9 (a) (1.6, 6.3)	18.8 (b) (16.4, 21.2)	19.0 (b) (16.7, 21.4)
TG ^b	-9.2 (a) (-18.8, 0.5)	-11.1 (a) (-15.8, -6.5)	-43.2 (b) ^c (-47.1, -39.2)	-44.0 (c) (-48.0, -40.1)
Non-HDL-C	-0.2 (a) (-3.6, 3.2)	-14.7 (b) (-16.7, -12.8)	-16.2 (b) (-18.2, -14.3)	-30.4 (c) (-32.4, -28.4)
Apo B	-1.2 (a) (-4.7, 2.3)	-11.3 (b) ^d (-13.4, -9.3)	-15.2 (c) (-17.3, -13.2)	-26.1 (d) (-28.2, -24.0)
Apo A-I	0.4 (a) (-3.6, 4.3)	0.9 (a) (-1.4, 3.2)	8.4 (b) (6.1, 10.7)	9.6 (b) (7.3, 12.0)
HsCRP ^b	9.1 (a) (-5.9, 24.1)	-6.1 (a) (-16.4, 4.3)	-28.0 (b) (-36.5, -19.5)	-27.3 (b) (-35.0, -19.5)
Fibrinogen ^b	-0.3 (a) (-6.3, 5.7)	-0.3 (a) (-2.8, 2.2)	-10.1 (b) (-12.4, -7.9)	-11.5 (b) (-14.0, -8.9)

For any comparison within a row, significant between-treatment differences are denoted by different online letters [e.g. within the first row, '(b)' means significantly different compared with '(a)' and '(c)', '(c)' significant compared with '(a)' and '(b)'] ($P < 0.001$ unless otherwise indicated by a symbol).

^aData are presented as least square mean per cent change (95% CI) unless otherwise indicated.

^bMedian per cent change (95% CI).

^c $P = 0.021$ compared with FENO + EZE.

^d $P = 0.009$ compared with FENO.

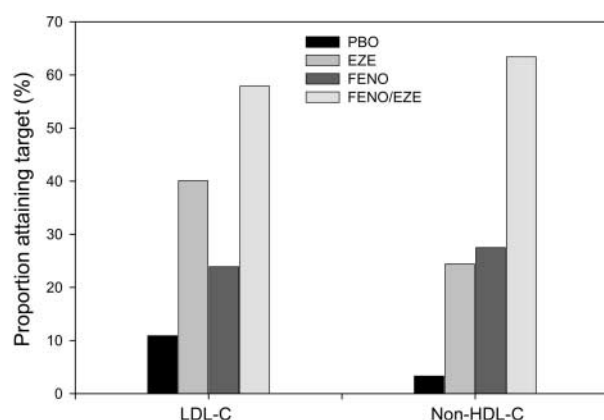


Figure 3 Proportion of patients attaining CHD risk-specific, NCEP ATP III LDL-C, and non-HDL-C treatment targets at study endpoint.

in ALT and/or AST in each of the FENO + EZE and FENO alone groups (Table 5). One patient in the coadministration group discontinued treatment after diagnosis of acute cholecystitis and cholelithiasis; the investigator determined that these adverse events were not related to study medications and were resolved after a cholecystectomy. One case of angio-oedema was reported in the FENO alone group and upon discontinuation of study medication the symptoms resolved. One patient in the EZE group was discontinued 21 days after randomization because of lack of efficacy (defined as on-treatment TG >6.8 mmol/L). The incidence of patients with serum creatinine ≥ 133 μ mol/L was significantly ($P < 0.05$) lower for the EZE group (2.7%) compared with those for the coadministration and FENO alone groups (8.7 vs.

8.5%, respectively), which were not significantly different from each other. No clinically meaningful differences were noted in any other clinical and laboratory AEs or tests assessed.

Discussion

Patients with mixed hyperlipidaemia have an atherogenic lipid profile characterized by increased LDL-C and TG levels, a preponderance of small, dense LDL particles, and also reduced HDL-C concentrations. The lipid triad (elevated LDL-C and TG and low HDL-C) increases the risk of CHD events beyond that of increased LDL-C alone.¹⁵ Furthermore, LDL particle size has been demonstrated to influence the progression of CAD in patients with type 2 diabetes.¹⁶ The lipid-modifying effects of EZE and FENO effectively target the dyslipidaemia associated with mixed hyperlipidaemia. In the present study, FENO and EZE administered together produced significant, positive benefits on the atherogenic lipid profiles and the inflammation biomarker, hsCRP, in patients with mixed hyperlipidaemia. Depending on the study variable, the effects of coadministration of FENO + EZE were either additive (LDL-C, TC, non-HDL-C, and apo B) or FENO-dependent (TG, HDL-C, apo A-I, hsCRP, fibrinogen, and LDL size pattern shift). Moreover, coadministered FENO + EZE demonstrated a good safety profile that was comparable to FENO alone.

Per cent reduction in LDL-C was greater with EZE treatment compared with FENO alone, but LDL-C reduction was additive when both FENO and EZE were used together. However, the change in LDL-C was influenced

Table 4 Change in LDL size pattern with treatment in patients with mixed hyperlipidaemia

LDL size pattern ^a	Placebo (n = 59)	EZE 10 mg (n = 165)	FENO 160 mg (n = 170)	FENO 160 mg/EZE 10 mg (n = 165)
Frequency at baseline, n (%)				
Pattern A	10 (16.9)	20 (12.1)	25 (14.7)	29 (17.6)
Pattern B	41 (69.5)	128 (77.6)	127 (74.7)	123 (74.5)
Pattern I (intermediate pattern)	8 (13.6)	17 (10.3)	18 (10.6)	13 (7.9)
Frequency of LDL size pattern change from baseline to study endpoint n (%)				
More dense → more buoyant ^b	7 (11.9)	37 (22.4)	106 (62.3)	106 (64.2)
No change	46 (77.9)	113 (68.5)	61 (35.9)	57 (34.6)
More buoyant → more dense ^c	6 (10.2)	15 (9.1)	3 (1.8)	2 (1.2)

^a LDL size pattern assessed using segmented gradient gel electrophoresis method.

^b Includes shifts in LDL size patterns from B → A, I → A, and B → I (less atherogenic shift).

^c Includes shifts in LDL size patterns from A → I, A → B, and I → B (more atherogenic shift).

Table 5 Safety and tolerability assessment

n (%) ^a	Placebo (n = 64)	EZE 10 mg (n = 187)	FENO 160 mg (n = 189)	FENO 160 mg/EZE 10 mg (n = 185)
All AEs	30 (46.9)	84 (44.9)	92 (48.7)	90 (48.6)
Treatment-related AEs	5 (7.8)	12 (6.4)	27 (14.3)	21 (11.4)
SAEs	0 (0)	4 (2.1)	1 (<1)	5 (2.7)
Treatment-related SAEs	0 (0)	0 (0)	0 (0)	0 (0)
Discontinuation due to AEs	0 (0)	4 (2.1)	9 (4.8)	7 (3.8)
Discontinuation due to treatment-related AEs	0 (0)	1 (<1)	6 (3.2)	4 (2.2)
Discontinuations due to SAEs	0 (0)	2 (1.1)	0 (0)	2 (1.1)
Special AEs of interest				
ALT and/or AST > 3×ULN (consecutive)	1 (1.6)	1 (<1)	4 (2.1)	4 (2.2)
CK > 10×ULN	0	0	0	0
Myopathy	0	0	0	0
Cholecystectomy	0	0	0	1 (<1) ^b
Pancreatitis	0	0	0	0
Angio-oedema	0	0	1 (<1)	0

SAEs, Serious AEs.

^aAlthough a patient may have had two or more adverse experiences, the patient is only counted once within a category. The same patient may appear in different categories.

^bInvestigator determined that the acute cholecystitis and cholelithiasis that preceded the cholecystectomy was not treatment-related.

by baseline TG levels in patients with mixed hyperlipidaemia in the present study. Greater LDL-C lowering was noted with all active treatments in patients with baseline TG ≤ 3.1 mmol/L. In contrast, in the high TG subgroup, FENO treatment produced virtually no change in LDL-C, whereas the effect of EZE was maintained. The coadministration provided comparable LDL-C reductions to EZE alone probably driven by the limited response to FENO monotherapy. The per cent of patients achieving LDL-C treatment targets was consistent with the LDL-C response data in that baseline TG appeared to influence the results. For patients with elevated TG, change in other apo-B containing lipoprotein parameters, non-HDL-C and apo B rather than LDL-C may be a better indicator of treatment response.¹⁷ In the present study, the effects of coadministration of FENO + EZE on non-HDL-C and apo B were additive with coadministration and not affected by baseline TG levels. Similarly, non-HDL-C goal attainment was comparable across baseline

TG strata in the present study. In agreement, a pooled analysis of patients on fluvastatin and fibrate demonstrated that reductions in non-HDL-C were unaffected by baseline TG levels, whereas LDL-C response to coadministration was significantly blunted with increasing TG levels.¹⁸

Similar results of additive reductions for apo B-containing lipoproteins have been demonstrated with coadministration of statin and FENO. Coadministration of simvastatin 20 mg and FENO 160 mg produced additional reductions in LDL-C, non-HDL-C, TC, and apo B when compared with simvastatin 20 mg alone in patients with combined hyperlipidaemia.¹⁹ Athyros *et al.*²⁰ reported that coadministration of atorvastatin 20 mg and FENO 200 mg produced significant reductions in LDL-C, TC, and apo B beyond either treatment alone in the type 2 diabetic patient with combined hyperlipidaemia. In patients with severe mixed hyperlipidaemia, atorvastatin 40 mg plus FENO 200 mg lowered LDL-C, TC, and apo B

more than either monotherapy.²¹ Conversely, the addition of FENO to simvastatin did not result in significant incremental reductions in LDL-C, TC, non-HDL-C, or apo B beyond that of simvastatin monotherapy in patients with both combined hyperlipidaemia and metabolic syndrome.²² Due to paradoxical increases in LDL-C levels with FENO therapy noted in patients with severely elevated TG,⁴ the high upper end of the TG entry criteria [9.0 mmol/L (800 mg/dL)], in Vega *et al.*,²² may have contributed to the small, non-significant changes in the apo B-containing particles with the addition of FENO treatment to statin therapy. Differences in patient selection may also account for the discrepant results between studies. Overall, these and the present study data suggest that combining an LDL-C-lowering therapy with FENO produced additional cholesterol reductions in apo B-containing lipoproteins.

Consistent LDL-C responses across age, race, and BMI were demonstrated with treatments in the present study. The LDL-C reductions were different between genders, high or low baseline lipid values, and diabetes status. Differences in baseline TG within these subgroups may account for the disparate responses to treatments. Further study will be needed to determine if the gender-related differences may be due to differences in body composition, plasma TG concentrations, and/or the hormonal milieu.

The coadministration of FENO + EZE resulted in comparable improvements in HDL-C and apo A-I when compared with FENO alone. There was significant reduction in TG with FENO + EZE vs. FENO alone, but this slight difference was not considered clinically meaningful. Similarly, the reductions in hsCRP and fibrinogen also appear to be a FENO-dependent effect. The pharmacokinetic profile of FENO was not affected with coadministration of EZE.¹⁴ Thus it was expected that EZE would not interfere with the therapeutic actions of FENO. The HDL-C and TG results of the present study were consistent with those that used fibrates with statins.^{23,24} EZE produced significant changes in apo B-containing lipoproteins and FENO improved TG and HDL-C, thus this drug combination may effectively treat the lipid triad associated with mixed hyperlipidaemia.

Mixed hyperlipidaemia is also associated with the preponderance of small, dense LDL particles (LDL size pattern B). At baseline, a majority of patients with mixed hyperlipidaemia presented with the LDL size pattern B in the present study. More than 62% of patients shifted to the larger, more buoyant LDL pattern from the smaller, more dense pattern with coadministration, and FENO alone treatments. This is in agreement with the reported effects of FENO on LDL particle size noted with patients with type 2 diabetes.²⁵ Slight improvement in the LDL size pattern was noted in the EZE group compared with placebo. The shift from an LDL size pattern that was more dense to more buoyant is consistent with an improvement in atherogenic dyslipidaemia.

Coadministration of drug therapies may produce synergistic effects, including toxicity.²⁶ EZE monotherapy has demonstrated a safety profile similar to placebo in patients with primary hypercholesterolaemia.¹⁰⁻¹² FENO

monotherapy is well tolerated, but may increase hepatic enzymes, biliary cholesterol concentration, gallstone formation, and the risk of myopathy.⁴ In a small pilot study, FENO significantly increased steady state exposure of total EZE by ~50%, which was not considered clinically relevant, and EZE did not significantly affect FENO pharmacokinetics.¹⁴ As the previous experience with coadministration of FENO + EZE was only 2 weeks in duration, the safety and tolerability of this combination were also evaluated over the 12 week period in the present study.

In patients with mixed hyperlipidaemia, the coadministration of FENO + EZE did not seem to influence the rate of AEs beyond that noted with FENO alone. The treatment-related AEs were also similar between the FENO + EZE and the FENO alone groups. The proportion of patients with consecutive elevations in liver function tests (ALT and/or AST >3×ULN) or serum creatinine ≥133 μmol/L was similar between the FENO + EZE and FENO, but greater than the proportion noted with EZE treatment. Increases in serum creatinine have been observed with FENO monotherapy.⁴ There were no cases of hepatitis in the study. One patient on FENO + EZE was discontinued after being diagnosed with cholelithiasis and subsequent cholecystectomy. The present study was, however, too small and short in duration to determine the effect of coadministration on the incidence of gallbladder-related disease. A long-term safety assessment of coadministration of FENO + EZE is part of an on-going, 48 week extension of the current study. Another patient in the FENO treatment group discontinued after developing angio-oedema. There were, however, no serious AEs related to any treatment. No cases of pancreatitis were recorded in these patients with moderately elevated TG. No cases of death, rhabdomyolysis, myopathy, and CK elevations >10×ULN were reported in the present study. Overall, treatment with FENO + EZE was well tolerated with a safety profile comparable to FENO alone.

Conclusions

The coadministration of EZE with FENO offers a well-tolerated, new lipid management strategy for patients with mixed hyperlipidaemia in this study. The combined use of these agents provides a therapy with complementary effects to improve the atherogenic lipid profile observed for these patients.

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Appendix

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Hyperlipidemia and Metabolic Syndrome

Safety and Efficacy of Long-Term Co-Administration of Fenofibrate and Ezetimibe in Patients With Mixed Hyperlipidemia

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OBJECTIVES	This study sought to determine the long-term safety and efficacy of co-administered fenofibrate (FENO) and ezetimibe (EZE) in patients with mixed hyperlipidemia.
BACKGROUND	Both EZE and FENO offer complementary benefits to the lipid profile of patients with mixed hyperlipidemia.
METHODS	After completing the 12-week randomized, double-blind base study that compared EZE 10 mg, FENO 160 mg, FENO 160 mg plus EZE 10 mg, and placebo in patients with mixed hyperlipidemia, patients continued into a double-blind, 48-week extension phase. Those patients in the FENO plus EZE and FENO groups continued on their respective base study treatment, and patients in the EZE and placebo groups were switched to FENO plus EZE and FENO, respectively.
RESULTS	Of the 587 patients who completed the base study, 576 continued into the extension study (n = 340 in FENO plus EZE and n = 236 in FENO). The FENO plus EZE produced significantly greater reductions in low-density lipoprotein-cholesterol compared with FENO (−22% vs. −9%, respectively; p < 0.001). There were also significantly greater improvements in triglycerides, high-density lipoprotein cholesterol (HDL-C), total cholesterol, non-HDL-C, and apolipoprotein B with FENO plus EZE compared with FENO. Changes in apolipoprotein A-I and high-sensitivity C-reactive protein were similar between groups. Overall, FENO plus EZE was well tolerated during the extension study. The proportion of patients with consecutive elevations of alanine aminotransferase/aspartate aminotransferase ≥3 times upper limit of normal were similar between the FENO plus EZE (1.2%) and FENO (1.7%) groups. No cases of creatine phosphokinase elevations ≥10 times upper limit of normal or myopathy were observed in either group.
CONCLUSIONS	Long-term, 48-week co-administration of FENO plus EZE was well tolerated and more efficacious than FENO in patients with mixed hyperlipidemia. (J Am Coll Cardiol 2006;47:1584–7) © 2006 by the American College of Cardiology Foundation

The cholesterol absorption inhibitor ezetimibe (EZE) effectively lowers low-density lipoprotein cholesterol (LDL-C) by inhibiting the intestinal absorption of dietary and biliary cholesterol without affecting absorption of triglycerides or fat-soluble vitamins (1). Fibrates have favorable effects on triglycerides, high-density lipoprotein cholesterol (HDL-C), and LDL particle size (2). Recently in patients with mixed hyperlipidemia, 12-week co-administration of fenofibrate (FENO) plus EZE was well tolerated and produced significant improvements in lipid profiles compared with either FENO or EZE alone (3). Thus, in the short term, the co-administration of FENO plus EZE, through their com-

plementary mechanisms of action, provides another therapeutic option for treating patients with mixed hyperlipidemia. The present study examined the long-term safety and efficacy of co-administered FENO plus EZE in patients with mixed hyperlipidemia over 48 weeks.

METHODS

Study design. Study design and results for the 12-week base study were published previously (3). For the base study, mixed hyperlipidemia was defined as a baseline LDL-C level of 130 to 220 mg/dl inclusive (100 to 180 mg/dl for patients with type

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Lederle, Marion Merrell Dow, Merck, Merck Schering Plough, Miles, Novartis, Parke Davis, Pfizer, Pliva, Purdue, Reliant, Roche, Rorer, Regeneron, Sandoz, Sankyo, Sanofi, Searle, Shering Plough, SmithKline Beecham, Takeda, TAP, UpJohn, Upsher Smith, Warner Lambert, and Wyeth-Ayerst. He has also served as a consultant, speaker, and/or advisor to and for pharmaceutical companies such as AstraZeneca, Aventis, Bayer, Bristol Myers Squibb, KOS, Merck, Merck Schering Plough, Metabasis Therapeutics, Microbia, Novartis, Ortho-McNeil, Parke Davis, Pfizer, Roche, Sandoz, Sankyo, Sanofi Aventis, Shering Plough, SmithKline Beecham, Takeda, UpJohn, and Warner Lambert. Drs. Perevovskaya, Carlson, Davies, Mitchel, and Gumbiner are employees of Merck and may hold stocks or stock options in Merck.

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Abbreviations and Acronyms

AE	=	adverse experience
ALT	=	alanine aminotransferase
AST	=	aspartate aminotransferase
CPK	=	creatinine phosphokinase
EZE	=	ezetimibe
FENO	=	fenofibrate
HDL-C	=	high-density lipoprotein-cholesterol
hs-CRP	=	high-sensitivity C-reactive protein
LDL-C	=	low-density lipoprotein-cholesterol
TC	=	total cholesterol
ULN	=	upper limit of normal

2 diabetes) and a baseline triglyceride level of 200 to 500 mg/dl inclusive. After completing the 12-week base study, which compared EZE 10 mg, FENO 160 mg, FENO 160 mg plus EZE 10 mg, and placebo, patients continued into the 48-week double-blind extension study unless there was a condition that would interfere with the patient's ability to participate. Patients in the FENO plus EZE and FENO groups continued on their respective base study treatment, and those in the EZE and placebo groups were switched to FENO plus EZE and FENO, respectively. All patients were instructed to continue following the National Cholesterol Education Program (NCEP) Step I or comparable diet throughout the study. Follow-up visits were conducted at weeks 6, 12, 24, 36, and 48 of the extension study.

Safety assessment. Safety and tolerability were evaluated by adverse experiences (AEs), laboratory measurements (specifically alanine aminotransferase [ALT], aspartate aminotransferase [AST], and creatine phosphokinase [CPK] levels), and physical examination findings for only the 48-week extension study. Results were not combined with the 12-week base study. The study investigators assessed the potential relationship of all AEs to drug treatment while blinded to treatment assignment (Appendix). The AEs of clinical interest that resulted in discontinuation included: consecutive, unexplained elevations of CPK ≥ 10 times the upper limit of normal (ULN) or ALT/AST ≥ 3 times ULN; myopathy (muscle symptoms accompanied by CPK ≥ 10 times ULN); persistent elevations in serum creatinine >1.8 mg/dl or $>30\%$ above the baseline value from base study for patients with baseline creatinine levels >1.0 mg/dl; persistent elevations in creatinine $>50\%$ above the baseline value of base study for patients with baseline creatinine levels ≤ 1.0 mg/dl. Beginning at week 12 of the extension, if the LDL-C concentration was >15 mg/dl above the patient's NCEP Adult Treatment Panel III risk-specific LDL-C target as established at baseline, the patient was discontinued for lack of efficacy.

Efficacy assessments. The primary efficacy variable was percent change in LDL-C from baseline of the base study to study end point in the extension. Secondary efficacy end points included percent change from baseline to study end point in total cholesterol (TC), HDL-C, triglycerides, non-HDL-C, apolipoprotein B, apolipoprotein A-I, and high-sensitivity C-reactive protein (hs-CRP).

Laboratory measurements. A central laboratory performed all clinical laboratory analyses of safety and efficacy variables as described previously (3).

Statistical analyses. Inferential testing was limited to a pre-specified number of safety parameters, including myopathy, persistent ALT and/or AST elevations ≥ 3 times ULN, persistent CPK elevations ≥ 10 times ULN, planned or performed cholecystectomy (pooled end point including performed cholecystectomy or diagnosed cholecystitis, cholangitis, or cholelithiasis), and serum creatinine ≥ 1.5 mg/dl. Proportions of patients were compared between treatments with the Fisher exact test. Given the differences in average duration of exposure to active therapy between groups in the present study, examining the crude incidence rates may be misleading. Therefore, adjusted incidence rates per 1,000 patient-years were calculated for the pre-specified safety parameters listed above based on cumulative patient-years available for each treatment (i.e., adjusted incidence rate = number of events/exposure [expressed in 1,000 patient-years]). The efficacy analysis was an all-patients-treated approach with an end point defined as percent change from baseline to the average of all measurements available throughout extension. A parametric analysis of covariance (ANCOVA) model with terms for treatment and baseline triglyceride values was used to compare each efficacy variable between treatment groups. Because triglycerides and hs-CRP were not normally distributed, a non-parametric ANCOVA was used to assess between-group differences. Least-squares mean or median differences between treatment groups with corresponding 95% CIs were summarized.

Table 1. Baseline* Summary of Patient Demographics, Lipid Parameters, and hs-CRP

Study Variable	FENO (n = 236)	FENO + EZE (n = 340)
Age, yrs	52.9 (10.4)	54.1 (9.5)
Patients ≥ 65 yrs, n (%)	34 (14.4)	53 (15.6)
Gender, n (%)		
Male	139 (58.9)	192 (56.5)
Female	97 (41.1)	148 (43.5)
Body mass index	29.3 (4.4)	29.5 (4.6)
Type 2 diabetes, n (%)	33 (14.0)	60 (17.6)
Metabolic syndrome, n (%)	138 (59.0)	190 (55.9)
LDL-C, mg/dl	164.1 (27.9)	159.7 (27.7)
HDL-C, mg/dl	41.9 (9.5)	41.7 (8.8)
Triglycerides,† mg/dl	277.0 (86.5)	275.0 (101.6)
TC, mg/dl	264.4 (33.5)	259.9 (32.2)
Non-HDL-C, mg/dl	222.6 (31.8)	218.2 (31.0)
Apo B, mg/dl	171.3 (25.0)	167.8 (24.5)
Apo A-I, mg/dl	151.0 (28.5)	149.1 (25.7)
hs-CRP,† mg/l	3.0 (4.0)	2.5 (3.1)

*Baseline values as recorded in the base study (reference 3). Data are expressed as mean (standard deviation [SD]) or frequency unless otherwise indicated. †Values are median (robust SD for median).

Apo = apolipoprotein; hs-CRP = high-sensitivity C-reactive protein; EZE = ezetimibe; FENO = fenofibrate; HDL-C = high-density lipoprotein-cholesterol; hs-CRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein-cholesterol; TC = total cholesterol.

Table 2. Disposition of Patients Entered Into the 48-Week Extension Study

	FENO (n = 236)	FENO + EZE (n = 340)
Patient completed	87 (36.9)	230 (67.6)
Patient discontinued	149 (63.1)	110 (32.4)
Due to lack of efficacy*	120 (50.8)	82 (24.1)
Due to clinical adverse experience	7 (3.0)	5 (1.5)
Due to laboratory adverse experience	7 (3.0)	10 (2.9)
Due to other reasons†	15 (6.4)	13 (3.8)

Data are expressed as n (%). *Lack of efficacy was defined as LDL-C >15 mg/dl above NCEP ATP III risk-specific LDL-C goal at week 12 or later during the extension. †Other reasons include patients who withdrew consent, moved, deviated from protocol, or were lost to follow-up.

NCEP ATP III = U.S. National Cholesterol Education Program Adult Treatment Panel III; other abbreviations as in Table 1.

RESULTS

Of the 587 patients who completed the 12-week base study, 576 patients continued into the 48-week extension study (N = 340 for FENO plus EZE and N = 236 for FENO; Table 1). During the extension phase, a greater proportion of participants in the FENO group discontinued treatment compared with those in the FENO plus EZE group, primarily because of the failure to meet the LDL-C efficacy criterion (Table 2). Thus, average exposure to study treatment was less in the FENO group (212.3 days) compared with the FENO plus EZE group (271.3 days).

The FENO plus EZE resulted in significantly greater percent reductions from baseline to average extension end point in LDL-C, TC, triglycerides, non-HDL-C, and apolipoprotein B compared with FENO (Table 3). The percent increase in HDL-C, but not apolipoprotein A-I, was significantly greater with FENO plus EZE versus FENO. Reductions in median hs-CRP levels were not different between treatments.

The FENO plus EZE was well tolerated during the 48-week extension study. Both groups were similar with regard to incidence of treatment-related AEs and discontinuations because of treatment-related AEs, respectively (Table 4). Five patients had treatment-related serious AEs

Table 4. Safety and Tolerability Summary for 48-Week Extension Study

Number (%) of Patients With	FENO (n = 236)	FENO + EZE (n = 340)
One or more AEs	145 (61.4)	229 (67.4)
Treatment-related AEs	38 (16.1)	47 (13.8)
SAEs	14 (5.9)	23 (6.8)
Treatment-related SAEs	3 (1.3)	2 (0.6)
Deaths	0 (0.0)	1 (0.3)
Discontinuations due to AEs	14 (5.9)	15 (4.4)
Discontinuations due to treatment-related AEs	13 (5.5)	13 (3.8)
Discontinuations due to SAEs	2 (0.9)	3 (0.8)
Discontinuations due to treatment-related SAEs	2 (0.9)	2 (0.6)
AEs of interest		
ALT and/or AST ≥3 times ULN consecutive	4/235 (1.7)	4/337 (1.2)
CPK ≥10 times ULN	0/235	0/337
Myopathy	0	0
Planned or performed cholecystectomy	1 (0.4)	4 (1.2)
Serum creatinine ≥1.5 mg/dl	21/235 (8.9)	36/338 (10.7)

AEs = adverse experiences; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; SAEs = serious adverse experiences; ULN = upper limit of normal; other abbreviations as in Table 1.

in the extension study: three in the FENO group (angio-neurotic edema, pancreatitis, polyarthropathy) and two in the FENO plus EZE group (cholangitis, cholecystitis). A patient on FENO plus EZE died in the extension study from a cerebral hemorrhage that the investigator reported was definitely not caused by study treatment.

No patient experienced CPK elevations ≥10 times ULN or myopathy. The proportion of patients with consecutive elevations of ALT and/or AST ≥3 times ULN was low and similar between treatment groups (Table 4). The proportion of patients with planned or performed cholecystectomy was not significantly different between treatments (Table 4). To account for differences in exposure to treatments, rates of planned or performed cholecystectomy were adjusted for exposure (expressed in 1,000 patient-years) and were still not signifi-

Table 3. Comparison of the Lipid and hs-CRP Effects of FENO and FENO Plus EZE With Regard to Percent Change From Baseline Values in the Base Study* to the End Point Values in the Extension Study

Parameter	Extension Study		p Value
	FENO (n = 235)	FENO + EZE (n = 337)	
LDL-C	-8.6 (-10.6 to -6.5)	-22.0 (-23.7 to -20.3)	<0.001
HDL-C	17.8 (15.9 to 19.8)	20.9 (19.2 to 22.5)	0.02
Triglycerides†	-41.8 (-44.9 to -38.7)	-46.0 (-48.2 to -43.8)	0.002
TC	-13.6 (-15.0 to -12.1)	-23.2 (-24.4 to -22.0)	<0.001
Non-HDL-C	-19.4 (-21.2 to -17.6)	-31.6 (-33.1 to -30.1)	<0.001
Apo B	-16.2 (-18.5 to -13.9)	-25.2 (-27.1 to -23.3)	<0.001
Apo A-I	7.8 (5.5 to 10.1)	10.1 (8.2 to 12.0)	0.12
hs-CRP†	-21.1 (-29.0 to -13.1)	-25.3 (-33.1 to -17.5)	0.46

*Baseline values were recorded at the beginning of the base study (reference 3); data are expressed as least-squares mean percent change (95% CI). †Median percent change (95% CI); for apolipoproteins B and A-I, n = 217 for FENO and n = 321 for FENO + EZE; for hs-CRP, n = 221 for FENO and n = 326 for FENO + EZE.

Abbreviations as in Table 1.

cantly different between FENO plus EZE and FENO groups (15.9 per 1,000 patient-years [95% CI 4.3 to 40.7] vs. 7.3 per 1,000 patient-years [95% CI 0.2 to 40.6], respectively). The proportion of patients with serum creatinine ≥ 1.5 mg/dl was not significantly different between groups (Table 4). The results of all other measures of safety did not suggest any clinically meaningful differences between treatment groups.

DISCUSSION

Co-administration of FENO plus EZE provided superior lipid-altering effects compared with FENO during the 48-week extension study. In the present study, FENO plus EZE produced an incremental LDL-C reduction of 13.5% compared with FENO. This was consistent with the incremental reduction observed for FENO plus EZE versus FENO in the base study (3) and also that observed with EZE plus statin versus statin monotherapy (4). Improvements in TC, non-HDL-C, TG, HDL-C, and apolipoprotein B were also greater in the co-administration group. The results from the extension study were generally consistent with those from the base study, and the small differences in efficacy between studies (TG and HDL-C) may be because the extension study was not randomly assigned and was imbalanced.

The safety profile for long-term co-administration of FENO plus EZE was similar to that of FENO in this study. Groups did dramatically differ in the overall rate of discontinuations, which was mainly attributable to an imbalance in the number of patients who discontinued because of the protocol-specified lack of LDL-C efficacy criterion used in the extension, which was more than double in the FENO group versus the FENO plus EZE group. This imbalance was related to the greater lipid efficacy of FENO plus EZE compared with FENO. As a result of this difference, patients in the FENO plus EZE group averaged approximately 8.5 more weeks of treatment exposure than those in the FENO group.

No clinically important elevations in CPK or cases of myopathy were observed in either treatment group during the extension. The incidence of elevated ALT and/or AST levels ≥ 3 times ULN was low and was not different between treatment groups. Fenofibrate increases cholesterol excretion into the bile, which may lead to cholelithiasis (5). Ezetimibe has inconsistent effects on biliary cholesterol in animal models (6). There seems, however, to be no evidence, based on short-term clinical study data available to date, that EZE monotherapy increases the risk of gallstones in patients with primary hypercholesterolemia (1,7,8). In this study, most randomized patients had numerous risk factors, including hyperlipidemia, obesity, age, female gender, and type 2 diabetes, that would predispose them to an increased risk for gallstones (9). Patients were excluded from the present study for a history of gallbladder disease and not previously having been treated with cholecystectomy. The proportion of patients with performed or planned cholecystectomy was not significantly different between groups when

expressed as either the proportion of patients with events or the incidence rates adjusted for group differences in patient exposure to treatments. This study was, however, not designed to assess infrequently occurring AEs such as cholecystectomy, and only a much larger, longer-term study could conclusively assess these infrequent biliary AEs.

Although modest increases in the incidence of serum creatinine level ≥ 1.5 mg/dl were found in both treatment groups, the proportion of patients with these elevated creatinine levels did not differ between groups. The increase in both groups might have been anticipated, because FENO is known to increase creatinine levels (5). The overall safety profile of co-administered FENO plus EZE in this longer-term 48-week study was consistent with the findings in the shorter 12-week base study (3). Furthermore, considering the greater mean duration of treatment exposure for patients in the FENO plus EZE group compared with those in the FENO group in this study, the comparable safety findings between treatment groups support co-administration of FENO plus EZE as a well-tolerated therapy.

In summary, the long-term FENO plus EZE therapy was a more effective treatment option than FENO, and was well-tolerated for up to 48 weeks of treatment for patients with mixed hyperlipidemia in this study.

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APPENDIX

For a list of the extension study investigators, please see the online version of this article.