

Efficacy and Safety of Ezetimibe Added to Ongoing Statin Therapy for Treatment of Patients With Primary Hypercholesterolemia

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Ezetimibe is a lipid-lowering drug that inhibits the intestinal absorption of dietary and biliary cholesterol by blocking passage across the intestinal wall. The efficacy and safety of adding ezetimibe to ongoing statin therapy in patients with primary hypercholesterolemia was evaluated in a randomized, double-blind, placebo-controlled study. The study group included 769 adults (aged ≥ 18 years) with primary hypercholesterolemia who had not achieved National Cholesterol Education Program (NCEP) Adult Treatment Panel II goals with dietary alteration and statin monotherapy. Patients receiving a stable dose of a statin for ≥ 6 weeks were randomized to receive concurrent treatment with placebo ($n = 390$) or ezetimibe ($n = 379$), 10 mg/day, in addition to continuing their open-label statin for 8 weeks. The primary efficacy variable was the percent change in low-density lipoprotein (LDL) cholesterol from baseline with statin monotherapy to end point after intervention (secondary variables: high-density lipoprotein [HDL] cholesterol and

triglycerides). Ongoing statin therapy plus ezetimibe led to changes of -25.1% for LDL cholesterol (HDL cholesterol $+2.7\%$; triglycerides -14.0%) compared with LDL cholesterol -3.7% ($p < 0.001$), HDL cholesterol $+1.0\%$ ($p < 0.05$), and triglycerides -2.9% ($p < 0.001$) for placebo added to ongoing statin therapy. Among patients not at LDL cholesterol goal at on-statin baseline, 71.5% receiving statin plus ezetimibe versus 18.9% receiving statin plus placebo reached goal at end point (odds ratio 23.7; $p < 0.001$). The co-administration of statin and ezetimibe was generally well tolerated. Adding ezetimibe to ongoing statin therapy led to substantial additional reduction in LDL cholesterol levels, facilitating attainment of NCEP goals. Ezetimibe offers a new therapeutic option for patients receiving statins who require further reduction in LDL cholesterol. ©2002 by Excerpta Medica, Inc.

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Ezetimibe is a new agent that inhibits the intestinal absorption of cholesterol from dietary and biliary sources by impeding the transport of cholesterol across the intestinal wall.^{1,2} Ezetimibe does not affect the absorption of bile acids, fatty acids, fat-soluble vitamins, or triglycerides.^{3,4} Ezetimibe has a half-life of about 22 hours, conducive to once-daily administration. Clinically important gender, age, or food effects have not been observed, nor does ezetimibe inhibit or induce cytochrome P450 (including CYP 3A4) or N-acetyltransferase enzyme systems.^{5,6} No clinically relevant drug-drug interactions have been

associated with ezetimibe administration, including statins.⁷⁻¹³ Combining a potent intestinal cholesterol absorption inhibitor with a statin offers the theoretical advantage of incremental lipid lowering resulting from complementary mechanisms of action.^{1,9}

Data from 2 large, replicate studies of monotherapy with ezetimibe 10 mg/day involving 1,719 hypercholesterolemic patients demonstrated a mean reduction in low-density lipoprotein (LDL) cholesterol of 19.1% relative to placebo, in conjunction with reductions in triglycerides and increases in high-density lipoprotein (HDL) cholesterol.^{14,15} Ezetimibe was well tolerated, with a clinical safety profile similar to that of placebo. Studies in which ezetimibe 10 mg/day was initiated simultaneously with simvastatin 10 to 80 mg/day¹⁶ or with atorvastatin 10 to 80 mg/day¹⁷ have demonstrated, across the dose ranges of these statins, clinically meaningful incremental reductions of LDL cholesterol.

The primary objective of the present study was to assess LDL cholesterol reduction resulting from adding ezetimibe 10 mg/day to the treatment regimen of patients already receiving a stable dose of a statin who required further LDL cholesterol lowering to meet their National Cholesterol Education Program (NCEP)

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targets.^{18,19} Secondary objectives were: (1) to assess the proportion of patients who achieved NCEP Adult Treatment Panel (ATP) II target LDL cholesterol levels after the addition of ezetimibe 10 mg/day versus placebo; and (2) to evaluate the safety and tolerability of concomitant treatment with ezetimibe.

METHODS

Study population: Prospective patients with primary hypercholesterolemia were provided information about the trial, had questions answered, and signed an informed consent. The patient population consisted of adults ≥ 18 years of age, currently taking a stable daily dose of a statin for ≥ 6 weeks. Patients must have been previously instructed on a cholesterol-lowering diet. Each patient's mean LDL cholesterol level, calculated from 2 separate determinations during screening (visits 1 and 2), had to be at or above the recommended target level for that patient's risk category. LDL cholesterol target levels were defined by guidelines in place at initiation: Category I: NCEP ATP II guideline LDL cholesterol target levels, < 160 mg/dl (4.14 mmol/L) for patients without coronary heart disease and ≤ 1 risk factor; category II: < 130 mg/dl (3.37 mmol/L) for those without coronary heart disease and ≥ 2 risk factors; and Category III: ≤ 100 mg/dl (2.59 mmol/L) for those with established but stable coronary heart disease or coronary heart disease-equivalent disease, including diabetes mellitus per American Diabetes Association recommendations in place when the protocol was conducted.²⁰ Serum triglyceride levels at each screening visit had to be ≤ 350 mg/dl (3.96 mmol/L).

Key exclusion criteria were heart failure; uncontrolled cardiac arrhythmias; myocardial infarction, coronary bypass surgery, coronary angioplasty, or severe peripheral artery disease within the past 3 months; unstable angina pectoris; poorly controlled (hemoglobin A_{1c} $> 9.0\%$) or newly diagnosed diabetes mellitus; uncontrolled endocrine or metabolic disease known to influence serum lipids or lipoproteins; impaired renal function; active or chronic hepatic or hepatobiliary disease; alanine aminotransferase and aspartate aminotransferase concentrations ≥ 2 times the upper limit of normal; creatine phosphokinase ≥ 1.5 times the upper limit of normal; and cancer, other than basal cell carcinoma, within the past 5 years.

Patients could be withdrawn from the study for any of the following reasons: persistent increase in aspartate aminotransferase or alanine aminotransferase values to ≥ 3 times the upper limit of normal; persistent increase in creatine phosphokinase values of 5 to 10 times the upper limit of normal associated with muscular symptoms; need for treatment with drugs known to interact with statins; persistent LDL cholesterol levels < 50 mg/dl (1.30 mmol/L); or a significant adverse event or laboratory abnormality.

Study design: This multicenter, double-blind, randomized, placebo-controlled study was conducted in accordance with good clinical practice guidelines. The appropriate institutional review board or independent

ethics committee for each participating clinical research center approved the protocol and statement of informed consent before study initiation. The duration of the study was ~ 15 consecutive weeks, including a 1-week screening period (visits 1 and 2), an 8-week active-treatment phase (visits 3 to 6), and a 6-week reversibility phase in which ezetimibe or placebo was discontinued (visits 7 to 9). Only the results from the 8-week treatment phase are reported here.

Eligible patients were enrolled and stratified by the severity of hypercholesterolemia at screening: stratum 1 included patients whose LDL cholesterol level was $< 18\%$ above target; stratum 2 included those who were $\geq 18\%$ above target. Efforts were made to achieve a distribution in which 1/3 of patients were taking simvastatin, 1/3 taking atorvastatin, and 1/3 taking all other statins (lovastatin, pravastatin, cerivastatin, fluvastatin). Patients were randomized in a 1:1 ratio to receive either blinded ezetimibe 10 mg/day or matching placebo, to be co-administered with their previously prescribed, ongoing, open-label statin therapy. Adherence to treatment with study drug was assessed by tablet count. The statin and dose used by the patient at screening was maintained for the duration of the 8-week treatment phase.

Because of daily biologic variation in fasting cholesterol levels, patients with an LDL cholesterol level $\leq 5\%$ below goal were allowed to enroll in the trial provided all other eligibility criteria were met. This allowance would not affect data analyzed for the primary efficacy end point (percent change in LDL cholesterol), but did result in data analysis, including baseline LDL cholesterol levels up to 5% below goal for some patients. As a consequence, $\sim 18\%$ of enrollees were technically at target at the time of randomization.

Efficacy assessments: The primary efficacy parameter was the mean percentage change in LDL cholesterol concentration from baseline to end point. Plasma lipids were evaluated at visits 1 and 2 for screening purposes (unblinded) and subsequently were measured in a blinded fashion at visits 3 to 6 (randomization and weeks 2, 4, and 8). Apolipoproteins A-I, A-II, and B were determined at visits 3 to 6. C-reactive protein was also measured at visits 3 and 6. The percentage of patients who achieved NCEP ATP II target levels for LDL cholesterol at end point (after 8 weeks of treatment) was computed.

A central laboratory (Medical Research Laboratories International, Highland Heights, Kentucky, and Brussels, Belgium) performed all clinical laboratory analyses. LDL cholesterol was calculated by the Friedewald equation.²¹ HDL cholesterol, total cholesterol, and triglycerides were quantified enzymatically with the Hitachi 747 analyzer (Roche Diagnostics Corporation, Indianapolis, Indiana). Apolipoproteins were determined by fixed-rate nephelometry. Concentrations of C-reactive protein were determined by immunonephelometry.

Safety and tolerability assessments: Safety and tolerability were evaluated throughout the study by reviewing patients' reports, investigators' observations,

TABLE 1 Baseline Demographics and Clinical Characteristics, Intent-to-Treat Data Set		
Characteristic	Statin + Placebo (n = 390)	Statin + Ezetimibe 10 mg (n = 379)
Age (yrs)		
Mean (median)	60.0 (61)	60.0 (61)
Range	22–83	25–85
<65 yrs	242 (62%)	233 (61%)
≥65 yrs	148 (38%)	146 (39%)
Men/women	221 (57%)/169 (43%)	222 (59%)/157 (41%)
Race		
White	356 (91%)	337 (89%)
Black	19 (5%)	27 (7%)
Hispanic	7 (2%)	8 (2%)
Asian	4 (1%)	5 (1%)
Other*	4 (1%)	2 (<1%)
Body weight (kg)		
Mean (median)	82.7 (80.0)	81.1 (78.0)
Range	42.0–154.6	47.6–154.0
Body mass index (kg/m ²) [†]		
Mean (median)	29.6 (28.3)	29.1 (28.2)
Range	18.1–67.6	18.4–88.1
Smoker	64 (16%)	61 (16%)
Waist circumference (cm) [‡]		
Mean (median)	99.2 (98.0)	97.5 (97.0)
Range	66.0–155.6	62.0–154.5
Cardiovascular risk factor category and stratum		
No coronary heart disease and < 2 risk factors, LDL cholesterol ≥160 mg/dl		
Stratum 1	19 (56%)	19 (48%)
Stratum 2	15 (44%)	21 (53%)
No coronary heart disease and ≥2 risk factors, LDL cholesterol ≥130 mg/dl		
Stratum 1	36 (45%)	55 (59%)
Stratum 2	44 (55%)	39 (41%)
Coronary heart disease and/or DM and LDL cholesterol ≥100 mg/dl		
Stratum 1	135 (49%)	125 (51%)
Stratum 2	141 (51%)	120 (49%)
Statin type at baseline		
Atorvastatin	162 (42%)	146 (39%)
Simvastatin	117 (30%)	123 (33%)
Pravastatin	55 (14%)	55 (15%)
Fluvastatin	19 (5%)	30 (8%)
Cerivastatin	25 (6%)	18 (5%)
Lovastatin	12 (3%)	7 (2%)

To convert values for cholesterol to millimoles per liter, multiply by 0.0259.
 *Includes 2 American Indians, 1 white/black, and 1 Pacific Islander in the statin + placebo group; includes 1 Pacific Islander and 1 white/Pacific Islander in the statin + ezetimibe group.
[†]n = 383 for statin + placebo group, and n = 374 for statin + ezetimibe group.
[‡]n = 389 for statin + placebo group, and n = 378 for statin + ezetimibe group.
 Stratum 1 <18% above NCEP II target LDL cholesterol; Stratum 2: ≥18% above NCEP II target LDL cholesterol.
 DM = diabetes mellitus.

and results of specific tests and measurements. Measurements of safety and tolerability included adverse events, physical examinations, and laboratory test results. The intensity of adverse events was rated by the investigator as mild, moderate, or severe. Whether an adverse event was serious—defined as an event that resulted in death, was considered life-threatening, was a persistent or significant disability, or required emergency treatment or hospitalization; including cancer, sequelae of an overdose, or other important medical

events—was also rated by investigator. The potential relation to study drug was rated by the investigator for each adverse event.

Data and statistical analysis: With a sample size of 769 patients, a difference between treatment groups in the mean percent change from baseline in LDL cholesterol of ≥10 percentage points could be detected with 95% power, assuming a SD of ~12% (as observed in the Scandinavian Simvastatin Survival Study [4S]²²) and a 2-tailed significance level of 0.05.

Data were analyzed by intention to treat; any patient who received a randomized treatment assignment and had ≥1 post-baseline value was included in the efficacy analyses. Primary and secondary efficacy parameters were assessed using an analysis-of-variance model, including terms for statin, stratum, region (domestic sites, international sites), and treatment. Assessment of the key secondary efficacy parameter, the percentage of patients who reached NCEP ATP II target for LDL cholesterol, was based on a logistic regression model with terms for statin, stratum, treatment, region, and baseline percent difference from the NCEP ATP II target. Comparisons between treatment groups were performed using the least-squares method. Statistical analysis was conducted using SAS software (version 6.12, SAS Institute, Inc., Cary, North Carolina).

Data for all randomized patients were included in the safety and/or tolerability assessments. The numbers of patients with adverse events or clinically significant laboratory test abnormalities were reported and tabulated by treatment group using a modification of the World Health Organization Adverse Reaction Terminology dictionary.²³ A treatment-emergent adverse event was defined as any adverse event that began in the treatment period, provided the

event was not present before randomization with the same or greater intensity.

RESULTS

Demographic and baseline characteristics and patient disposition: Between December 2000 and April 2001, 769 patients taking statin monotherapy were randomized to treatment with either the addition of ezetimibe 10 mg/day (n = 379) or matching placebo (n = 390) at 80 study centers (51 United States

TABLE 2 Number of Patients (%) by Baseline on Marketed Dose of Statin, Intent-to-Treat Data Set*

Statin Type/ Dose (mg)	Statin + Placebo (n = 390)	Statin + Ezetimibe 10 mg (n = 379)
Simvastatin		
10	8 (2.1%)	12 (3.2%)
20	41 (10.5%)	43 (11.3%)
40	40 (10.3%)	41 (10.8%)
80	23 (5.9%)	18 (4.7%)
Atorvastatin		
10	46 (11.8%)	38 (10.0%)
20	41 (10.5%)	42 (11.1%)
40	35 (9.0%)	28 (7.4%)
80	30 (7.7%)	28 (7.4%)
Lovastatin		
10	4 (1.0%)	0
20	4 (1.0%)	4 (1.1%)
40	2 (0.5%)	3 (0.8%)
Pravastatin		
10	4 (1.0%)	8 (2.1%)
20	27 (6.9%)	18 (4.7%)
40	20 (5.1%)	26 (6.9%)
Fluvastatin		
20	7 (1.8%)	12 (3.2%)
40	10 (2.6%)	17 (4.5%)
80	2 (0.5%)	1 (0.3%)
Cerivastatin		
0.2	6 (1.5%)	1 (0.3%)
0.3	3 (0.8%)	4 (1.1%)
0.4	15 (3.8%)	8 (2.1%)
0.8	1 (0.3%)	4 (1.1%)

*Twenty-one patients (5.3%) in the statin + placebo group and 23 patients (6.1%) in the statin + ezetimibe group were enrolled while taking nonmarketed doses of statins.

centers, 29 international). Patient demographics and baseline characteristics are listed in Table 1. Treatment groups were generally balanced with respect to age, gender, race, diet, weight, and body mass index. Approximately 68% of patients had coronary heart disease and/or diabetes (or coronary heart disease-equivalent disease) with LDL cholesterol ≥ 100 mg/dl (2.59 mmol/L). Table 2 lists the baseline doses of statins by type and by treatment group.

Efficacy: The addition of ezetimibe 10 mg/day to ongoing statin monotherapy resulted in an additional LDL cholesterol reduction of -25.1% compared with -3.7% for the addition of placebo ($p < 0.001$ for between-group difference; Table 3). Near-maximal lowering of LDL cholesterol was observed at week 2 and was maintained throughout the 8-week treatment period (Figure 1). When evaluated by statin type, the addition of ezetimibe 10 mg/day to ongoing simvastatin, atorvastatin, or “other statin” therapy further reduced LDL cholesterol to similar degrees, -26.8% , -25.0% , or -23.5% , respectively, compared with -3.1% , -4.0% , and -3.8% reductions when placebo was added to the respective monotherapies (Figure 1). Within the “other statin” category, the results were generally consistent across statin type and with those for simvastatin and atorvastatin (data not shown). The LDL cholesterol response to adding ezetimibe to ongoing statin monotherapy was generally consistent across subgroups defined by gender, age, race, NCEP ATP II category, body mass index, and waist circum-

ference (≤ 102 cm for men and ≤ 88 cm for women vs > 102 cm for men and > 88 cm for women²⁴; data not shown) for all patients as well as for patients with on-statin baseline LDL cholesterol above goal (Figure 2).

For the entire study cohort, including patients who were technically at LDL cholesterol goal at baseline, 75.5% of the statin plus ezetimibe group achieved the prespecified NCEP ATP II target LDL cholesterol levels at end point versus 27.3% of the statin plus placebo group (odds ratio 19.6; $p < 0.001$). For those patients whose LDL cholesterol levels were above NCEP ATP II LDL cholesterol target levels at baseline, the proportion that achieved the target LDL cholesterol levels at end point were 71.5% of the statin plus ezetimibe group and 18.9% of the statin plus placebo group (odds ratio 23.7; $p < 0.001$).

The addition of ezetimibe to ongoing statin monotherapy increased HDL cholesterol by $+2.7\%$ compared with $+1.0\%$ when placebo was added to ongoing statin therapy ($p < 0.05$). Triglycerides decreased -14.0% when ezetimibe was added to ongoing statin monotherapy compared with a -2.9% decrease in triglycerides when placebo was added to ongoing statin monotherapy ($p < 0.001$) (Table 3 and Figure 3). Other indicators of coronary heart disease risk, specifically total cholesterol, non-HDL cholesterol, apolipoprotein B, LDL cholesterol:HDL cholesterol, and total cholesterol:HDL cholesterol (all $p < 0.001$), as well as C-reactive protein ($p < 0.05$), were significantly improved with the co-administration of statin plus ezetimibe compared with statin plus placebo (Table 3).

Safety and tolerability: Of the 769 patients randomized, $\sim 95\%$ completed treatment in each study arm. Forty-one patients (5%) discontinued treatment before visit 6 (8 weeks) for the following reasons: adverse events (28 patients: 14 on statin plus ezetimibe and 14 on statin plus placebo), patient’s request (7 patients), lost to follow-up (4 patients), noncompliance with protocol (1 patient), and administrative reason (1 patient). There was no pattern or trend suggesting any difference in the distribution of reasons for discontinuation between the treatment groups. Among the 28 patients discontinued for an adverse event, gastrointestinal system disorders were the most common reason (5 patients [1%] in each treatment group). Adverse events associated with discontinuation and classified by the investigator as possibly or probably related to the study drug occurred in only 17 cases.

Overall, the incidence of individual “treatment-related” adverse events (possibly or probably study drug related) was similar across the 2 groups, with a pattern of occurrence similar to that of all treatment-emergent adverse events: 81 (21%) for patients receiving statin plus ezetimibe compared with 66 (17%) in patients receiving statin plus placebo. When adverse events were evaluated for each of the statin groups (simvastatin, atorvastatin, and other), no particular pattern was found among patients receiving ezetimibe versus placebo for any adverse event category. Among all the body systems, gastrointestinal system

TABLE 3 Least-Squares Mean Percent Changes (SEM) from On-Statin Baseline to End Point in Plasma Concentrations of Efficacy Variables After Addition of Ezetimibe or Placebo, Intent-to-Treat Data Set*

Variable	Statin + Placebo (n = 390)		Statin + Ezetimibe 10 mg (n = 379)		Between-Treatment p Value
	On-statin Baseline		On-statin Baseline		
	(mg/dl [SEM])	% Change	(mg/dl [SEM])	% Change	
LDL cholesterol	139 (2.0)	-3.7 (0.7)	138 (2.2)	-25 (0.7)	<.001
Total cholesterol	219 (2.1)	-2.3 (0.5)	218 (2.3)	-17 (0.6)	<.001
Triglycerides†	137 (3.8)	-2.9 (1.5)	136 (4.1)	-14 (1.4)	<.001
HDL cholesterol	50 (0.6)	1.0 (0.5)	49 (0.6)	2.7 (0.5)	<.05
Non-HDL cholesterol	169 (2.0)	-3.1 (0.7)	169 (2.3)	-23 (0.7)	<.001
Apolipoprotein B‡	141 (1.5)	-3.5 (0.7)	141 (1.7)	-19 (0.7)	<.001
Apolipoprotein A-I‡	159 (1.5)	-1.3 (0.6)	157 (1.4)	-1.2 (0.7)	>.2
Apolipoprotein A-II‡	33 (0.3)	-0.7 (0.6)	33 (0.3)	-2.5 (0.6)	<.05
LDL cholesterol:HDL cholesterol	2.9 (0.1)	-4.1 (0.8)	3.0 (0.1)	-27 (0.8)	<.001
Total cholesterol:HDL cholesterol	4.6 (0.1)	-2.8 (0.6)	4.6 (0.1)	-19 (0.6)	<.001
C-reactive protein‡§	2.1 (0.2)	0 (4.0)	1.7 (0.1)	-9.7 (3.1)	<.05

To convert values for cholesterol to millimoles per liter, multiply by 0.0259; to convert values for triglycerides to millimoles per liter, multiply by 0.0113.

*Not every patient had an endpoint measurement for every variable.

†Based on median percentage changes from baseline.

‡n = 386 for the statin + placebo group, and n = 375 for the statin + ezetimibe group.

§n = 388 for the statin + placebo group, and n = 376 for the statin + ezetimibe group.

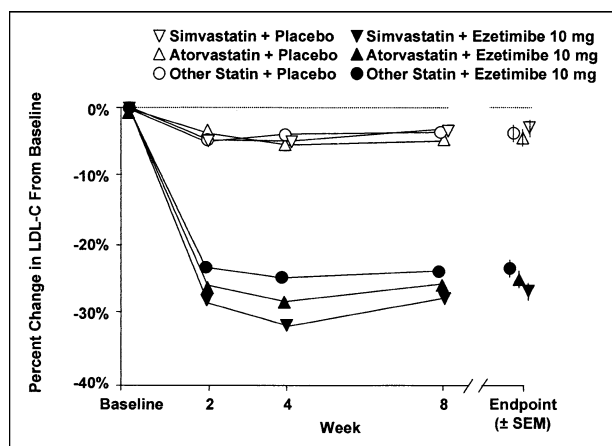


FIGURE 1. Least-squares mean percent changes in plasma concentration of LDL cholesterol (LDL-C) from baseline for ezetimibe and placebo groups by individual statins.

disorders were the most commonly reported treatment-related adverse events by investigators, with ~10% incidence in both treatment groups.

No patient died during the study; 28 patients had adverse events that were rated serious by blinded investigators: 19 of 379 (5%) in the statin plus ezetimibe group and 9 of 390 (2%) in the statin plus placebo group. No apparent pattern of diagnoses was observed. Among reported serious adverse events, 3 were considered possibly or probably related to study drug treatment. One patient who was on statin plus ezetimibe had abdominal pain, diarrhea, syncope, and elevated liver enzymes after travel in Africa; 1 patient with a history of seizures had a seizure while taking statin plus ezetimibe; and 1 patient had chest heaviness and dyspnea while taking statin plus placebo.

Elevations in either alanine aminotransferase or aspartate aminotransferase ≥ 3 times upper limit of

normal on 2 consecutive (or presumed consecutive) post-baseline measurements were reported in 5 patients (4 treated with statin plus ezetimibe and 1 treated with statin plus placebo). Of the 4 ezetimibe-treated patients, 3 had alanine aminotransferase and/or aspartate aminotransferase values above the upper limit of normal before treatment intervention but within the ≤ 2 times the upper limit of normal required for enrollment. Transaminases returned to normal range after discontinuation of statin plus study drug in all 5 cases. There were no reported adverse experiences of hepatitis in the study; however, as noted above, 1 patient treated with simvastatin 40 mg plus ezetimibe had a transient illness with elevations of alanine aminotransferase and aspartate aminotransferase to >10 times the upper limit of normal. These values returned to normal range after discontinuation of the statin and study drug.

Clinically important muscle-related adverse experiences were monitored by medical assessment of myopathy and/or by critical elevations in creatine phosphokinase (≥ 10 times the upper limit of normal on 2 consecutive [or presumed consecutive] post-baseline measurements). No case of rhabdomyolysis was reported. Only 1 patient had consecutive elevations in creatine phosphokinase ≥ 10 times the upper limit of normal; this patient was receiving cerivastatin plus placebo and experienced muscle pain consistent with the diagnosis of myopathy. No other patient experienced elevations in creatine phosphokinase ≥ 10 times the upper limit of normal, with or without associated muscle symptoms.

Results of additional measurements of safety revealed no evidence of any adverse effects of ezetimibe treatment compared with placebo relative to statin monotherapy. Surveillance of all other measured laboratory safety parameters, including routine chemistries, urinalyses, tests of renal function, and hemato-

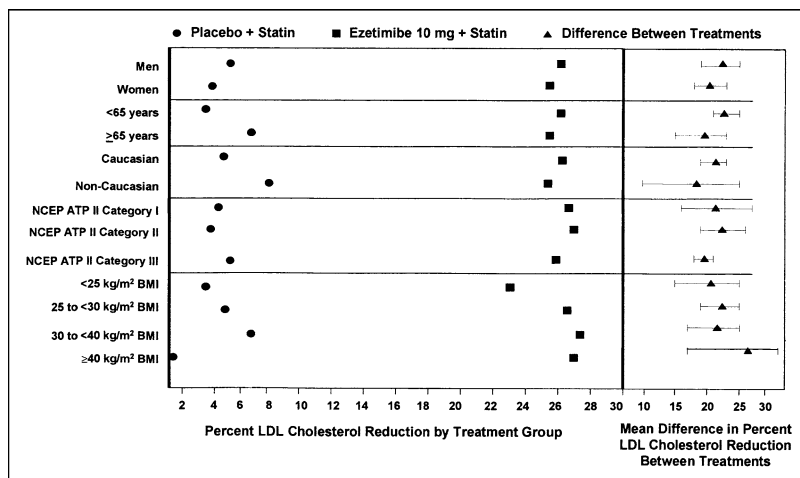


FIGURE 2. Least-squares mean percent changes in plasma concentration of LDL cholesterol from on-statin baseline by subgroup and differences between groups with 95% confidence interval. BMI = body mass index.

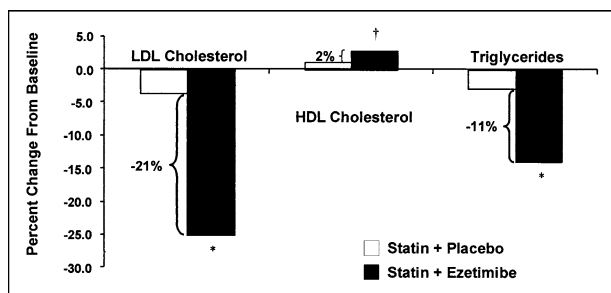


FIGURE 3. Least-squares mean or median percent changes in key lipid parameters. Patients entered into study ($n = 769$) were receiving a statin and not at NCEP goal for LDL cholesterol. * $p < 0.001$ versus placebo; † $p < 0.05$ versus placebo.

logic parameters, as well as electrocardiographic changes and findings on physical examinations, revealed no clinically relevant differences between the groups.

DISCUSSION

The objective of the present study was to evaluate the efficacy and safety of ezetimibe when added to ongoing statin therapy in a population of patients at high cardiovascular risk who had not achieved their recommended LDL cholesterol goal. The results indicate that a clinically meaningful reduction in LDL cholesterol occurs when ezetimibe is added to ongoing statin therapy. Moreover, this reduction is associated with achievement of the treatment goal in a substantial number of patients not previously at recommended LDL cholesterol levels.

To avoid potential bias due to between-group differences in baseline LDL cholesterol level relative to NCEP ATP II target levels for LDL cholesterol, the groups were balanced by stratification for severity of hypercholesterolemia within each risk category. The goal of enrolling approximately 1/3 of patients taking atorvastatin, 1/3 taking simvastatin, and 1/3 taking

other statins was also achieved. Thus, most patients were taking the 2 most widely used statins across a wide range of doses and levels of hypercholesterolemia, facilitating reliable subgroup assessment of the efficacy of ezetimibe with these agents.

As would be expected in a population already taking statin monotherapy, the mean baseline LDL cholesterol was in the moderately elevated range relative to target, with a study-wide mean of ~ 138 mg/dl (3.57 mmol/L). The addition of ezetimibe to statin monotherapy resulted in about a -25% decrease in LDL cholesterol across the dosing range of all statins compared with -4% with the addition of placebo to statin monotherapy. This reduction occurred within the first 2 weeks of treatment (Figure 1) and was sustained for the duration of the study. The efficacy of co-administration of ezetimibe with a statin was consistent within all subgroups assessed, including gender, age, race, adiposity, and cardiovascular risk factor category.

Other lipid parameters improved with the addition of ezetimibe as well, including non-HDL cholesterol and ratios of LDL cholesterol:HDL cholesterol and total cholesterol:HDL cholesterol. C-reactive protein, a nonspecific inflammatory marker associated with cardiovascular risk, also demonstrated statistically significant improvement.

Treatment with ezetimibe added to ongoing statin therapy was generally well tolerated. A major safety concern with statin therapy is the rare occurrence of myopathy²⁵ and rhabdomyolysis.²⁶ Although larger numbers of patients than provided by this single study are needed to estimate the incidence of myopathy in patients prescribed statin plus ezetimibe, it is reassuring that the single myopathy case observed in this study occurred in a placebo-treated patient taking cerivastatin. (During the course of this clinical trial, cerivastatin was withdrawn from the market.) No case occurred in the statin plus ezetimibe group, despite the greater reduction in LDL cholesterol in this group. Larger, long-term studies will be needed to ascertain if the addition of ezetimibe to low-dose statins reduces the rare risk of high-dose statin-related muscle toxicity while producing the same degree of LDL cholesterol reduction.

Another effect of lipid-lowering therapies is the potential for elevating serum transaminases. In this study, there were 4 cases with threefold consecutive elevations in alanine aminotransferase and/or aspartate aminotransferase in the statin plus ezetimibe group compared with 1 case in the statin plus placebo group. In all cases, elevations returned to the normal range with discontinuation of the statin and study drug, a clinical response to discontinuation that has also been observed in statin monotherapy studies.

Another effect of lipid-lowering therapies is the potential for elevating serum transaminases. In this study, there were 4 cases with threefold consecutive elevations in alanine aminotransferase and/or aspartate aminotransferase in the statin plus ezetimibe group compared with 1 case in the statin plus placebo group. In all cases, elevations returned to the normal range with discontinuation of the statin and study drug, a clinical response to discontinuation that has also been observed in statin monotherapy studies.

The small number of cases, however, makes it difficult to determine the significance of the results.

The present study provides support for the value of adding ezetimibe to ongoing statin therapy when additional lowering of LDL cholesterol is desirable. This new paradigm for treating hypercholesterolemia also decreases triglycerides and increases HDL cholesterol beyond that provided by the statin. Whether the results of the present study translate into long-term efficacy remains to be determined. This study is also limited in the insight it provides about the pleiotropic effects of adding ezetimibe to ongoing statin therapy and the effects on LDL cholesterol particle size.³ Ongoing studies will further elucidate the therapeutic comparability of titrating a statin versus adding ezetimibe, including accounting more fully for the higher risks of muscle toxicity and transaminase elevation with high-dose statin therapy.

In summary, the addition of ezetimibe 10 mg/day to ongoing statin therapy provides an effective means for further reducing LDL cholesterol levels and bringing more high-risk patients to their LDL cholesterol goals. The results of this study demonstrate that this regimen is generally well tolerated across a wide dose range of different statins. Co-administration of ezetimibe with a statin offers a new approach to LDL cholesterol reduction while avoiding high doses of statins, thus providing practitioners with a safe, convenient alternative to stepwise statin titration.

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APPENDIX

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1. van Heek M, France CF, Compton DS, McLeod RL, Yumibe NP, Alton KB, Sybertz EJ, Davis HR Jr. In vivo metabolism-based discovery of a potent cholesterol absorption inhibitor, SCH58235, in the rat and rhesus monkey through the identification of the active metabolites of SCH48461. *J Pharmacol Exp Ther* 1997;283:157-163.
2. van Heek M, Farley C, Compton DS, Hoos L, Alton KB, Sybertz EJ, Davis HR Jr. Comparison of the activity and disposition of the novel cholesterol absorption inhibitor, SCH58235, and its glucuronide, SCH60663. *Br J Pharmacol* 2000;129:1748-1754.
3. van Heek M, Farley C, Compton D, Hoos L, Davis HR. Ezetimibe selectively inhibits intestinal cholesterol absorption in rodents in the presence and absence of exocrine pancreatic function. *Br J Pharmacol* 2001;134:409-417.
4. Knopp RH, Bays H, Manion CV, Lipka LJ, Melani L, LeBeaut AP, Suresh R, Veltri EP, the Ezetimibe Study Group. Effect of ezetimibe on serum concentrations of lipid-soluble vitamins (abstr). *Atherosclerosis* 2001;2(suppl):90.
5. Zhu Y, Statkevich P, Maxwell S, Patrick JE, Calzetta A, Kosoglou T, Cayen MN, Batra VK. The effect of gender on the pharmacokinetics of SCH 58235, a cholesterol absorption inhibitor (abstr). AAPS Pharmaceutical Science 1999 AAPS Annual Meeting Supplement 1999;1:S24. Available at: http://www.pharmsci.org/scientificjournals/pharmsci/am_abstracts/1999/1623.htm.
6. Zhu Y, Statkevich P, Kosoglou T, Zambas D, Patrick J, Cayen MN, Batra V. Effect of SCH 58235 on the activity of drug metabolizing enzymes in vivo (abstr). *Clin Pharmacol Ther* 2000;67:152.
7. Kosoglou T, Guillaume M, Sun S, Pember LJC, Reyderman L, Statkevich P, Cutler DL, Veltri EP, Affrime MB. Pharmacodynamic interaction between fenofibrate and the cholesterol absorption inhibitor ezetimibe (abstr). *Atherosclerosis* 2001;2(suppl):38.
8. Bauer KS, Kosoglou T, Statkevich P, Calzetta A, Maxwell SE, Patrick JE, Batra V. Ezetimibe does not affect the pharmacokinetics or pharmacodynamics of warfarin (abstr). *Clin Pharmacol Ther* 2001;69:P5.
9. Kosoglou T, Meyer I, Musiol B, Anderson L, Reyderman L, Statkevich P, Cutler DL, Veltri EP, Affrime MB. Pharmacodynamic interaction between fluvastatin and ezetimibe has favorable clinical implications (abstr). *Atherosclerosis* 2001;2(suppl):89.
10. Statkevich P, Reyderman L, Kosoglou T, Woloj M, Maxwell SE, Cutler DL, Batra V, Kleinerms D. Ezetimibe does not affect the pharmacokinetics and pharmacodynamics of glipizide (abstr). *Clin Pharmacol Ther* 2001;68:P67.
11. Keung ACF, Kosoglou T, Statkevich P, Anderson L, Boutros T, Cutler DL, Batra V, Sellers EM. Ezetimibe does not affect the pharmacokinetics of oral contraceptives (abstr). *Clin Pharmacol Ther* 2001;69:P55.
12. Kosoglou T, Statkevich P, Bauer KS, Cutler DL, Maxwell SE, Yang B, Soni PP, Batra VK. Ezetimibe does not alter the pharmacokinetics and pharmacodynamics of digoxin (abstr). AAPS Pharmaceutical Science 2001 AAPS Annual Meeting Supplement. 2001;3. Available at: http://www.aapspharmaceutica.com/search/abstract_view.asp?id=290.
13. Krishna G, Kosoglou T, Ezzet F, Pember L, Statkevich P, Boutros T, Maxwell SE, Basso L, Batra VK. Effect of cimetidine on the pharmacokinetics of ezetimibe (abstr). AAPS Pharmaceutical Science 2001 AAPS Annual Meeting Supplement. 2001;3. Available at: http://www.aapspharmaceutica.com/search/abstract_view.asp?id=304.
14. Dujovne C, Ettinger MP, McNeer JF, Lipka LJ, LeBeaut AP, Suresh R, Veltri EP. Ezetimibe, a selective cholesterol absorption inhibitor, improves plasma lipids in hypercholesterolemic patients (abstr). *Circulation* 2001;104(suppl II):176.
15. Knopp RH, Gitter H, Truitt T, Lipka LJ, LeBeaut AP, Suresh R, Veltri EP. Ezetimibe reduces low-density lipoprotein cholesterol: results of a Phase III, randomized, double-blind, placebo-controlled trial (abstr). *Atherosclerosis* 2001;2(suppl):38.
16. Davidson M, McGarry T, Bettis R, Melani L, Lipka L, LeBeaut A, Suresh R, Sun S, Veltri E, for the Ezetimibe Study Group. Ezetimibe co-administered with simvastatin in 668 patients with primary hypercholesterolemia. *J Am Coll Cardiol* 2002;39(suppl A):226A-227A.
17. Ballantyne C, Houri J, Notarbartolo A, Melani L, Lipka L, LeBeaut A, Suresh R, Sun S, Veltri E, for the Ezetimibe Study Group. Ezetimibe co-administered with atorvastatin in 628 patients with primary hypercholesterolemia. *J Am Coll Cardiol* 2002;39(suppl A):227A.
18. NCEP Expert Panel. Summary of the second report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel II). *JAMA* 1993;269:3015-3023.
19. NCEP Expert Panel. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA* 2001;285:2486-2497.
20. American Diabetes Association. Management of dyslipidemia in adults with diabetes. *Diabetes Care* 1998;21:179-182.
21. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of

low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972;18:499–502.

22. Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383–1389.

23. World Health Organization. Adverse Reaction Terminology. December 1999. Available at <http://www.who-umc.org/pdfs/ardguide.pdf>.

24. NHLBI Obesity Education Expert Panel. Treatment guidelines. In: Clin-

ical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report. Bethesda, MD: National Institutes of Health/National Heart, Lung, and Blood Institute, 1998;98-4083: 56–93.

25. Garnett WR. Interactions with hydroxymethylglutaryl-coenzyme A reductase inhibitors. *Am J Health-Syst Pharm* 1995;52:1639–1645.

26. Omar MA, Wilson JP, Cox TS. Rhabdomyolysis, and HMG-CoA reductase inhibitors. *Ann Pharmacother* 2001;35:1096–1107.