Efficacy and Safety of a Potent New Selective Cholesterol Absorption Inhibitor, *Ezetimibe*, in Patients With Primary Hypercholesterolemia

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The efficacy and safety of ezetimibe, a new cholesterol absorption inhibitor, was evaluated in this randomized, double-blind, placebo-controlled trial of 892 patients with primary hypercholesterolemia. After ≥2 weeks on the National Cholesterol Education Program (NCEP) Step I or a stricter diet and a 4- to 8-week single-blind placebo lead-in, patients with low-density lipoprotein (LDL) cholesterol 130 to 250 mg/dl and triglycerides ≤350 mg/dl were randomized 3:1 to receive ezetimibe 10 mg or placebo orally each morning for 12 weeks. The primary efficacy end point was the percent reduction in direct plasma LDL cholesterol from baseline to end point. A total of 434 men and 458 women (ages 18 to 85 years) received randomized treatment (666 ezetimibe 10 mg, 226 placebo). Demographics and baseline characteristics were similar between treatment groups. Ezetimibe significantly reduced direct LDL cholesterol by a mean of 16.9%, compared with an increase of 0.4% with placebo ($p < 0.01$). Subgroup analysis indicated that response to ezetimibe was generally consistent across all subgroups, regardless of risk-factor status, gender, age, race, or baseline lipid profile. Ezetimibe effects on LDL cholesterol occurred early (2 weeks) and persisted throughout the 12-week treatment period. Compared with placebo, ezetimibe 10 mg also significantly improved calculated LDL cholesterol, apolipoprotein B, total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, and HDL_3 cholesterol ($p < 0.01$). Ezetimibe was well tolerated. There were no differences in laboratory or clinical safety parameters, or gastrointestinal, liver, or muscle side effects from that of placebo. Ezetimibe 10 mg/day is well tolerated, reduces LDL cholesterol approximately 17%, and improves other key lipid parameters. ©2002 by Excerpta Medica, Inc.

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Reduction of low-density lipoprotein (LDL) cholesterol has been well established as a primary strategy for lowering the risk of coronary heart disease.[1] Multiple processes, including de novo cholesterol synthesis, as well as intestinal absorption of exogenous (dietary) and endogenous (biliary) cholesterol, contribute to a patient's lipid and atherogenic profile. The most commonly prescribed agents for the treatment of hypercholesterolemia, the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) exert their cholesterol-lowering effects by inhibiting cholesterol synthesis. An additional and potentially complementary component of lipid management involves inhibition of cholesterol absorption in the intestine. This study evaluates the efficacy and safety of a new selective cholesterol absorption inhibitor, ezetimibe 10 mg/day, in a large population of patients with primary hypercholesterolemia.

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METHODS

Study design: This multicenter, randomized, double-blind, placebo-controlled trial was conducted at 53 centers in the United States. The study consisted of 3 phases: a 2- to 12-week initial screening/drug-washout phase (no treatment; visits 1 to 2); a 4- to 8-week single-blind, placebo run-in phase (visits 2 to 4); and a 12-week double-blind treatment phase (visits 4 to 8). Commonly used lipid-lowering medication required 6 to 12 weeks of drug washout. Washout requirements were 12 weeks for fibric acid derivatives and 6 weeks for statins and other agents or supplements administered specifically to modulate lipid levels. Hormone replacement therapy for postmenopausal women was allowed if the regimen was maintained throughout the study.

The study protocol was approved by the institutional review board of each participating study center and conducted according to good clinical practice guidelines. All patients provided written informed consent before enrollment.

Patients: Adult women and men ≥18 years of age with a diagnosis of primary hypercholesterolemia (calculated LDL cholesterol 130 to 250 mg/dl, and

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plasma triglycerides ≤350 mg/dl after adequate lipid-lowering drug washout) were eligible for consideration. A medical history was recorded, including presence of a family history of cardiac disease and presence of cardiovascular risk factors, as assessed via the National Cholesterol Education Program (NCEP) guidelines.[1]

Key exclusion criteria included: pregnancy or lactation; congestive heart failure (New York Heart Association class III or IV)[2]; uncontrolled cardiac arrhythmia; myocardial infarction, coronary bypass surgery, or angioplasty within 6 months of study entry; history of unstable or severe peripheral artery disease within 3 months of study entry; unstable angina pectoris; disorders of the hematologic, digestive, or central nervous system that would limit evaluation or participation; uncontrolled or newly diagnosed diabetes mellitus; uncontrolled endocrine or metabolic disease known to influence serum lipids or lipoproteins; known impairment of renal function; active or chronic hepatic or hepatobiliary disease; positive test for human immunodeficiency virus; and coagulopathy.

Therapies specifically prohibited during the study included oral corticosteroids, cyclosporine, and orlistat, as well as any other investigational drug (within 30 days before study entry). Treatment with psyllium or other fiber-based laxatives was not allowed unless the patient was treated with a stable regimen for ≥4 weeks before the first qualifying lipid level (Q_1, visit 2). Cardiovascular drugs were allowed during the study provided that the patient had received a stable dose for 8 weeks before Q_1 and would be anticipated to maintain the same drug regimen throughout the study. Aspirin ≤325 mg/day was permitted.

Study drug: Patients were randomly assigned treatment with either ezetimibe 10 mg or placebo in a 3:1 ratio according to a computerized randomization schedule with treatment codes in blocks of 4. Treatment (a single tablet) was administered orally once daily in the morning for 12 weeks, without reference to meals. Bulk ezetimibe was manufactured by Schering-Plough Research Institute (Kenilworth, New Jersey). All study medication, including placebo, was provided as identically appearing, white, capsule-shaped, unscored tablets.

Measurement of lipids: The primary efficacy variable was the percent change from baseline to end point (week 12) in the plasma concentration of direct LDL cholesterol, which was determined following standard ultracentrifugation and/or precipitation procedures (β quantification). Secondary variables included changes and percent changes from baseline in LDL cholesterol calculated via the Friedewald equation,[3] total cholesterol, triglycerides, and HDL cholesterol over time and at end point, and changes from baseline in HDL cholesterol subfractions HDL_2 cholesterol and HDL_3 cholesterol, apolipoprotein A-I, apolipoprotein B, and lipoprotein (a) (Lp[a]) at end point. Total cholesterol and triglycerides were quantified enzymatically with the Hitachi 747 analyzer (Roche Diagnostics Corporation, Indianapolis, Indiana). Total HDL cholesterol was determined enzymatically after LDL cholesterol and very LDL cholesterol had been selectively removed by heparin and manganese chloride precipitation. The HDL_3 cholesterol subfraction was quantified enzymatically after separation by ultracentrifugation, and the HDL_2 cholesterol subfraction was calculated by subtracting HDL_3 cholesterol from total HDL cholesterol. Apolipoproteins A-I and B were determined by fixed-rate nephelometry. Lp(a) was quantified by competitive enzyme-linked immunosorbent assay. After baseline measurements and randomized treatment assignment, samples for lipid measurements were collected at weeks 2, 4, 8, and 12, although direct LDL cholesterol, the HDL cholesterol subfractions, apolipoproteins, and Lp(a) were measured only from the sample collected at baseline and at week 12. Medical Research Laboratories (Highland Heights, Kentucky) performed all clinical laboratory analyses for this study, including analyses of lipids and safety parameters.

Assessment of diet: The results of the central diet analysis for each patient were reported as a ratio of ingested saturated fat and cholesterol to calories score[4] and as dietary components (total calories, milligrams of cholesterol, and grams of saturated fat) for the 3 days. Ratio of ingested saturated fat and cholesterol to calories scores indicate the potential for a diet to influence plasma lipid levels. Ranges of scores generally correlate to diets as follows: ≤13 = NCEP Step II, 14 to 20 = NCEP Step I, and 24 to 29 = typical American diet.[4]

During the screening and/or drug-washout phase, patients received dietary counseling, and all prior lipid-altering drugs were discontinued. A registered dietitian or designee instructed all patients to follow a low-fat, low-cholesterol diet (NCEP Step I[1] or stricter diet) to be started during this period and maintained throughout the 12-week study. An initial diet diary was issued for completion over 3 consecutive days. The diary from the screening visit was returned at visit 2, at which time the dietitian reviewed it with the patient and provided appropriate counseling; the diary was then sent to Professional Nutrition Systems, Inc. (Overland Park, Kansas) for central analysis. Results of the central analysis were reviewed with the patient at the next visit. The same pattern was followed for subsequent diaries. Four additional diaries (distributed at visits 2, 4, 6, and 7) were completed during the study.

Safety and tolerability: Safety was evaluated through reports of patients, observations of investigators, and results of specific tests and measurements. At each visit, the investigator or designated staff member recorded adverse events reported by patients since the last visit or directly observed by the investigator or staff. Other measures of safety included the results of laboratory tests (blood chemistry, prothrombin time, hematology, urinalysis), physical examinations (including vital signs and body weight), electrocardiograms, and tests for fecal occult blood.

Statistical analysis: The total target sample size was approximately 800 patients: 600 treated with ezetimibe 10 mg/day and 200 treated with placebo.

The primary efficacy analysis included all patients who received randomized treatment assignment and had ≥1 post-baseline lipid determination. A 2-way analysis of variance model that extracted sources of variation due to treatment and center was used to evaluate the effect of ezetimibe on the percent change in each of the lipid parameters from baseline to end point. The baseline value for the lipid variables was defined as the average of the determinations at visit 2 through visit 4, except for those variables determined only at visit 4 (week 0), for which the single determination was to be the baseline value. Pairwise comparisons between treatment groups were made using the previoulsy mentioned analysis of variance model. Significance was defined as $p < 0.05$. Statistical analysis was conducted using SAS software (Version 6.09, SAS Institute, Inc., Cary, North Carolina).

RESULTS

Overall, 816 of the 892 patients (91%) completed the study. Sixteen patients in the placebo group (7%) and 60 (9%) in the ezetimibe 10-mg group discontinued treatment for the following reasons: adverse events (35 patients, 46%), patient request (26 patients, 34%), loss to follow-up (10 patients, 13%), and noncompliance with protocol (5 patients, 7%). There was no pattern or trend in the distribution of the reasons for discontinuation between the 2 treatment groups.

The mean baseline plasma concentration of direct LDL cholesterol was approximately 168 mg/dl for patients in both treatment groups (Table 1). In general, the 2 treatment groups were comparable regarding diet, weight, gender, age, race, physical activity, and smoking history. Approximately 1/3 of the patients had a known family history of coronary artery disease, and approximately 1/3 had some degree of hypertension. Other cardiovascular risk factors were much less frequent (≤12% of patients in either treatment group).

Ratio of ingested saturated fat and cholesterol to calories scores during treatment were generally within a range indicative of the NCEP Step I diet (14 to 20); relatively few scores represented failure to follow the diet (≥24), with no differences between treatments.

Changes in lipid parameters: Ezetimibe 10 mg resulted in a mean percent reduction from baseline to end point in the plasma concentration of LDL cholesterol of approximately 17%, compared with an increase of 0.4% with placebo ($p < 0.01$) (Figure 1). Ten percent of placebo recipients compared with 60% of ezetimibe-treated patients had a ≥15% reduction in direct LDL cholesterol from baseline to end point. The reduction of LDL cholesterol by ezetimibe occurred early (2 weeks) and was maintained throughout the 12-week treatment period. The effects of ezetimibe on LDL cholesterol were generally consistent among the subgroups analyzed, regardless of risk-factor status, race, gender, age, or baseline lipid profile. Relative to placebo, ezetimibe also significantly decreased calculated LDL cholesterol, apolipoprotein B, total cholesterol, and triglycerides, and significantly increased HDL cholesterol and HDL_3 cholesterol ($p < 0.01$) (Table 2 and Figure 1).

TABLE 1 Baseline Demographic Characteristics and Habits for All Randomized Patients

Characteristics and Habits	Placebo (n = 226)	Ezetimibe 10 mg (n = 666)
Age (yrs)		
Mean	58.1	57.9
Range	30–85	18–85
<65	155 (69%)	458 (69%)
≥65	71 (31%)	208 (31%)
Women	124 (55%)	334 (50%)
Men	102 (45%)	332 (50%)
Race		
Caucasian	211 (93%)	598 (90%)
Black	9 (4%)	35 (5%)
American Indian	0	1 (<1%)
Asian	3 (1%)	8 (1%)
Hispanic	3 (1%)	23 (3%)
Pacific Islander	0	1 (<1%)
Body weight (kg)		
Mean	82.1	82.6
Range	43.2–146.3	45.5–158
Body mass index (kg/m^2)*		
Mean	28.4	28.6
Range	19.4–49.5	17.5–47
Diet (RISCC) scores†		
Mean	16.1	16.7
Range	5–29	4–34
Physically active	126 (56%)	379 (57%)
Smoker	20 (9%)	81 (12%)
Washout information	67 (30%)	204 (31%)
Statins	52 (23%)	149 (22%)
Fibrates	3 (1%)	2 (<1%)
Bile acid sequestrant	2 (<1%)	2 (<1%)
Nicotinic acid	2 (<1%)	10 (2%)
Other	12 (5%)	55 (8%)

*n = 225 for placebo, n = 662 for ezetimibe; †n = 224 for placebo, n = 662 for ezetimibe.

RISCC = ratio of ingested saturated fat and cholesterol to calories (a single score that conveys the potential effect of the diet on lipoproteins).

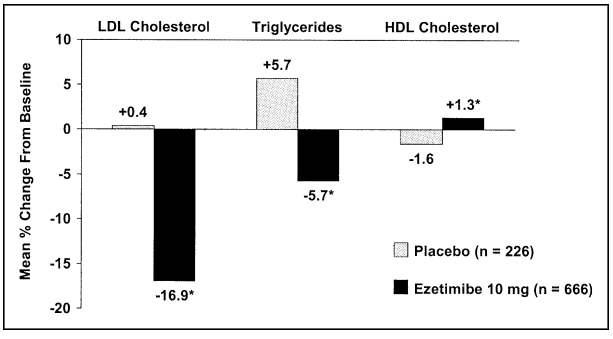

FIGURE 1. Mean percent change in plasma concentrations of direct LDL cholesterol, triglycerides, and HDL cholesterol from baseline to end point for all randomized patients. *Significantly different from placebo ($p < 0.01$).

Adverse events: Treatment-emergent adverse events were reported for 64% of patients (567 of 892): 66% of placebo recipients (150 of 226) and 63% of patients treated with ezetimibe (417 of 666). No individual adverse event was particularly prevalent in either treatment group. The most commonly reported adverse events in both treatment groups were upper respiratory tract infection (11% of patients receiving placebo compared with 9% of patients receiving

TABLE 2 Baseline Values (mean) and Least-square Mean Percentage Changes (SEM) in Plasma Concentrations of Various Lipid-related Variables from Baseline to End Point for All Randomized Patients

Variable	Placebo (n = 226)*		Ezetimibe 10 mg (n = 666)*		p Value
	Baseline	% Change	Baseline	% Change	
Direct LDL cholesterol (mg/dl)	168.0	0.36 (0.83)	167.8	−16.86 (0.55)	<0.01
Calculated LDL cholesterol (mg/dl)	167.5	1.11 (0.76)	166.9	−17.68 (0.51)	<0.01
Apolipoprotein B (mg/dl)	164.4	−1.42 (0.79)	164.2	−15.52 (0.53)	<0.01
HDL cholesterol (mg/dl)	52.2	−1.60 (0.73)	52.1	1.31 (0.49)	<0.01
HDL_2 cholesterol (mg/dl)	19.5	0.55 (2.11)	19.6	1.25 (1.42)	0.76
HDL_3 cholesterol (mg/dl)	32.6	1.01 (1.35)	32.4	5.65 (0.91)	<0.01
Apolipoprotein A-I (mg/dl)	152.31	1.91 (0.86)	152.3	2.53 (0.57)	0.50
Total cholesterol	254.5	0.84(0.56)	252.8	12.48 (0.38)	<0.01
Direct LDL cholesterol:HDL cholesterol	3.4	2.66 (0.95)	3.4	−17.47 (0.63)	<0.01
Total cholesterol:HDL cholesterol	5.1	2.99 (0.76)	5.1	−13.13 (0.51)	<0.01
Triglycerides (mg/dl)	174.8	5.74 (1.97)	169.0	−5.65 (1.31)	<0.01
Lipoprotein (a) (mg/dl)	27.5	16.32 (5.50)	33.5	2.83 (3.67)	0.02

*Not every patient had an end-of-treatment measurement for every variable; during the study, "n" varied from 193 to 226 for the placebo group and from 570 to 666 for the ezetimibe group.

TABLE 3 Number (%) of Patients Reporting the Most Common* Treatment-emergent Adverse Events

Adverse Event	Placebo (n = 226)	Ezetimibe (n = 666)
Upper respiratory infection	25 (11%)	57 (9%)
Headache	18 (8%)	53 (8%)
Back pain	11 (5%)	33 (5%)
Musculoskeletal pain	9 (4%)	31 (5%)
Arthralgia	12 (5%)	28 (4%)

*Incidence ≥4%.

ezetimibe) and headache (8% of patients in both treatment groups) (Table 3). No other adverse event was reported for >5% of patients in either treatment group. Most patients (approximately 95%) reported adverse events that were considered by the investigator to be mild to moderate at their greatest intensity. The adverse event profiles were similar between treatment groups.

Thirty-five patients (6 patients [3%] who received placebo and 29 patients [4%] who received ezetimibe) discontinued randomized treatment because of adverse events. The nature, number, and pattern of occurrences of events suggested no differential risk with active treatment relative to placebo. Results of the additional measures of safety—laboratory tests, vital signs, electrocardiograms, and so forth—revealed no evidence of an adverse effect of active treatment compared with placebo.

One area that received careful inspection during review of the tolerability profile was adverse events of allergic reaction or aggravated allergy. Although varied in nature and infrequent, these events were reported by more ezetimibe-treated patients (13 of 666 [2%]) than placebo recipients (0 of 226). Most of these patients had a known history of allergy, the events resolved without interruption of therapy, and the investigators considered all events unlikely to be related to treatment.

Laboratory test results: Results of laboratory tests (blood chemistry, prothrombin time, hematology, urinalysis) were generally similar between the treatment groups in terms of mean and median changes over time and numbers of patients having predefined high or low values or shifts from baseline. Identifiable category shifts from baseline consisted mainly of changes from within the reference ranges to values less than twice the upper reference limits. Few values were ≥3 times the upper reference limit, with similar occurrences in the placebo group (alanine aminotransferase 1 of 224 [<1%], aspartate aminotranferase 2 of 224 [<1%]) and ezetimibe group (alanine aminotransferase 3 of 659 [<1%], aspartate aminotranferase 3 of 659 [<1%]). Two ezetimibe-treated patients (<1%) and no placebo recipients had treatment halted because of the results of liver function tests. High values tended to decline despite continued treatment.

The number of ezetimibe-treated patients who had values for creatine phosphokinase activity ≥10 times the upper reference limit at some time during double-blind treatment was similar to that for placebo-treated patients (3 of 659 [<1%] vs 1 of 224 [<1%]). In both treatment groups, these values were transient despite continued treatment or were reversible following treatment discontinuation and were not correlated with musculoskeletal adverse events, and in 1 ezetimibe- and 1 placebo-treated patient were coincident with exercise.

DISCUSSION

Ezetimibe is a new cholesterol absorption inhibitor that potently inhibits dietary and biliary cholesterol absorption at the brush border of the intestine without affecting the absorption of triglycerides or fat-soluble vitamins.[5–9] Ezetimibe is rapidly absorbed, extensively conjugated to glucuronide in the intestine, and excreted primarily in the stool.[6,10,11] Ezetimibe and/or its glucuronide circulate enterohepatically, repeatedly delivering the agent back to the intestine and reducing systemic exposure.[6,10] These properties and its 24-hour half-life allow for once-daily dosing at any

time.[12] No clinically important gender or food effects, CYP 3A4 drug interactions, or known drug–drug interactions have been identified.[11,13–17]

In this randomized, double-blind trial, ezetimibe 10 mg taken orally once daily in the morning for 12 weeks by patients with mild-to-moderate primary hypercholesterolemia was shown to be an effective LDL cholesterol lowering agent with favorable effects on other lipid variables, and to have a safety and tolerability profile similar to that of placebo. Ezetimibe caused a mean percent decrease from baseline to end point in direct LDL cholesterol of about 17%, relative to an increase of <1% with placebo. This result is similar to those from previous, smaller trials[12,18] and with the results of a companion study of equivalent size and design.[19] The LDL cholesterol reduction was apparent at 2 weeks and was maintained to end point, consistent with results from other controlled studies.[12,18,19]

In this trial and the previously cited others, the concentration of apolipoprotein B decreased significantly relative to placebo. Because apolipoprotein B is the major protein constituent of LDL cholesterol, with 1 molecule/LDL cholesterol particle, the effect of ezetimibe on plasma LDL cholesterol concentrations involves a decrease in the concentration of circulating LDL cholesterol particles. In the present trial, the mean percentage increase in HDL cholesterol was 1.3% with ezetimibe versus a decrease of 1.6% with placebo ($p < 0.01$). The difference between the treatment groups was apparent early during the double-blind treatment phase and was maintained throughout treatment. A similar pattern was observed in the companion study[19] and in an earlier phase 2 study.[12] The observed increases in HDL cholesterol are consistent with the observations of numerically greater increases in the concentration of apolipoprotein A-I with ezetimibe relative to placebo.[12,18,19]

The mean plasma concentration of triglycerides decreased significantly from baseline to end point with ezetimibe relative to placebo. Treatment differences occurred early during the double-blind treatment phase and were maintained throughout treatment. A similar pattern was observed in the companion study,[19] although the between-group difference was not as great at end point and was not statistically significant. Numerical differences favoring ezetimibe 10 mg versus placebo were also found in the results of 2 of the 3 previous phase 2 studies.[12,18] The trend toward decrease in concentration of triglycerides with ezetimibe versus placebo is interesting because antihypercholesterolemic agents that act by interfering with enterohepatic recycling of bile acids have been associated with increases in triglyceride concentration.[20,21]

Adverse events were reported in similar proportions of patients and with similar degrees of intensity between the placebo and ezetimibe treatment groups. The profile of adverse events was generally similar between the groups. The difference in incidence of allergic reaction and aggravated allergy between the study groups probably represents a chance finding; there was a smaller difference in the occurrences of these events in the companion study (19 of 622 [3%] with ezetimibe vs 4 of 205 [2%] with placebo).[22] Thus, there was no evidence of any clinically meaningful difference between the adverse event profiles of ezetimibe and placebo.

Mean and median changes from baseline for alanine aminotranferase and aspartate aminotranfersase activity tended to be ≤2 mU/ml greater with ezetimibe than with placebo during treatment; there was no finding of this kind for γ-glutamyltransferase activity, alkaline phosphatase activity, or total bilirubin. Overall, the increases in mean alanine aminotransferase and aspartate aminotranfersase activity from baseline were not clinically significant and may represent a secondary effect of changes in lipid metabolism observed with lipid-altering agents, as has been suggested previously.[20] Most patients with elevated creatine phosphokinase levels had baseline values that were already greater than the upper reference limit. Mean changes from baseline over time were similar between the groups; median changes from baseline were essentially identical between the 2 treatment groups at all times. Thus, it is likely that the changes in creatine phosphokinase activity represent isolated observations in individual patients with a predisposition toward increased creatine phosphokinase activity or a non–drug-related reason for increase in creatine phosphokinase activity. This contention is supported by the results in the companion study, which revealed overlapping mean and median changes from baseline over time in both treatment groups.[22] The results of all other measures of safety did not suggest any clinically meaningful difference between the profiles of ezetimibe and placebo.

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APPENDIX

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