Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 52, No. 17, 2008
ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2008.09.002

Efficacy and Safety of Coadministration of Ezetimibe and Simvastatin in Adolescents With Heterozygous Familial Hypercholesterolemia

Anouk van der Graaf, MD,* Cynthia Cuffie-Jackson, MD,‡ Maud N. Vissers, PHD,* Mieke D. Trip, MD, PHD,† Claude Gagné, MD,‖ Genming Shi, PHD,§ Enrico Veltri, MD,‡ Hans J. Avis, MD,* John J. P. Kastelein, MD, PHD*

Amsterdam, the Netherlands; Kenilworth, New Jersey; and Quebec, Canada

Objectives The study evaluated the efficacy and safety of long-term coadministration of ezetimibe and simvastatin in adolescents with heterozygous familial hypercholesterolemia (HeFH).

Background Aggressive intervention to achieve lipid goals for adolescents with HeFH is recommended to reduce risk of premature cardiovascular disease.

Methods In a multicenter, randomized, double-blind, placebo-controlled study, 248 male and female subjects ages ≥10 and ≤17 years with HeFH were randomized to receive: step 1: simvastatin 10, 20, or 40 mg/day plus ezetimibe 10 mg/day or placebo for 6 weeks, followed by step 2: simvastatin 40 mg/day plus ezetimibe 10 mg/day or placebo for 27 weeks; followed by step 3: all subjects received open-label simvastatin 10 or 20 mg/day (titrated to maximum 40 mg/day) plus ezetimibe 10 mg/day for 20 weeks. Safety was assessed throughout the study.

Results Coadministered ezetimibe and simvastatin for 6 weeks (step 1) resulted in significantly greater mean reduction in low-density lipoprotein cholesterol (LDL-C) from baseline (49.5%) compared with simvastatin monotherapy (34.4%; $p < 0.01$) in pooled dose groups and in individual dose groups (46.7% vs. 30.4%, 49.5% vs. 34.3%, 52.1% vs. 38.6%, respectively; $p < 0.01$). At 33 weeks (step 2), ezetimibe-simvastatin subjects had a mean 54.0% reduction in LDL-C compared with a mean 38.1% reduction in simvastatin monotherapy subjects ($p < 0.01$). At 53 weeks (step 3), the pooled reduction in LDL-C was 49.1%. All treatment regimens were well tolerated throughout 53 weeks.

Conclusions Coadministration of ezetimibe with simvastatin was safe, well tolerated, and provided higher LDL-C reduction compared with simvastatin alone in adolescents with HeFH studied up to 53 weeks. (Effects of Ezetimibe With Simvastatin in the Therapy of Adolescents With Heterozygous Familial Hypercholesterolemia; NCT00129402) (J Am Coll Cardiol 2008;52:1421–9) © 2008 by the American College of Cardiology Foundation

Familial hypercholesterolemia (FH) is an inherited autosomal dominant disorder associated with abnormally high serum low-density lipoprotein cholesterol (LDL-C) levels and the risk of premature atherosclerosis and coronary heart disease. Although young patients may be asymptomatic, vascular abnormalities, such as increased carotid intima media thickness (IMT) (1), carotid stiffness (2), and endothelial dysfunction (3), have been found in studies of children and adolescents with heterozygous FH (HeFH). Because of the high risk of progression to premature clinical cardiovascular disease associated with these findings, the National Cholesterol Education Program (NCEP), the American Heart Association, and the American Academy of Pediatrics (AAP) recommend aggressive intervention and specific lipid goals for children and adolescents with HeFH. Diet and lifestyle changes in conjunction with lipid-lowering therapy are usually required to achieve these goals (4–6).

An LDL-C level of <130 mg/dl is considered acceptable and <110 mg/dl ideal for children with HeFH according to NCEP and AAP guidelines (5,7). Statin therapy has been

From the Departments of *Vascular Medicine and †Cardiology, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; ‡Global Clinical Development–Cardiovascular and Metabolic Diseases and §Biostatistics, Schering-Plough Research Institute, Kenilworth, New Jersey; and the ‖Lipid Research Center (S-102), CHUL Research Center, Laval University, Quebec, Canada. This study was supported by Merck/Schering-Plough Pharmaceuticals, North Wales, Pennsylvania. Dr. Kastelein has received consulting fees from Pfizer, AstraZeneca, Merck, Schering-Plough; lecture fees from Pfizer, AstraZeneca, and Merck/Schering-Plough; and research grants for clinical studies from Pfizer and AstraZeneca. Dr. Gagné has received consultant honoraria and a grant from Merck-Schering-Plough Canada. Drs. Cuffie-Jackson, Shi, and Veltri are employees of Schering-Plough. Drs. Cuffie-Jackson and Veltri own stock in Schering-Plough.

Manuscript received May 26, 2008; revised manuscript received July 29, 2008, accepted September 9, 2008.

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Abbreviations and Acronyms

AAP = American Academy of Pediatrics
apo B = apolipoprotein B
CPK = creatinine phosphokinase
FH = familial hypercholesterolemia
HDL-C = high-density lipoprotein cholesterol
HeFH = heterozygous familial hypercholesterolemia
IMT = intima media thickness
LDL-C = low-density lipoprotein cholesterol
NCEP = National Cholesterol Education Program
ULN = upper limit of normal

proven efficacious and safe for improving lipid parameters, as well as reversing vascular abnormalities, in children and adolescents with HeFH (8–11). In young subjects who are affected by HeFH, however, administration of a statin with additional lipid-lowering therapy may be required to achieve desired LDL-C levels. Ezetimibe is a selective inhibitor of intestinal absorption of cholesterol and related phytosterols through interactions with the sterol transporter Niemann-Pick C1-Like 1, thereby reducing the amount of cholesterol in the blood in a complementary mechanism to that of statins. In adults, coadministration of ezetimibe with statin results in incremental lowering of LDL-C levels of approximately 14% compared with statin monotherapy (12,13).

This phase 3 clinical trial was designed to assess whether coadministration of ezetimibe with simvastatin provides incremental lowering of LDL-C and improvement in other lipid parameters compared with simvastatin monotherapy under several different conditions in adolescents with HeFH. The focus of step 2 of the study was to evaluate lipid responses and achievement of lipid goals during coadministration of ezetimibe with simvastatin at the highest statin dose recommended for pediatric patients (8,10). The intent of the final, long-term portion of the study, during which the dose of simvastatin could be titrated according to physician judgment, was to evaluate ezetimibe-simvastatin coadministration under conditions that simulate normal clinical practice. The dose titration was based upon response and was to be in accordance with NCEP guidelines (5). An additional objective was to evaluate the long-term safety and tolerability of coadministration of ezetimibe and simvastatin in this population. Compared with simvastatin monotherapy, coadministration of ezetimibe with simvastatin also has the potential to allow a greater proportion of subjects to achieve target LDL-C levels and reduction in the dose of simvastatin while maintaining long-term safety and tolerability.

Methods

Study population. Male and post-menarchal female adolescent subjects ≥10 to ≤17 years of age, Tanner stage II or higher with a body weight of at least 40 kg and above the 10th percentile with HeFH were enrolled. All subjects had to meet at least 1 of the clinical criteria for HeFH at screening in Table 1.

Inclusion and exclusion criteria. Subjects were required to have a fasting triglyceride ≤350 mg/dl at screening and lipid-qualifying visits and to have been on a diet in accordance with AAP guidelines for children with hypercholesterolemia for at least 13 weeks before the lipid-qualifying visit. Clinical laboratory values had to be within normal limits, with baseline liver function tests and creatine phosphokinase ≤1.5× the upper limit of normal (ULN). Female subjects could not be pregnant, and sexually active females were required to use adequate contraception.

Subjects were excluded from the study if they had any of the following conditions: any cardiac disorder including congenital cardiac disorders or hematologic, digestive, or central nervous system disorders; inadequately controlled or newly diagnosed diabetes mellitus; uncontrolled endocrine or metabolic disease known to influence serum lipids or lipoproteins; known impairment of renal function or other renal disease; active or chronic hepatobiliary or hepatic disease; human immunodeficiency virus; known coagulopathy; documented homozygous FH or laboratory values consistent with homozygous FH; use of LDL apheresis or plasma apheresis; partial ileal bypass; excessive alcohol use or drug abuse; delayed puberty. Subjects with documented mutations in the apolipoprotein B (apo B) gene in the absence of mutations in the LDL-C receptor gene were excluded.

Concomitant therapy or prior therapy within designated washout periods with any of the following medications was prohibited during the study: lipid altering drugs; oral, intramuscular, or intravascular corticosteroids; aspirin greater than 325 mg/day; orlistat or sibutramine; cyclosporine; and agents that interact with simvastatin, including amiodarone, verapamil, and fusidic acid.

Study design. This was a randomized, placebo-controlled, multicenter, phase 3 study conducted in 3 steps. Subjects were stratified by gender to achieve balance in the 6 arms of step 1. During step 1, subjects were randomized to receive double-blind 10-, 20-, or 40-mg/day simvastatin plus placebo or 10-mg/day ezetimibe for 6 weeks. Step 2 was a double-blind study of subjects who received 40-mg/day simvastatin plus placebo or 10-mg/day ezetimibe for 27 weeks (to week 33 of the study). Subjects who received placebo or ezetimibe in step 1 continued that assignment in step 2. Step 3 consisted of an

Table 1 Clinical Criteria for HeFH in Adolescent Patients

All Patients Had to Meet at Least 1 of the Following Criteria for HeFH
1. Genotype-confirmed HeFH and LDL-C >159 mg/dl and <400 mg/dl
2. LDL-C >159 mg/dl and <400 mg/dl and at least 1 biological parent with genotype-confirmed HeFH and historical untreated LDL-C >159 mg/dl
3. LDL-C >159 mg/dl and <400 mg/dl and at least 1 biological parent with untreated LDL-C of at least 210 mg/dl in the absence of another condition associated with secondary elevated LDL-C
4. LDL-C >189 mg/dl and <400 mg/dl and a family history of hypercholesterolemia consistent with dominant autosomal transmission
5. LDL-C >159 mg/dl and <400 mg/dl and tendinous xanthomas, without another condition associated with secondary elevated LDL-C

HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol

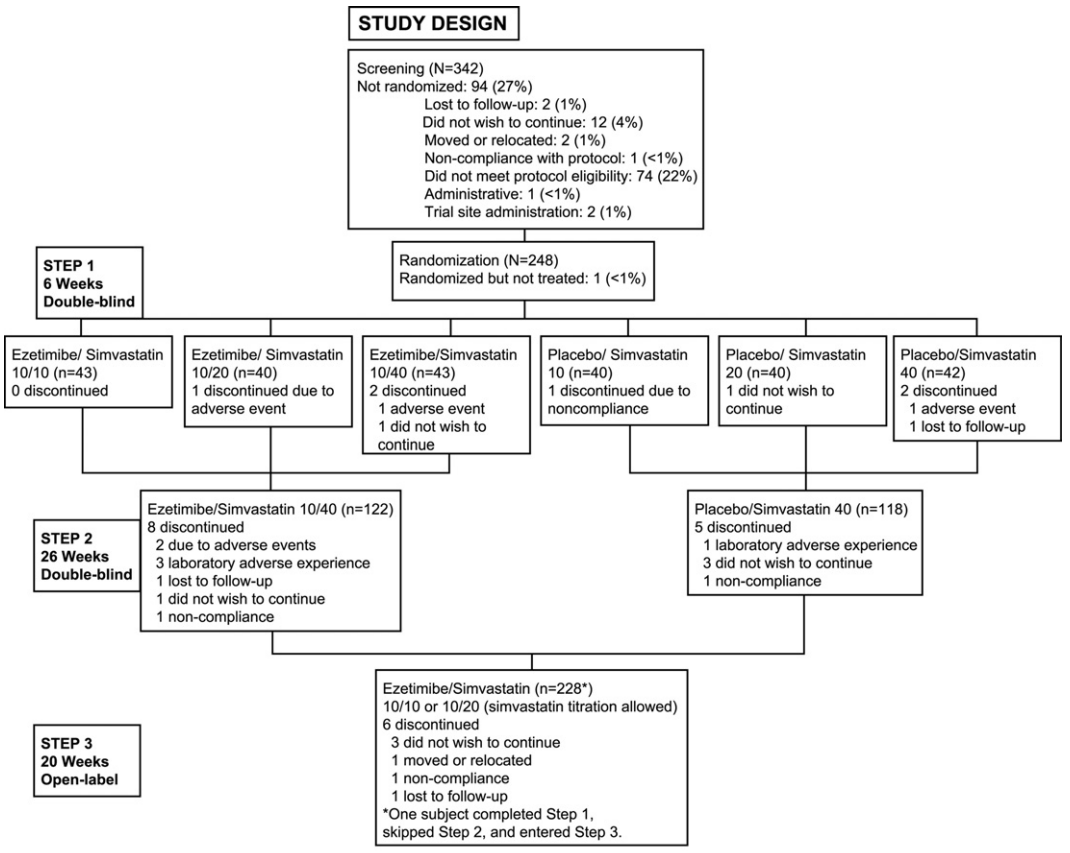

Figure 1 **Study Design**

Study design and subject disposition throughout study.

open-label regimen during which all subjects received 10- or 20-mg/day simvastatin (based on physician judgment of initial dose) plus 10-mg/day ezetimibe for 20 weeks (to week 53). During step 3, simvastatin doses could be titrated up to 20 or 40 mg/day to reach individualized LDL-C goals or down as determined by investigators' judgment. All medications were administered orally in the evening.

Study end points. The primary end point was percent change from baseline in LDL-C in the pooled simvastatin plus ezetimibe versus pooled simvastatin monotherapy groups after 6 weeks of treatment (step 1). The key secondary end points included comparison of other lipid parameters, such as total cholesterol, high-density lipoprotein cholesterol (HDL-C), non–HDL-C, triglycerides, and apo B in the pooled simvastatin plus ezetimibe versus simvastatin monotherapy groups after 6 weeks. Reductions in LDL-C in the individual simvastatin (10, 20, and 40 mg/day) plus ezetimibe 10-mg/day groups and individual simvastatin (10, 20, and 40 mg/day) monotherapy groups were also compared after 6 weeks. Evaluation of all lipid parameters and analysis of comparative percentages of subjects who reached recommended LDL-C treatment goals in coadministered ezetimibe-simvastatin and simvastatin monotherapy groups after 33 weeks (end of step 2) were other secondary end points.

Safety and tolerability were assessed throughout the study using physical examination, electrocardiograms, assessment of sexual maturation and growth, monitoring of menstrual periods for female subjects, adverse event reports, and laboratory assessments. A treatment-emergent adverse event was an adverse event that began after randomization and/or after any increase in intensity of therapy during the study. Laboratory investigations included safety and lipid panels, hormone assessments, thyroid function tests, and pregnancy tests for female subjects. Safety panels included hematology (differential, white blood cells, platelet counts, hemoglobin, and hematocrit); blood chemistries (total protein, albumin, calcium, inorganic phosphorus, fasting glucose, blood urea nitrogen, uric acid, total bilirubin, alkaline phosphatase, serum glutamic pyruvic transaminase/alanine aminotransferase, serum glutamic oxaloacetic transaminase/aspartate aminotransferase, serum creatinine, serum electrolytes, creatinine phosphokinase (CPK), and gamma-glutamyl transpeptidase), and urinalysis (specific gravity, pH, blood, ketones, protein, glucose, and microscopic evaluation of white and red blood cells).

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Statistical analysis. In each of the 6 treatment groups 30 patients were needed for the study to have a power of 90% to detect a difference of 7% in LDL-C between the pooled treatment groups (ezetimibe plus simvastatin versus simvastatin monotherapy) at 6 weeks with a 2-sided alpha of 0.05, assuming a common standard deviation of 14%.

Analysis of the primary end point, percent change from baseline in LDL-C at 6 weeks (end of step 1), was performed using an analysis of variance model with fixed effects for simvastatin dose (simvastatin 10, 20, and 40 mg), treatment (ezetimibe, placebo), simvastatin dose by treatment interaction, and gender. The poolability across the doses of simvastatin was assessed using the test of interaction. If the primary comparison of pooled ezetimibe-simvastatin groups versus pooled simvastatin monotherapy groups was significant, pairwise comparisons in groups who received individual doses of simvastatin plus ezetimibe versus the corresponding simvastatin monotherapy doses were performed. The primary end point was also evaluated for pre-specified subgroups including sex, race, baseline triglyceride, baseline LDL-C, and baseline HDL-C.

Comparisons of percent change from baseline in total cholesterol, non–HDL-C, apo B, and HDL-C at 6 weeks were univariately evaluated using a similar approach as the primary efficacy variable. Due to the large variability associated with triglycerides noted in the literature, a nonparametric approach was used for the percent change from baseline in triglycerides at 6 weeks. The Hochberg's procedure was implemented for these comparisons to control the overall type I error of 0.05. For the analyses at 33 weeks (end of step 2), an analysis of variance model with fixed effects for treatment and gender were performed for the percent change from baseline in LDL-C, HDL-C, total cholesterol, non–HDL-C, apo B, and a nonparametric approach was used for the percent change from baseline in triglycerides. The proportion of subjects who reached the recommended LDL-C treatment goal from baseline to 33 weeks was evaluated using a chi-square test.

Safety and tolerability evaluations included all randomized patients. The safety data, including adverse events, laboratory safety parameters, growth and development parameters, were summarized descriptively by each treatment group.

Results

Subject characteristics. The study design and disposition of all subjects who were screened for this study are shown in Figure 1. Randomization of 248 eligible subjects for step 1 produced 6 treatment groups and pooled ezetimibe-simvastatin and simvastatin monotherapy groups that were well balanced for age, race, baseline LDL-C, and disease characteristics (Table 2).

Extent of exposure. The extent of exposure, as measured by duration of any treatment during the study, was a mean of 228 days and ranged from <13 days to a maximum of 395 days.

Table 2 Baseline Demographic and Disease Characteristics for All Randomized Subjects in Steps 1 and 2

	Pooled EZE+SIM Groups (n = 126)	Pooled SIM Monotherapy Groups (n = 122)
Gender, n (%)		
Female	53 (42)	53 (43)
Male	73 (58)	69 (57)
Race, n (%)		
White	105 (83)	98 (80)
Asian	5 (4)	4 (3)
Black or African American	3 (2)	1 (1)
Multiracial	13 (10)	19 (16)
Age, yrs		
Mean (SD)	14.0 (1.9)	14.3 (1.8)
Median	14.0	14.0
Range	10–17	10–17
Baseline LDL-C, mg/dl		
Mean (SD)	225.2 (41.7)	218.6 (44.1)
Median	217.8	207.0
Range	160.5–351.0	148.5–336.0
Baseline NCEP cardiovascular risk categories, n (%)		
CHD		
No	126 (100)	122 (100)
Other forms of atherosclerosis*		
No	126 (100)	122 (100)
Diabetes		
No	126 (100)	122 (100)
Cigarette smoking in previous month		
Yes	1 (1)	12 (10)
No	125 (99)	110 (90)
Family history of premature CHD†		
Yes	50 (40)	46 (38)
No	76 (69)	76 (62)
Hypertension‡		
No	126 (100)	122 (100)
HDL-C value, mg/dl		
<40	27 (21)	25 (20)
40–49	61 (48)	58 (48)
50–59	29 (23)	31 (25)
≥60	9 (7)	8 (7)

*Peripheral artery disease, abdominal aortic aneurysm, symptomatic carotid artery disease, transient ischemic attack, stroke. †Coronary heart disease in male first-degree relative <55 years old or CHD in female first-degree relative <65 years old. ‡Blood pressure >140/90 mm Hg or on antihypertensive medication.

CHD = coronary heart disease; EZE = ezetimibe; HDL-C = high-density lipoprotein cholesterol; NCEP = National Cholesterol Education Program; SIM = simvastatin.

Efficacy of coadministration of ezetimibe and simvastatin. The percent change from baseline in LDL-C after 6 weeks of treatment in the pooled simvastatin groups with ezetimibe compared with simvastatin monotherapy groups, the primary end point for this study, showed a significantly greater reduction in LDL-C in subjects who received coadministered ezetimibe and simvastatin compared with those who received simvastatin alone ($p < 0.01$) (Table 3). Similar differences between the respective pooled groups in total cholesterol reductions ($p < 0.01$), non–HDL-C lipids ($p < 0.01$), and apo B levels ($p < 0.01$) were also observed.

Table 3 LDL-C and Other Lipid Parameters in Pooled Ezetimibe Plus Simvastatin and Simvastatin Monotherapy Groups at Baseline and at the Step 1 End Point

Parameter	Pooled EZE+SIM Groups	Pooled SIM Monotherapy Groups*	p Value
LDL-C baseline			
No. patients	126	120	
Mean actual level, mg/dl	225.36 ± 3.80	219.41 ± 3.90	0.27
LDL-C at step 1 end point			
Mean actual level, mg/dl	114.10 ± 3.50	144.08 ± 3.59	<0.01
Mean % change	−49.45 ± 1.19	−34.43 ± 1.22	<0.01
Total cholesterol baseline			
No. of patients	126	120	
Mean actual level, mg/dl	292.20 ± 4.01	285.63 ± 4.11	0.25
Total cholesterol at step 1 end point			
Mean actual level, mg/dl	179.84 ± 3.67	210.15 ± 3.76	<0.01
Mean % change	−38.23 ± 0.96	−26.28 ± 0.99	<0.01
Non–HDL-C baseline			
No. of patients	126	120	
Mean actual level, mg/dl	245.87 ± 4.05	239.66 ± 4.14	0.28
Non–HDL-C at step 1 end point			
Mean actual level, mg/dl	130.84 ± 3.68	161.42 ± 3.76	<0.01
Mean % change	−46.84 ± 1.13	−32.68 ± 1.16	<0.01
HDL-C baseline			
No. of patients	126	120	
Mean actual level, mg/dl	46.34 ± 0.82	45.97 ± 0.84	0.75
HDL-C at step 1 end point			
Mean actual level, mg/dl	49.00 ± 0.87	48.78 ± 0.89	0.86
Mean % change	6.58 ± 1.16	6.47 ± 1.19	0.95
Triglyceride baseline†			
No. of patients	126	120	
Median actual level, mg/dl	89.00 ± 49.30	88.00 ± 38.84	0.88
Triglyceride at step 1 end point†			
Median actual level, mg/dl	74.00 ± 35.35	75.50 ± 40.47	0.73
Median % change	−16.56 ± 30.26	−12.28 ± 31.49	0.48
Apo B baseline			
No. of patients	120	118	
Mean actual level, mg/dl	177.96 ± 2.87	170.98 ± 2.92	0.09
Apo B at step 1 end point			
Mean actual level, mg/dl	108.29 ± 2.57	125.27 ± 2.59	<0.01
Mean % change	−38.92 ± 1.10	−26.69 ± 1.11	<0.01

*Patients not having at least 1 post-baseline value were not included. †For triglycerides, median and standard deviation derived by (interquartile range)/1.075 are provided. The p values are based on nonparametric analysis of variance on the ranks extracting treatment and gender effects.
Apo B = apolipoprotein B; other abbreviations as in Tables 1 and 2.

No significant differences in HDL-C increases ($p = 0.95$) or decreased triglyceride levels ($p = 0.48$) between the respective groups were observed at 6 weeks. The test for simvastatin dose by treatment interaction was not significant ($p = 0.79$, 0.52, 0.80, and 0.91 for LDL-C, non–HDL-C, apo B, and HDL-C, respectively), which suggests that it is appropriate to pool across the doses of simvastatin. Subgroup analysis revealed no significant differences in LDL-C reductions according to gender, race, baseline triglycerides (</≥ median), baseline LDL-C (</≥ median), or baseline HDL-C (</≥ median) by the end of step 1 (Table 4).

Percent changes in LDL-C levels from baseline at the end of step 1 in the pooled and individual dosing groups are shown in Figure 2. Coadministration of ezetimibe with 10-, 20-, or 40-mg simvastatin compared with simvastatin monotherapy resulted in differences of −46.7% versus −30.4%, −49.5% versus −34.3%, and −52.1% versus −38.6% from baseline, respectively ($p < 0.01$ for all comparisons), resulting in incremental differences between groups of 16.3%, 15.2%, and 13.6%, respectively. Similar reductions were found in pairwise comparisons of total cholesterol, non–HDL-C, and apo B in the individual simvastatin dosing groups that received ezetimibe or placebo.

At the end of step 2 (week 33), lipid parameters in subjects in the coadministration of ezetimibe with 40-mg simvastatin group compared with the 40-mg simvastatin monotherapy group showed significant incremental lowering of LDL-C (15.9% difference between groups), total cholesterol (13.2% difference), non–HDL-C (15.6% differ-

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Table 4 Subgroup Analysis of Changes From Baseline in LDL-C in the Pooled Ezetimibe Plus Simvastatin Group and Pooled Simvastatin Group at the End of Step 1

Subgroup	Pooled EZE+SIM N	Pooled EZE+SIM Mean LDL-C Change (SE) (mg/dl)	Pooled SIM Monotherapy N	Pooled SIM Monotherapy Mean LDL-C Change (SE) (mg/dl)
Gender				
Male	73	−49.44 ± 1.52	69	−33.71 ± 1.39
Female	53	−49.32 ± 2.15	51	−35.51 ± 1.97
Race				
Caucasian	105	−48.79 ± 1.44	96	−33.66 ± 1.35
Non-Caucasian	21	−52.43 ± 2.18	24	−37.73 ± 1.99
Baseline LDL-C				
<Median*	57	−50.07 ± 1.63	63	−36.23 ± 1.60
≥Median*	69	−48.84 ± 1.87	57	−32.53 ± 1.64
Baseline HDL-C				
<Median†	61	−47.70 ± 1.72	56	−33.12 ± 1.80
≥Median†	65	−50.98 ± 1.82	64	−35.66 ± 1.48
Baseline triglycerides				
<Median‡	61	−51.26 ± 1.56	61	−34.89 ± 1.59
≥Median‡	65	−47.64 ± 1.94	59	−34.04 ± 1.69

*Median baseline LDL-C = 212.5 mg/dl. †Median baseline HDL-C = 45.0 mg/dl. ‡Median baseline triglycerides = 88.5 mg/dl.
SE = standard error; other abbreviations as in Tables 1 and 2.

ence), and apo B (14.8% difference) with coadministration (Table 5). Significantly more subjects had achieved NCEP/AAP acceptable (<130 mg/dl) and ideal (<110 mg/dl) LDL-C levels in the coadministration of ezetimibe with 40-mg simvastatin group than in the simvastatin 40-mg monotherapy group ($p < 0.01$ for both comparisons) by the end of step 2. Again, no significant differences in increased HDL-C levels were observed ($p = 0.58$), but median triglyceride levels had decreased significantly in the coadministered ezetimibe-simvastatin group (9.5% difference) compared with the simvastatin monotherapy group ($p < 0.01$) (Table 5).

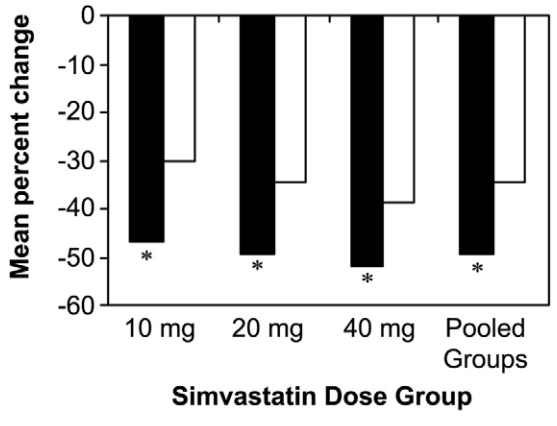

Figure 2 Step 1 (6 Weeks) Reduction in LDL-C From Baseline

Changes from baseline in LDL-C in subjects who received coadministered ezetimibe with 10-, 20-, or 40-mg simvastatin **(solid bars)** or 10-, 20-, or 40-mg simvastatin **(open bars)** monotherapy after 6 weeks (step 1). *$p < 0.01$ compared with monotherapy group.

At week 53, the mean percent change in LDL-C in the overall population (n = 200 at end of study) was −49.1% from baseline. Mean percent changes were −38.5% in total cholesterol, −46.4% in non–HDL-C, and median percent changes of −16.6% were observed in triglycerides. The HDL-C levels were 3.3% above baseline levels at the end of step 3 (Table 6).

Safety. Treatment-emergent adverse events that were reported by the end of step 2 (33 weeks total) in 5% or more of subjects in the pooled ezetimibe with simvastatin and simvastatin monotherapy groups are shown in Table 7. Both treatment regimens were well tolerated. Treatment-emergent adverse events occurred in 105 subjects (83%) in the coadministered ezetimibe plus simvastatin group and in 103 subjects (84%) in the simvastatin monotherapy group. By the end of step 3 (53 weeks), treatment-emergent adverse events were reported in 168 subjects (71%) in the study overall. Influenza (8%), nasopharyngitis (17%), and headache (9%) were the only treatment-emergent adverse events that were reported in more than 5% of subjects. No deaths occurred during the study.

There were 6 subjects who had consecutive transaminase elevations of at least 3× ULN during the study (1 subject in the ezetimibe with 20-mg simvastatin group, 2 cases in the ezetimibe with 40-mg simvastatin group, 2 in the 40-mg simvastatin monotherapy group, and 1 additional case during step 3). Maximum post-baseline levels of alanine aminotransferase and aspartate aminotransferase in patients who had 2 consecutive levels of ≥3× ULN ranged from 92 to 316 mU/ml (reference range: 5 to 25 mU/ml) and 102 to 257 mU/ml (reference range: 8 to 30 mU/ml), respectively. All elevated alanine aminotransferase and aspartate aminotransferase values resolved with interruption or discontinuation of therapy.

Table 5 Lipid Parameters at the End of Step 2 (33 Weeks) in Ezetimibe Plus Simvastatin 40-mg Group and Simvastatin 40-mg Group

Parameter	EZE+SIM 40-mg Group	SIM 40-mg Group	p Value
LDL-C baseline			
No. of patients	126	120	
Mean actual level, mg/dl	225.63 ± 3.86	219.27 ± 3.95	0.25
LDL-C step 2 end point			
Mean actual level, mg/dl	103.47 ± 3.65	134.60 ± 3.69	<0.01
Mean % change	−53.99 ± 1.41	−38.14 ± 1.43	<0.01
Total cholesterol baseline			
No. of patients	126	120	
Mean actual level, mg/dl	292.43 ± 4.05	285.47 ± 4.15	0.23
Total cholesterol at step 2 end point			
Mean actual level, mg/dl	167.02 ± 3.75	200.20 ± 3.79	<0.01
Mean % change	−42.45 ± 1.15	−29.25 ± 1.17	<0.01
Non–HDL-C baseline			
No. of patients	126	120	
Mean actual level, mg/dl	246.15 ± 4.06	239.51 ± 4.19	0.25
Non–HDL-C at step 2 end point			
Mean actual level, mg/dl	119.37 ± 3.83	152.67 ± 3.87	<0.01
Mean % change	−51.31 ± 1.37	−35.73 ± 1.38	<0.01
HDL-C baseline			
No. of patients	126	120	
Mean actual level, mg/dl	46.27 ± 0.82	45.96 ± 0.84	0.79
HDL-C at step 2 end point			
Mean actual level, mg/dl	47.66 ± 0.86	47.47 ± 0.87	0.87
Mean % change	4.67 ± 1.27	3.68 ± 1.28	0.58
Triglyceride baseline*			
No. of patients	126	120	
Median actual level, mg/dl	89.00 ± 49.30	88.00 ± 38.84	0.88
Triglyceride at step 2 end point*			
Median actual level, mg/dl	71.00 ± 38.14	81.00 ± 39.07	0.01
Median % change	−20.00 ± 23.76	−13.04 ± 39.00	<0.01
Apo B baseline			
No. of patients	122	118	
Mean actual level, mg/dl	178.31 ± 2.91	170.83 ± 2.96	0.07
Apo B at step 2 end point			
Mean actual level, mg/dl	101.25 ± 2.72	122.08 ± 2.79	<0.01
Mean % change	−42.64 ± 1.39	−27.88 ± 1.43	<0.01
Subjects achieving AAP acceptable LDL-C goal (<130 mg/dl), n (%)	97 (77)	64 (53)	<0.01
Subjects achieving AAP ideal LDL-C goal (<110 mg/dl), n (%)	79 (63)	32 (27)	<0.01

*For triglycerides, median and standard deviation derived by (interquartile range)/1.075 are provided. The p values are based on nonparametric analysis of variance on the ranks extracting treatment and gender effects.

AAP = American Academy of Pediatrics; other abbreviations as in Tables 1, 2 and 3.

Two subjects had CPK elevations ≥10× ULN without associated muscle symptoms. No subject had CPK elevations ≥5× ULN with associated muscle symptoms. Of the 2 patients with any CPK value ≥10× ULN, 1 female subject had an isolated maximum value of 19,530 mU/ml (reference range: 20 to 120 mU/ml) on day 232 during step 2 treatment with ezetimibe 10 mg/day and simvastatin 40 mg/day. Her CPK value returned to within the reference range 7 days later upon interruption of treatment. She subsequently continued in the study for 371 days of treatment without recurrent elevations in CPK levels. One male subject had a maximum value of 3,666 mU/ml (reference range: 30 to 180 mU/ml) on day 47 during step 1 treatment with ezetimibe 10 mg/day and simvastatin 20 mg/day. His CPK value returned to 214 mU/ml on day 63 after discontinuation of treatment.

Eight subjects reported myalgia (7 who received ezetimibe with simvastatin vs. 1 who received simvastatin monotherapy). In these 8 patients, CPK levels were unremarkable and no subject with myalgia had CPK values of ≥3× ULN.

There were no clinically significant adverse effects on growth, as assessed by measurement of height and weight; sexual maturation, as assessed by clinical examination; or steroid hormones, as assessed by clinical review of the number of subjects with steroid hormones outside normal

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Table 6 Lipid Parameters at the End of Step 3 (53 Weeks) in the Overall Population

Parameter	EZE+SIM
LDL-C baseline	
No. of patients	246
Mean actual level, mg/dl	222.10 ± 2.75
LDL-C end point	
No. of patients	200
Mean actual level, mg/dl	112.44 ± 2.76
Mean % change	−49.13 ± 1.09
Total cholesterol baseline	
No. of patients	246
Mean actual level, mg/dl	288.34 ± 2.89
Total cholesterol end point	
No. of patients	200
Mean actual level, mg/dl	175.93 ± 2.90
Mean % change	−38.54 ± 0.91
Non–HDL-C baseline	
No. of patients	246
Mean actual level, mg/dl	242.46 ± 2.91
Non–HDL-C end point	
No. of patients	200
Mean actual level, mg/dl	129.18 ± 2.93
Mean % change	−46.42 ± 1.07
HDL-C baseline	
No. of patients	246
Mean actual level, mg/dl	45.88 ± 0.59
HDL-C end point	
No. of patients	200
Mean actual level, mg/dl	46.75 ± 0.71
Mean % change	3.32 ± 1.16
Triglyceride baseline*	
No. of patients	246
Median actual level, mg/dl	88.50 ± 40.91
Triglyceride end point*	
No. of patients	200
Median actual level, mg/dl	75.50 ± 37.00
Median % change	−16.63 ± 43.50

*For triglycerides, median and standard deviation derived by (interquartile range)/1.075 are provided.

Abbreviations as in Tables 1 and 2.

range (estradiol in females, testosterone in males, and cortisol, dehydroepiandrosterone, follicle-stimulating hormone, and luteinizing hormone levels in all subjects). Similar changes in weight and height were found in groups who were randomized to receive ezetimibe with simvastatin or simvastatin monotherapy for steps 1 and 2 (Table 8). Furthermore, no trends in changes in menstrual cycle duration were associated with either treatment regimen, and hormone levels were generally similar between treatment groups (data not shown).

In 238 subjects who received coadministration of ezetimibe plus simvastatin during the study (up to 53 weeks), only 7 (3%) discontinued treatment because of adverse events. Adverse events leading to discontinuation were myalgia and increased alanine aminotransferase in 2 subjects each (1%) and nausea, increased blood CPK, and muscle spasms in 1 subject each (<1%).

Table 7 Treatment-Emergent Adverse Events Occurring in 5% or More of Subjects Through the End of Step 2 (33 Weeks Total) in the Pooled Ezetimibe Plus Simvastatin 40-mg Group and Pooled Simvastatin 40-mg Group

Adverse Event (n, %)	Pooled EZE+SIM 40 mg (n = 126)	Pooled SIM 40 mg (n = 122)
Any	105 (83)	103 (84)
Gastrointestinal		
Abdominal pain	6 (5)	3 (2)
Diarrhea	9 (7)	3 (2)
Nausea	8 (6)	4 (3)
Vomiting	5 (4)	6 (5)
Infections and infestations		
Influenza	8 (6)	12 (10)
Nasopharyngitis	27 (21)	27 (22)
Sinusitis	6 (5)	5 (4)
Investigations		
ALT increased*	6 (5)	3 (2)
Musculoskeletal and connective tissue		
Myalgia	7 (6)	1 (1)
Nervous system		
Headache	16 (13)	16 (13)
Respiratory/thoracic/mediastinal		
Cough	4 (3)	8 (7)
Pharyngolaryngeal pain	6 (5)	3 (2)
Skin and subcutaneous tissue		
Acne	4 (3)	9 (7)

*It should be noted that some elevations in ALT/AST may have been reported as adverse events by individual investigators without reaching the level of consecutive elevations of ≥3× upper limit of normal.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; other abbreviations as in Table 2.

Discussion

We show that, consistent with studies of ezetimibe coadministration with simvastatin in adults, significant incremental decreases of approximately 15% in LDL-C levels compared with administration of simvastatin alone were achieved within 6 weeks of treatment. These decreases were sustained throughout the subsequent 26-week, double-blind

Table 8 Height and Weight Changes in Adolescent Subjects With HeFH Who Received Coadministration of Ezetimibe With Simvastatin or Simvastatin Monotherapy

	Pooled EZE+SIM Groups (n = 126)	Pooled SIM Monotherapy Groups (n = 122)
Mean baseline weight, kg	58.1 ± 12.9	61.0 ± 15.7
Change at end of step 2, kg	+2.8 ± 3.7	+2.8 ± 3.3
Change at end of step 3 (all patients), kg	61.6 ± 13.1	
Changes in height, % of patients		
0 to <10% change in height at end of step 2	88	87
0 to 10% change in height at end of step 3 (all patients)	94	

Abbreviations as in Tables 1 and 2.

phase of the study in adolescent subjects with HeFH. Prolonged reductions were maintained through 53 weeks in the overall study population. Significantly greater reductions from baseline in total cholesterol, non–HDL-C, and apo B levels were also documented after 6 weeks and again at 33 weeks in subjects who received coadministration of ezetimibe with simvastatin compared with simvastatin monotherapy. These parameters also remained at reduced levels throughout the final 20-week phase of the study.

Mean incremental LDL-C reductions associated with coadministration of ezetimibe were consistent across the 10-, 20-, and 40-mg simvastatin dosing groups after 6 weeks of treatment and significantly more subjects had reached NCEP/AAP recommended LDL-C goals in the coadministration group than in the monotherapy group by the end of 33 weeks. These results suggest that ezetimibe coadministration may help more adolescent subjects with HeFH reach their lipid goals, as well as allow lower doses of simvastatin to be used. Achievement of specific lipid goals in adolescence has not been demonstrated to provide long-term reduction in cardiovascular risk for patients with HeFH in this study and requires further work to establish target lipid goals as they relate to long-term outcome. However, initiation of intervention for dyslipidemias by pediatricians with specific lipid goals for pediatric patients have been recommended by expert opinion (4,5) and are useful in clinical practice to assess progress and efficacy of therapy.

There were no important differences between groups in treatment-emergent adverse events or serious adverse events, suggesting no additional toxicity associated with ezetimibe coadministration with simvastatin compared with simvastatin monotherapy. Although the study was not powered to detect significant differences between groups in safety parameters, these data as well as the low rates of discontinuation in all 3 phases of the study are promising with respect to tolerability and safety of these agents in this population. These considerations are important for this population, whose exposure to lipid abnormalities is lifelong unless treatment is consistently maintained. Previous work suggests that the timing of treatment of dyslipidemias with statins in children is an independent predictor of carotid IMT within 5 years, suggesting that earlier exposure to treatment delays progression of carotid IMT compared with later initiation of treatment (11). Increasing the exposure to low levels of cholesterol by the addition of ezetimibe to statin therapy in young patients would be expected to provide additional benefit. Further work in the context of optimized lipid-lowering therapy, using carotid IMT measurements and other markers, is needed to evaluate long-term benefits for these high-risk patients.

We conclude that coadministration of ezetimibe with simvastatin was significantly more efficacious for reducing LDL-C levels and improving lipid profiles than simvastatin monotherapy in adolescent subjects with HeFH. Regimens of ezetimibe with simvastatin were well tolerated. Coadministration of ezetimibe may be considered an important treatment strategy for adolescent patients 10 to 17 years of age with HeFH who require a statin plus adjunctive therapy to reach recommended LDL-C goals.

Acknowledgments

The authors thank the investigators and staff at study sites for their significant contributions to the success of this clinical trial.

Reprint requests and correspondence: Dr. John J. P. Kastelein, Department of Vascular Medicine, Academic Medical Centre, Meibergdreef 9, Room F4-159.2, 1105 AZ Amsterdam, the Netherlands. E-mail: j.j.kastelein@amc.uva.nl.

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Key Words: ezetimibe ■ simvastatin ■ heterozygous familial hypercholesterolemia ■ efficacy ■ safety ■ pediatric.

APPENDIX

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