Efficacy and Safety of Ezetimibe Monotherapy in Children with Heterozygous Familial or Nonfamilial Hypercholesterolemia

D. Meeike Kusters, MD[1], Maria Caceres, MS[2], Mauricio Coll, MD[3], Cynthia Cuffie, MD[2], Claude Gagné, MD[4], Marc S. Jacobson, MD, FAHA[5], Peter O. Kwiterovich, MD[6,†], Raymond Lee, BS[2], Robert S. Lowe, PhD[2], Rachid Massaad, MS[7], Brian W. McCrindle, MD, MPH[8], Thomas A. Musliner, MD[2], Joseph Triscari, PhD[2], and John J. P. Kastelein, MD, PhD[1]

Objectives To evaluate the lipid-altering efficacy and safety of ezetimibe monotherapy in young children with heterozygous familial hypercholesterolemia (HeFH) or nonfamilial hypercholesterolemia (nonFH).

Study design One hundred thirty-eight children 6-10 years of age with diagnosed HeFH or clinically important nonFH (low-density lipoprotein cholesterol [LDL-C] ≥160 mg/dL [4.1 mmol/L]) were enrolled into a multicenter, 12-week, randomized, double-blind, placebo-controlled study. Following screening/drug washout and a 5-week single-blind placebo-run-in with diet stabilization, subjects were randomized 2:1 to daily ezetimibe 10 mg (n = 93) or placebo (n = 45) for 12 weeks. Lipid-altering efficacy and safety were assessed in all treated patients.

Results Overall, mean age was 8.3 years, 57% were girls, 80% were white, mean baseline LDL-C was 228 mg/dL (5.9 mmol/L), and 91% had HeFH. After 12 weeks, ezetimibe significantly reduced LDL-C by 27% after adjustment for placebo ($P < .001$) and produced significant reductions in total cholesterol (21%), nonhigh-density lipoprotein cholesterol (26%), and apolipoprotein B (20%) ($P < .001$ for all). LDL-C lowering response in sex, race, baseline lipids, and HeFH/nonFH subgroups was generally consistent with overall study results. Ezetimibe was well tolerated, with a safety profile similar to studies in older children, adolescents, and adults.

Conclusions Ezetimibe monotherapy produced clinically relevant reductions in LDL-C and other key lipid variables in young children with primary HeFH or clinically important nonFH, with a favorable safety/tolerability profile. *(J Pediatr 2015;166:1377-84)*.

Trial registration ClinicalTrials.gov: NCT00867165.

Familial hypercholesterolemia (FH) is an inherited disorder of lipoprotein metabolism and the most prevalent cause for primary dyslipidemia in children.[1] Studies of FH highlight the direct link between elevated levels of low-density lipoprotein cholesterol (LDL-C) from birth, increased risk for atherosclerosis beginning in childhood, and premature development of cardiovascular disease.[2] Recent reports from the American Academy of Pediatrics,[3] National Heart, Lung, and Blood Institute,[4] National Lipid Association,[5] and European Society of Cardiology/European Atherosclerosis Society[6] provide guidelines for early identification and treatment of children and adolescents at high risk for development of cardiovascular disease. For adolescents with high-risk dyslipidemia who do not achieve recommended lipid targets with therapeutic lifestyle/diet intervention, initiation of statin therapy is considered based on evaluation of overall cardiovascular risk. Other lipid-lowering drugs may also be used when dyslipidemia is not adequately controlled by statins alone, or when issues of statin intolerance occur.

Ezetimibe is a cholesterol absorption inhibitor that lowers LDL-C and other key lipid/lipoprotein variables by selective inhibition of the NPC1L1 sterol transporter, thereby reducing dietary and biliary cholesterol uptake in the small intestines.[7] Evidence suggests that ezetimibe may also inhibit hepatic NPC1L1 transporter function and block biliary cholesterol absorption back to the liver. Coadministration of ezetimibe with statins has been evaluated in adult and adolescent patients with homozygous and heterozygous FH (HoFH, HeFH) and shown to produce significant incremental reductions in LDL-C of ~15%-

AE	Adverse event	HeFH	Heterozygous FH
ALT	Alanine aminotransferase	HoFH	Homozygous FH
AST	Aspartate aminotransferase	hs-CRP	High-sensitivity C-reactive protein
AUC	Area under the curve	LDL-C	Low-density lipoprotein cholesterol
C_{max}	Peak plasma concentration	NonFH	Nonfamilial hypercholesterolemia
FH	Familial hypercholesterolemia	PH	Polygenic hypercholesterolemia
HDL-C	High-density lipoprotein cholesterol	ULN	Upper limit of normal

From the [1]Department of Vascular Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; [2]Merck and Co, Inc, Whitehouse Station, NJ; [3]Centro Almirante Colon, Bogota, Colombia; [4]La Clinique des Maladies Lipidiques de Quebec, Inc, Quebec, Quebec, Canada; [5]ProHealth Care Associates, New York, NY; [6]The Johns Hopkins University, Baltimore, MD; [7]MSD Belgium, Brussels, Belgium; and [8]The Hospital for Sick Children, Toronto, Ontario, Canada

†Deceased.

Supported by Merck & Co, Inc, Whitehouse Station, NJ. C.G. has participated in clinical trials with AstraZeneca, Pfizer, Merck, Amgen, Regeneron, Sanofi, Genzyme, and Novartis. M.J. has received research grants from Merck. P. K. has received consulting fees/honoraria from Merck and research grants from Abbott Laboratories, GlaxoSmithKline, Merck, and Pfizer. R. M. is an employee of MSD Belgium. B. M. received reimbursement from Merck for participation in this study; serves as a consultant for Bristol Myers Squibb, Eli Lilly, Genzyme, and Janssen; is a DSMB member for Medpace; and participated in a trial sponsored by Astra Zeneca. J. K. has received consulting fees/honoraria from Merck. M. Ca., C. C., R. Le., R. Lo., T. M., and J. T. are employees or former employees of Merck and may own stock/stock options in the company. M. K. and M. Co. declare no conflicts of interest.

Portions of the study were presented at the American Cardiology Annual Scientific sessions (March 9-11, 2013, San Fransisco, CA) and the National Lipid Association Annual Scientific Sessions (May 30-June 2, 2013, Las Vegas, Nevada).

http://dx.doi.org/10.1016/j.jpeds.2015.02.043

20%,[8-11] consistent with studies in other high risk populations.[12] Studies of ezetimibe monotherapy in patients with HeFH have primarily focused on treatment of children and young adolescents, and are limited to open-label prospective trials[13] or retrospective data evaluation.[14,15] This current study is a randomized placebo-controlled trial to investigate the efficacy and safety of ezetimibe monotherapy in children with HeFH or clinically important nonfamilial hypercholesterolemia (nonFH).

Methods

Boys and girls ≥6 and ≤10 years of age with HeFH or clinically important nonFH (LDL-C >160 mg/dL [4.1 mmol/L]) while on a lipid-lowering diet[3,16] for ≥3 months were eligible for the trial. Clinical criteria for HeFH included LDL-C levels >189-<400 mg/dL (4.9-10.4 mmol/L) with a family history of hypercholesterolemia consistent with dominant autosomal transmission, or LDL-C >159-<400 mg/dL (4.1-10.4 mmol/L) and at least 1 of the following: (1) genotype confirmed HeFH; (2) at least 1 biological parent with genotype-confirmed HeFH and a historic untreated LDL-C of >159 mg/dL (4.2 mmol/L); (3) at least 1 biological parent with an untreated LDL-C value ≥210 mg/dL (5.4 mmol/L) not associated with a disorder known to elevate LDL-C; or (4) tendinous xanthomas not associated with a disorder known to elevate LDL-C. Clinical criteria for primary nonFH was an LDL-C >159-<400 mg/dL (4.1-10.4 mmol/L) and a clinical diagnosis of primary nonFH.

Subjects eligible for study entry had fasting triglyceride levels ≤300 mg/dL (7.8 mmol/L), clinical laboratory values within normal limits or clinically acceptable to the investigator, alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≤1.5 the upper limit of normal (ULN), serum creatinine <2.0 mg/dL (177 umol/L), and were free of any clinically important disease other than hypercholesterolemia that would interfere with study evaluation. Main exclusion criteria included hypersensitivity or any contraindication to ezetimibe; any cardiac disorder or disorders of the hematologic, digestive, or central nervous systems including cerebrovascular disease, anorexia nervosa, and degenerative disease that would limit study evaluation/participation; diabetes mellitus type 1 or 2; uncontrolled endocrine metabolic disease known to influence serum lipids or lipoproteins; unstable thyroid hormone replacement therapy with thyroid stimulating hormone levels outside the normal range; clinically significant impairment of renal function, dysproteinemia, nephrotic syndrome, or other renal disease; active or chronic hepatic or biliary disease; history of partial ileal bypass or disease that affects significant function of the ileum; HIV infection; known coagulopathy; medical history consistent with HoFH; and use of LDL apheresis or plasma apheresis. Known lipid-altering therapies, foods, or supplements were prohibited within a predefined time period prior to randomization.

This multicenter, 12-week, randomized, double-blind, placebo-controlled study (P05522) was conducted at 29 research sites (Canada [5 sites], Colombia [4 sites], France [2 sites], Greece [1 site], Israel [2 sites], Italy [4 sites], Norway [1 site], The Netherlands [2 sites], US [8 sites]) in accordance with principles of the International Conference on Harmonization Good Clinical Practice and all local and/or national regulations and directives. All independent ethics committees approved the protocol and applicable amendments, and written informed consent was provided by all parents/guardians on behalf of the child prior to enrollment.

Following a screening/drug washout period (up to 13 weeks), subjects underwent a single-blind placebo run-in and diet (step 2) stabilization[3,16] period of 5 weeks. On week 4 of the run-in/diet stabilization period, qualifying LDL-C (Friedewald calculation) and triglyceride levels were measured. Following the run-in, subjects who qualified were randomized 2:1 to double-blind treatment with either ezetimibe 10 mg tablets or matching placebo tablets, once daily for 12 weeks. Blood samples were obtained at weeks 0, 2, 4, 8, and 12 after a 12-hour fast; trial medication was taken after sampling. Subjects willing to participate in a pharmacokinetic substudy were randomized to daily ezetimibe 10 mg or placebo 4:1, and blood samples collected 2 weeks after randomization included time 0 (predose), and 1.5, 4, 5, 8, and 12 hours after administration of allocated study drug. Randomization was performed using a central interactive voice response system, and stratified (except for the pharmacokinetic substudy) by sex and by primary diagnosis of HeFH and nonFH. All study personnel, including investigators, study site personnel, patients, and monitors remained blinded to treatment allocation throughout the study; the final database was not unblinded until medical/scientific review was performed, protocol violators were identified, and the data file was declared final and frozen.

The primary trial objective was to determine the efficacy of ezetimibe 10 mg/d compared with placebo in reducing LDL-C in 6- to 10-year-old children with HeFH or clinically important nonFH. The primary efficacy endpoint variable was percent change from baseline in LDL-C levels after 12 weeks of treatment. Key secondary endpoint variables included percent change from baseline in total cholesterol, high-density lipoprotein cholesterol (HDL-C), non-HDL-C, triglycerides, and apolipoprotein B after 12 weeks of treatment. Other secondary efficacy endpoints included percent change from baseline in lipid/lipoprotein measures (weeks 2, 4, and 8), high-sensitivity C-reactive protein (hs-CRP, weeks 4 and 8), and plasma sterols (weeks 2, 4, 8, and 12). peak plasma concentration (C_{max}), area under the curve $(AUC)_{0\text{-}12\ hour}$, $AUC_{0\text{-}24\ hour}$, and time to peak plasma concentration for ezetimibe and total ezetimibe after 2 weeks of treatment were determined for a subset of study participants.

Evaluation of efficacy endpoints utilized the full analysis set population, including all randomized subjects receiving ≥1 dose of blinded study treatment with baseline and ≥1 postbaseline measurements. Percent change from baseline in LDL-C was analyzed using an ANCOVA mixed model with fixed effects for baseline LDL-C, treatment, sex, primary