CLINICAL REVIEW

Application Type	21-687
Submission Number	023
Submission Code	(b) (4)
Letter Date	17 December 2007
Stamp Date	19 December 2007
PDUFA Goal Date	19 June 2008
Reviewer Name	Eileen Craig, MD
Review Completion Date	04 June 2008
Established Name	Ezetimibe/simvastatin
(Proposed) Trade Name	Vytorin®
Therapeutic Class	Lipid-lowering drug
Applicant	Merck Schering Plough Singapore Co., LLC
Priority Designation	S
Formulation	Oral tablet
Dosing Regimen	10/10, 10/20, 10/40 mg Vytorin once daily
Indication	Ezetimibe/simvastatin (b) (4)

Intended Population	Heterozygous Familial Hypercholesterolemia Adolescents (10 to 17 years of age)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

(b) (4)

1.2 Risk Benefit Assessment

Study P02579 was conducted in order to fulfill the Written Request to evaluate the efficacy, safety and tolerability of Zetia and Vytorin in adolescents (≥ 10 to ≤ 17 years of age) with heterozygous familial hypercholesterolemia who have failed previous dietary intervention. Protocol P02579 was a randomized, double-blind, controlled, parallel-group, multicenter, phase 3 study of the effects and safety of coadministration of ezetimibe 10 mg/day plus simvastatin 10 mg/day, 20 mg/day, or 40 mg/day vs. simvastatin 10 mg/day, 20 mg/day, or 40 mg/day as monotherapy on LDL-C reduction for up to one year in 248 boys and post-menarchal girls with HeFH.

The study entry requirements for subjects ensured that the trial included a pediatric population

with HeFH and are summarized below:

Subjects were ≥10 to ≤17 years with a Tanner stage II or higher, body weight at least 40 kg, and above 10th percentile. Girls were postmenarchal (defined as at least 1 year after first menstrual period and having had at least 3 menstrual periods). The HeFH diagnosis was to be made by documentation of the genetic diagnosis or evidence of persistent elevation of LDL-C associated with a familial history of hypercholesterolemia according to the following criteria:

- genotype-confirmed HeFH with written documentation of the genetic diagnosis prior to or at the time of screening and LDL-C >159 mg/dL and <400 mg/dL.
- LDL-C values >159 mg/dL and <400 mg/dL with at least one biological parent with genotype confirmed HeFH and a historical untreated LDL-C of >159 mg/dL.
- LDL-C values >159 mg/dL and <400 mg/dL with at least one biological parent with an untreated LDL-C value of at least 210 mg/dL not associated with a disorder known to produce secondary elevation of LDL-C.
- LDL-C values >189 mg/dL and <400 mg/dL and a family history of hypercholesterolemia consistent with dominant autosomal transmission.
- LDL-C values >159 mg/dL and <400 mg/dL with tendinous xanthomas, not associated with a disorder known to produce secondary elevation of LDL-C.

Efficacy

The primary endpoint for this study is the percent change from Baseline in LDL-C at the end of 6 weeks in the pooled groups assigned to receive randomized treatment with ezetimibe plus simvastatin compared with that observed in the pooled groups assigned to receive randomized treatment with simvastatin monotherapy. Mean percent change of approximately −49% was evident in the Pooled ezetimibe/simvastatin coadministration treatment group compared with approximately −34% in the Pooled simvastatin monotherapy treatment group. The difference in low density lipoprotein cholesterol (LDL-C) between the pooled ezetimibe/simvastatin coadministration group and the pooled simvastatin monotherapy group was approximately -15%, (CI -18% to -12%), which was statistically significant. Since the overall treatment effect was significant, results between individual treatment groups were analyzed in a pairwise manner, as follows:

• EZ/simva 10/10 mg vs simva 10 mg monotherapy;
• EZ/simva 10/20 mg vs simva 20 mg monotherapy;
• EZ/simva 10/40 mg vs simva 40 mg monotherapy.

The incremental mean percent changes observed in the pairwise analyses were -16.34%, -15.19%, and -13.55%, respectively, and each result was statistically significant ($p<0.01$).

Analyses based on gender and race and baseline TG, LDL and HDL showed consistency of the treatment effect across these predefined subgroups, with a greater drop in LDL for EZ/simva over simvastatin alone after 6 and 33 weeks of treatment. Additional analyses by the FDA biostatistician showed consistency of effect across age as well.

Pooled ezetimibe/simvastatin coadministration treatment was more efficacious than the pooled simvastatin monotherapy in reducing total cholesterol (TC), non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), the ratio LDL-C:HDL:C, and the ratio TC:HDL-C from Baseline to Week 6 in adolescent boys and girls with heterozygous familial hypercholesterolemia (HeFH). The results were statistically significant ($p<0.01$, when adjusted for multiplicity). The difference in high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) between the pooled ezetimibe/simvastatin coadministration group and the pooled simvastatin monotherapy group was not statistically significant.

Treatment with ezetimibe/simvastatin coadministration was more efficacious than simvastatin monotherapy in reducing LDL-C, TC, non-HDL-C, ApoB, and TG, and the ratios LDL-C: HDL-C and TC:HDL-C from Baseline to Week 33 in adolescent boys and girls with heterozygous familial hypercholesterolemia (HeFH). The results were statistically significant ($p<0.01$).

Safety

Ezetimibe/simvastatin coadministration had no apparent effect on sexual maturation of adolescent boys and girls measured by rates of growth, Tanner staging, and steroid biosynthesis, and had no effect on menstrual cycles in adolescent girls.

There were no deaths reported for subjects enrolled in the P02579 trial. Serious adverse events were reported for 3% of subjects assigned to receive ezetimibe/simvastatin 10/40 mg coadministration therapy (4/126) and 1% of subjects assigned to receive simvastatin 40 mg monotherapy (1/122) from the start of the trial to the end of Week 33, and for 3% of subjects (6/238) during Long-Term Coadministration (Weeks 34-53). No adverse event was reported as serious by more than one subject during the trial.

A total of 9 subjects were discontinued from the study at the end of Week 33 due to adverse events: 7 subjects (6%), ezetimibe/simvastatin 10/40 mg coadministration and 2 subjects (2%), simvastatin 40 mg monotherapy group. The number of discontinuations were small but were numerically larger for EZ/simva for ALT increased, CPK increased, muscle spasms, and myalgia.

Hepatic

The number of subjects who had ALT or AST values that were ≥3xULN on at least two consecutive occasions from Baseline to the end of Week 33 was small overall and slightly larger in the EZ/simva group (4, 3%) as compared to the simva 40 mg group (2, 2%). Three out 238 subjects (1%) had ALT or AST values that were ≥3xULN on at least two consecutive occasions from Week 34 to the end of Week 53. Nine subjects had ALT increased reported as an adverse event (6 subjects [5%] assigned ezetimibe/simvastatin 10/40 mg and 3 subjects [2%] assigned simvastatin 40 mg monotherapy) from Baseline to the end of Week 33. Investigators reported AST increased as adverse event for three subjects: two subjects assigned to receive ezetimibe/simvastatin 10/40 mg and one subject assigned to receive simvastatin 40 mg monotherapy. There were 2 additional subjects for whom ALT increased was reported as an AE during Long-Term Coadministration (Weeks 34-53).

Musculoskeletal
The number of subjects who had blood creatine phosphokinase (CPK) values that were ≥3xULN from Baseline to the end of Week 33 were numerically larger in the EZ/simva 10/40 group (9, 7%) as compared to the simva 40 mg group (2, 2%). During the trial there were no subjects with CPK elevations ≥5xULN with "associated muscle symptoms." There were 2 subjects with transient CPK elevations ≥10xULN without "associated muscle symptoms", both of these subjects were in the EZ/simva 10/20 group. Six subjects had "CPK increased" reported as an adverse event (4 subjects [3%] assigned ezetimibe/simvastatin 10/40 mg and two subjects [2%] assigned simvastatin 40 mg monotherapy) from Baseline through the end of Week 33. Investigators reported myalgia as an adverse event for eight subjects (7 subjects [6%] assigned to ezetimibe/simvastatin 10/40 mg and 1 subject [1%] assigned simvastatin 40 mg monotherapy) from Baseline through the end of Week 33. The reports of myalgia were considered mild or moderate in severity. There were no new reports of myalgia as an adverse event during Long-Term Coadministration (Weeks 34-53). None of the reports of myalgia was associated with elevated CPK. Three subjects (2%) were discontinued from the study due to adverse events related to musculoskeletal function (myalgia or muscle spasm). All 3 subjects were female and were on EZ/simva (2 on 10/40; 1 on 10/20 mg).

During the trial there were no reports of angioedema, rhabdomyolysis, myopathy, pancreatitis, hepatitis, jaundice, clinical signs of liver dysfunction, cholecystectomies, or cholecystitis.

Conclusion
Results of study P02579 demonstrated that ezetimibe coadministered with simvastatin to pediatric subjects (≥10 to ≤17 years of age) with HeFH provided the same lipid-lowering effect with a similar safety profile as observed in adult patients. The adult safety profile, similar to the pediatric profile, shows that when ezetimibe is co-administered with a statin, modest (≥3x ULN but <10x ULN) increases in consecutive transaminases occur more frequently than with statin monotherapy. The frequencies of CPK elevations and myopathy were not consistently higher in adult patients treated with ezetimibe 10 mg+statin compared to the same type and dose of statin given alone. However, in the adolescent experience, there was an increase in the frequencies of CPK elevations in the ezetimibe + statin group as compared to the dose of statin given alone but there were no cases of myopathy in either group.

The approval of ezetimibe coadministered daily with approved pediatric doses of a statin for the treatment of HeFH in pediatric patients will provide a more effective means for lowering cholesterol levels over lifestyle and dietary changes. Although LDL-C is an established risk factor for cardiovascular disease, the effect of initiating therapy with ezetimibe/statin in childhood on the risks for CV events manifested in adulthood are not known. To the extent that long-term safety data are limited and the clinical benefits of initiating therapy in children are not yet established, the decision to initiate therapy in children with primary hyperlipidemia and heterozygous FH should be based on the individual's risk profile and family history.

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1.3 Recommendations for Postmarketing Risk Management Activities

None

1.4 Recommendations for other Post Marketing Study Commitments

None

2 Introduction and Regulatory Background

Merck Schering Plough Singapore has submitted this supplemental new drug application for Zetia® and Vytorin® seeking to fulfill the Pediatric Written Request and gain pediatric exclusivity. The Written Request was issued by FDA on April 14, 2004, and amended on November 23, 2004, requesting that the applicant conduct a clinical study in pediatric boys and girls with heterozygous familial hypercholesterolemia (HeFH) to characterize the efficacy and safety of Zetia as add-on therapy to a statin. Ezetimibe, Zetia®, is in a class of lipid-lowering compounds that selectively inhibits the intestinal absorption of cholesterol and related phytosterols; it was approved in October 2002 for the treatment of hypercholesterolemia. Vytorin contains ezetimibe and simvastatin, a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor.

Familial hypercholesterolemia is a monogenic autosomal codominant form of hypercholesterolemia that results from mutation of the LDL-receptor gene and produces a clinically recognizable pattern of severe hypercholesterolemia, cholesterol deposition in tendons, and a high risk of atherosclerosis and premature coronary artery disease. Patients with homozygous FH have two mutant alleles at the genetic locus for the LDL receptor. Depending on the type of LDL receptor mutation ('receptor defective' with < 20% of normal receptor activity or 'receptor negative' with < 5% of normal receptor activity), these individuals have minimal or no ability, respectively, to clear LDL from the circulation via the LDL receptor. The homozygous form of the genetic defect has an overall prevalence of 1 in 1 million individuals. Homozygotes are clinically described by elevated plasma cholesterol levels up to 10-fold higher than normal and by both maternal and paternal history of premature heart disease. Premature death from a major adverse cardiovascular event is the predominant outcome of this genetic defect.

Patients with heterozygous FH (HeFH) have a single mutant allele at the genetic locus for the LDL receptor. HeFH has a prevalence of 1 in 500 worldwide making it the most common inherited dyslipidemic syndrome affecting the pediatric population. HeFH carries with it a similarly poor prognosis if left undiagnosed and/or inadequately treated. The manifestations of the disease in heterozygotes are variable depending on the functional activity of the mutated receptor and may range from mildly elevated cholesterol to severe hypercholesterolemia and clinical manifestations approaching those of the homozygotes. Clinically, the symptoms are the result of LDL deposition in the skin, tendons and arterial plaques. Without treatment, the average age of onset of CAD is 40-45 years in men and 50-55 years in women. Although patients with HeFH respond better to LDL-C-lowering drug therapy than patients with HoFH, they do not respond to higher doses of statins as well as patients with polygenic hypercholesterolemia. Drug therapy for pediatric HeFH patients was initially limited primarily to use of bile-acid sequestrants because of the concerns about the safety of absorbable pharmacotherapies. The American Academy of Pediatrics' position paper (AAP 1998) cites the documented efficacy and apparent safety of bile acid sequestrants in children as reasons for the preferred use of this class. However, these drugs do not have an FDA-approved indication for use in children and adolescents. Additionally, problems with tolerability exist and bile acid sequestrants result in relatively modest reductions in LDL (15-19%) in children (Groot 1983, Tonstad 1996). Several large placebo-controlled studies have, however, evaluated the efficacy and safety of statins in pediatric FH heterozygotes. The results of Lovastatin in Adolescent Males (LAMS) (Stein 1999) along with a similar study conducted in females (GALS) were submitted to the FDA in April 2001. In addition, many of the statins have been evaluated in large, placebo-controlled trials in adults with evidence of reduction in cardiovascular mortality and morbidity with a reasonable adverse event profile. These data provided the rationale for evaluating the safety and efficacy of statins in pediatric patients. Currently, statins with FDA-approval for use in pediatric patients with HeFH are Mevacor (lovastatin), Zocor (simvastatin), Lipitor (atorvastatin), Lescol (fluvastatin) and Pravachol (pravastatin).

2.1 Product Information

Vytorin contains ezetimibe, a selective inhibitor of intestinal cholesterol and related phytosterol absorption, and simvastatin, a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor. Ezetimibe monotherapy has been shown to reduce LDL-C, apo B, and TG, and to slightly increase HDL-C. Simvastatin reduces cholesterol by inhibiting the conversion of HMG-CoA to mevalonate, an early step in the biosynthetic pathway for cholesterol. Simvastatin reduces LDL-C, very low density lipoprotein cholesterol (VLDL-C) and TG and increases HDL-C.

Mode of Action
Plasma cholesterol is derived from intestinal absorption and endogenous synthesis. Vytorin contains ezetimibe and simvastatin, two lipid-lowering compounds with complementary mechanisms of action. Ezetimibe reduces cholesterol by inhibition of dietary and biliary cholesterol absorption at the level of the intestinal brush border. Decreased delivery of intestinal cholesterol to the liver is associated with reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from blood. Inhibition of absorption of triglycerides and fat-soluble vitamins has not occurred. 1

Simvastatin reduces cholesterol by inhibiting the conversion of HMG-CoA to mevalonate, an early step in the biosynthetic pathway for cholesterol. In addition, simvastatin reduces VLDL and TG and increases HDL-C. Vytorin reduces elevated total-C, LDL-C, Apo B, TG, and non-HDL-C, and increases HDL-C through dual inhibition of cholesterol absorption and synthesis.2

Pharmacology
Ezetimibe is insoluble, but has been [redacted], resulting in rapid absorption. The drug is extensively conjugated in the intestine, forming an active metabolite, ezetimibe-glucuronide, which represents 80-90% of total drug in plasma. It is excreted primarily in stool. The drug recirculates enterohepatically and is repeatedly redelivered to intestine, with associated reported reduced systemic exposure.3 Ezetimibe can be administered with or without food and is dosed once daily at any time.

No clinically significant pharmacokinetic interaction was seen when ezetimibe was coadministered with simvastatin. Four-fold increased exposure occurred in moderate-severe liver disease, and two-fold increased exposure occurred in elderly patients. Active liver disease is a contraindication to use of the drug. No other significant effects occurred involving the activity of CYP-1A2, -2C8, -2C9, -2D6 and -3A4.

Simvastatin is a lactone that is readily hydrolyzed *in vivo* to the corresponding β-hydroxyacid, a potent inhibitor of HMG-CoA reductase. Simvastatin undergoes extensive first-pass extraction in the liver, its primary site of action, with subsequent excretion of drug equivalents in the bile. As

1 Zetia approved product label, March 2005
2 Vytorin approved product label, March 2005
3 van Heek M et al. The potent chol absorp inhibitor, ezetimibe, is glucuronidated in the intestine, localizes to the intestine, and circulates enterohepatically (abstr). Atherosclerosis 2000. 151:155.

a consequence of extensive hepatic extraction of simvastatin (estimated to be >60% in man), the availability of drug to the general circulation is low.

Efficacy
Vytorin reduces total-C, LDL-C, Apo B, TG, and non-HDL-C, and increases HDL-C in patients with hypercholesterolemia. Maximal to near maximal response is generally achieved within 2 weeks and maintained during chronic therapy. In a multicenter, double-blind, placebo-controlled, 12-week trial, Vytorin reduced the mean % change in LDL-C from 45 (Vytorin 10/10) to 60 (Vytorin 10/80).

Safety
Myopathy and rhabdomyolysis are known adverse reactions to HMG-CoA reductase inhibitors and other lipid-lowering drugs. In clinical trials, the incidence of CK >10 X the upper limit of normal [ULN] was 0.2% for Vytorin.

When ezetimibe is co-administered with a statin, modest (≥3x ULN but <10x ULN) increases in transaminases occurred somewhat more frequently when ezetimibe and statins were coadministered (1.3%) than with statin alone (0.4%).

Vytorin should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards.

Vytorin's approved label indications read:

Primary Hypercholesterolemia
VYTORIN is indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, Apo B, TG, and non-HDL-C, and to increase HDL-C in patients with primary (heterozygous familial and non-familial) hypercholesterolemia or mixed hyperlipidemia.

Homozygous Familial Hypercholesterolemia (HoFH)
VYTORIN is indicated for the reduction of elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

2.2 Tables of Currently Available Treatments for Proposed Indications

The following sections contain the current (as of 04 Feb 08) information from the INDICATIONS AND USAGE sections of the labels of drugs that have indications for Hypercholesterolemia in adolescents:

Drug	Indication
Lescol/Lescol XL/fluvastatin	adjunct to diet to reduce Total-C, LDL-C, and Apo B levels in adolescent boys and girls who are at least one year post-menarche, 10-16 years of age, with heterozygous familial hypercholesterolemia whose response to dietary restriction has not been adequate and the following findings are present: 1. LDL-C remains ≥ 190 mg/dL or 2. LDL-C remains ≥ 160 mg/dL and: • there is a positive family history of premature cardiovascular disease or • two or more other cardiovascular disease risk factors are present.
Lovastatin/Mevacor	adjunct to diet to reduce total-C, LDL-C and apolipoprotein B levels in adolescent boys and girls who are at least one year post-menarche, 10-17 years of age, with heFH if after an adequate trial of diet therapy the following findings are present: 1. LDL-C remains >189 mg/dL or 2. LDL-C remains >160 mg/dL and: • there is a positive family history of premature cardiovascular disease or • two or more other CVD risk factors are present in the adolescent patient
Zocor/simvastatin	adjunct to diet to reduce total-C, LDL-C, and Apo B levels in adolescent boys and girls who are at least one year post-menarche, 10-17 years of age, with heterozygous familial hypercholesterolemia, if after an adequate trial of diet therapy the following findings are present: 1. LDL cholesterol remains ≥190 mg/dL; or 2. LDL cholesterol remains ≥160 mg/dL and • There is a positive family history of premature cardiovascular disease (CVD) or • Two or more other CVD risk factors are present in the adolescent patient. The minimum goal of treatment in pediatric and adolescent patients is to achieve a mean LDL-C <130 mg/dL. The optimal age at which to initiate lipid-lowering therapy to decrease the risk of symptomatic adulthood CAD has not been determined.
Pravachol/pravastatin	adjunct to diet and lifestyle modification for treatment of HeFH in children and adolescent patients ages 8 years and older if after an adequate trial of diet the following findings are present: 1. LDL-C remains ≥190 mg/dL or 2. LDL-C remains ≥160 mg/dL and: • there is a positive family history of premature cardiovascular disease or • two or more other CVD risk factors are present in the patient.
Lipitor/atorvastatin	adjunct to diet to reduce total-C, LDL-C, and apoB levels in boys and postmenarchal girls, 10-17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present:

	1. LDL-C remains ≥190 mg/dL or 2. LDL-C remains ≥160 mg/dL and: • there is a positive family history of premature cardiovascular disease or • two or more other CVD risk factors are present in the pediatric patient.

2.3 Availability of Proposed Active Ingredient in the United States

Vytorin® is widely available by prescription in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

Statins inhibit cholesterol biosynthesis and the concern has been that they may have adverse effects on gonadal and adrenal steroid biosynthesis. Such effects might then mediate disruption of growth and sexual development. The development of lovastatin and then subsequently other statins provided information that lessened this concern. The information includes an understanding that even FH homozygotes without LDL-receptors have normal adrenal and gonadal function and normal ACTH stimulation test responses; ACTH stimulation testing in adults and gonadal steroid levels in adults are not impacted by statin therapy; and previous studies in children have not revealed any gross problems with growth or sexual development. Growth and sexual development monitoring was requested in this study to provide further assurance of safety in this regard. The Division realizes that the size and scope of this study is such that only gross adverse effects on growth and sexual development would be detectable.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

At the time of initial approval of ezetimibe in the United States, the FDA granted a waiver of pediatric studies for the treatment of hypercholesterolemia in children <10 years of age and granted a deferral of pediatric studies in children ≥10 years of age (October 25, 2002). On June 28, 2003, FDA provided recommendations regarding the study design for the applicant's proposed pediatric protocol P02579. It was agreed that for pediatric use, a study evaluating ezetimibe and simvastatin would suffice to demonstrate safety and efficacy of ezetimibe coadministered with all approved statins; individual studies evaluating ezetimibe coadministered with each statin were not required.

October 25, 2002
In the letter granting the initial US approval of ezetimibe, FDA granted a waiver of pediatric studies for the treatment of hypercholesterolemia in children < 10 years of age and granted a deferral of pediatric studies in children ≥ 10.

June 28, 2003
FDA provided recommendations regarding the study design for pediatric protocol

P02579. It was agreed that for pediatric use, a study evaluating ezetimibe and simvastatin would suffice to demonstrate safety and efficacy of ezetimibe coadministered with all approved statins; individual studies evaluating ezetimibe coadministered with each statin were not required. Accordingly, the written request and labeling reflect ezetimibe in combination with an approved HMG-CoA reductase inhibitor.

April 15, 2004
A written request was issued for a three period efficacy and safety study of ezetimibe coadministered with an approved statin in adolescents (≥ 10 to ≤ 17 years of age) with heterozygous familial hypercholesterolemia who have failed previous dietary intervention.

(b) (4)

October 6, 2004
Correspondence to NDA 21-687 dated October 6, 2004, states the following: We have reviewed the submission and agree that a waiver is justified for Vytorin (b) (4) for the entire pediatric population because the information will be provided when you comply with the April 15, 2004 Written Request issues for Zetia (ezetimibe) Tablets (NDA 21-445).

November 23, 2004
An amendment to the written request was issued removing insulin-like growth factor 1 and bone age from the list of secondary efficacy endpoints.

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2.6 Other Relevant Background Information

On January 14, 2008, Merck/Schering Plough Pharmaceuticals issued a Press Release reporting preliminary results from the Effect of Combination Ezetimibe and High-Dose Simvastatin vs. Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia (ENHANCE) trial. On January 25, 2008, FDA issued an "early communication" describing the study and the FDA's current recommendation, which is summarized below.

ENHANCE was designed to evaluate the amount of atherosclerotic plaque in the carotid vessels located based on images obtained through ultrasound in patients treated with Vytorin (ezetimibe plus simvastatin) or simvastatin alone. Merck/Schering Plough Pharmaceuticals stated that there was no significant difference between Vytorin and simvastatin in the amount of atherosclerotic plaque in the inner walls of the carotid arteries despite greater lowering of LDL-cholesterol with Vytorin compared to simvastatin.

ENHANCE was a 2-year, multi-national, randomized, double-blind study conducted in 720 patients with heterozygous familial hypercholesterolemia (HeFH). Half of the patients were treated with 10 mg of ezetimibe combined with 80 mg of simvastatin and half with 80 mg of simvastatin alone.

There are no clinical studies available that demonstrate a reduction in risk of heart attack or stroke when ezetimibe is used alone or in combination with a statin, including the fixed-dosed combination drug of ezetimibe and simvastatin, Vytorin. While the overall incidence of cardiovascular events in ENHANCE was similar in both the ezetimibe/simvastatin and simvastatin-alone groups, there were not enough patients in this study to reliably test whether treatment with ezetimibe/simvastatin compared with simvastatin alone reduces the risk of cardiovascular events. An ongoing trial known as IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) is examining this question in 18,000 patients and will likely be completed in 2012.

After reviewing the data from the ENHANCE study, and considering all other available information about the link between LDL lowering and reduction of cardiovascular events, FDA will determine whether any further regulatory action is warranted with regard to Zetia and Vytorin and also whether any changes to FDA's current approach to drugs that lower LDL cholesterol are warranted.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

3.1.1 Provisions to Enhance Data Integrity

The following provisions were included to enhance data integrity:

- All lipid determinations for the protocol-specified visits were obtained through the central laboratory.
- All details of the study were reviewed and discussed among the participants, and a manual was provided to each investigator for future reference.
- Quality of the data collected at the study site of the clinical investigation was assured by the procedures specified in the standard operating procedures (SOPs) of Schering Plough.

- Regular monitoring visits were made to the site to confirm that the study was being conducted in accordance with the protocol and the SOPs of Schering Plough, and with adherence to applicable regulatory requirements.

3.1.2 Division of Scientific Investigations (DSI)

The Division of Scientific Investigations was not asked and did not conduct an audit or site visit for this application. Patients were enrolled at 47 US and international study sites.

3.2 Compliance with Good Clinical Practices

3.2.1 Ethics

The applicant asserts that prior to study initiation, the study protocol and written informed consent were reviewed and approved by an Institutional Review Board (IRB). The applicant asserts that the study was conducted in accordance with good clinical practice (GCP) and with the internal standard operating procedures (SOPs) of Schering- Plough Research Institute.

3.2.2 Informed Consent

Written informed consent was obtained prior to any study-related activity. A sample written information/consent form was provided

3.2.3 Protocol Violations

There was only one subject who was discontinued from the treatment phase for non-compliance with the protocol. Minor protocol deviations did occur but were not likely to have had a significant effect on the study results.

3.3 Financial Disclosures

Schering Plough
There is one covered study for this NDA. Schering Plough states that all investigators have certified that they have not entered into any financial arrangements with Schering Plough and a review of internal records showed no significant payments of any sort. Per Form 3454, certification is provided for 146 of the 146 investigators indicating that they have no Financial Arrangement as defined in 21 CFR 54.2

Merck

Table A-1 Summary of Covered Clinical Study				
Product/Protocol	**Protocol Title**	**First Patient Screened**	**Last Patient Out**	**Financial Disclosure Information Cut-Off Date**
0653-049	Phase III Study to Evaluate the Efficacy, Safety, and Tolerability of Ezetimibe in Coadministration With Simvastatin in the Therapy of Adolescents With Heterozygous Familial Hypercholesterolemia	10-Aug-2005	29-Jun-2007	14-Nov-2007

Table A-3 details the total number of investigators in each of the categories that require reporting as defined in 21 CFR 54.2(a,b,c,f). As it is possible for an investigator to meet the definition for more than one category, the number of investigators in each sub-total may not add up to the total number of investigators.

Table A-3 Summary of Investigators by Category for the Covered Clinical Study

Category	Description	Sub-Total	Total
B-1	Grand Total Number of All Investigators/Subinvestigators	N/A	126
C-1	Total Number of Investigators/ Subinvestigators Certified Regarding the Absence of Financial Interests and Arrangements	N/A	119
C-2 *	Total Number of Investigators/ Subinvestigators Not Certified	• Investigator deceased n= 0 • Investigator did not return requested information n= 3 • Investigator no longer at site n= 2 • Other n= 0 • No forwarding address available n= 0	5
D-1 **	Total Number of Investigators/ Subinvestigators Who Hold Financial Interests or Arrangements Requiring Disclosure	• Compensation n= 0 • Equity Interest n= 0 • Proprietary or Financial Interest n= 0 • Significant Payments of Other Sorts n= 2	2

* Refer to Table C-2 for investigator details as it is possible for an investigator to meet more than one sub-total description within Table A-3.

** Refer to Table D-1 for investigator details as it is possible for an investigator to meet more than one sub-total description within Table A-3.

Table C-2 lists the names of all identified clinical investigators/subinvestigators by product, protocol and site number for the covered clinical study who did not provide the requested information by the cut-off date and includes the reason(s) the investigator could not be certified. In compliance with the regulatory requirement for the Sponsor to demonstrate "due diligence" (21 CFR 54.4), Merck states that multiple requests for this information were made, when possible, to investigators who did not respond.

Table C-2 Table of All Clinical Investigators/Subinvestigators Not Certified		
Product/Protocol/Site	**Investigator/ Subinvestigator**	**Reason**
0653-049-0001	(b) (4)	Did not return form with requested information. Forms sent on 04-18-2006
0653-049-0003		Investigator Left Site. Forms sent on 05-31-2006
0653-049-0004		Investigator Left Site. Forms sent on 07-24-2007
0653-049-0047		Did not return form with requested information. Forms sent on 04-03-2006
0653-049-0047		Did not return form with requested information. Forms sent on 04-21-2006

Table D-1 lists the names of all identified clinical investigators/subinvestigators by product, protocol and site number for the covered clinical study who have met the disclosure criteria regarding financial interests and arrangements as defined in 21 CFR 54.2(a,b,c,f).

Table D-1 Table of All Clinical Investigators/Subinvestigators Who Hold Financial Interests or Arrangements Requiring Disclosure		
Product/Protocol/Site	**Investigator/ Subinvestigator**	**Financial Interests or Arrangements**
0653-049-0021	(b) (4)	Significant Payments of Other Sorts: Amount: $90,000.00 ($90,000.00 in payments for consultant fees as reported by investigator on 11-01-2007).
0653-049-0023		Significant Payments of Other Sorts: Amount: $50,000.00 ($50,000.00 in speaker and consultant fees as reported by investigator on 04-24-2006).

The study was designed to minimize bias from an individual investigator (multicenter, randomized, and blinded with endpoints that included objective measures assessed in central laboratories). Thus, it appears unlikely that the results of these investigators and their sub-investigators receiving SPOOS would have biased the overall results.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please see relevant review by Dr. Janice Brown.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

Not applicable.

4.4 Clinical Pharmacology

Please see relevant pharmacology/toxicology review by Dr. Johnny S. W. Lau.
In protocol P02579, the marketed fixed-dose combination of Vytorin was not used. Ezetimibe (manufactured by the Schering Corporation) and simvastatin (manufactured by Merck & Co., Inc.) were used in this study. The fixed combination of ezetimibe/simvastatin is bioequivalent to coadministration of the individual components.

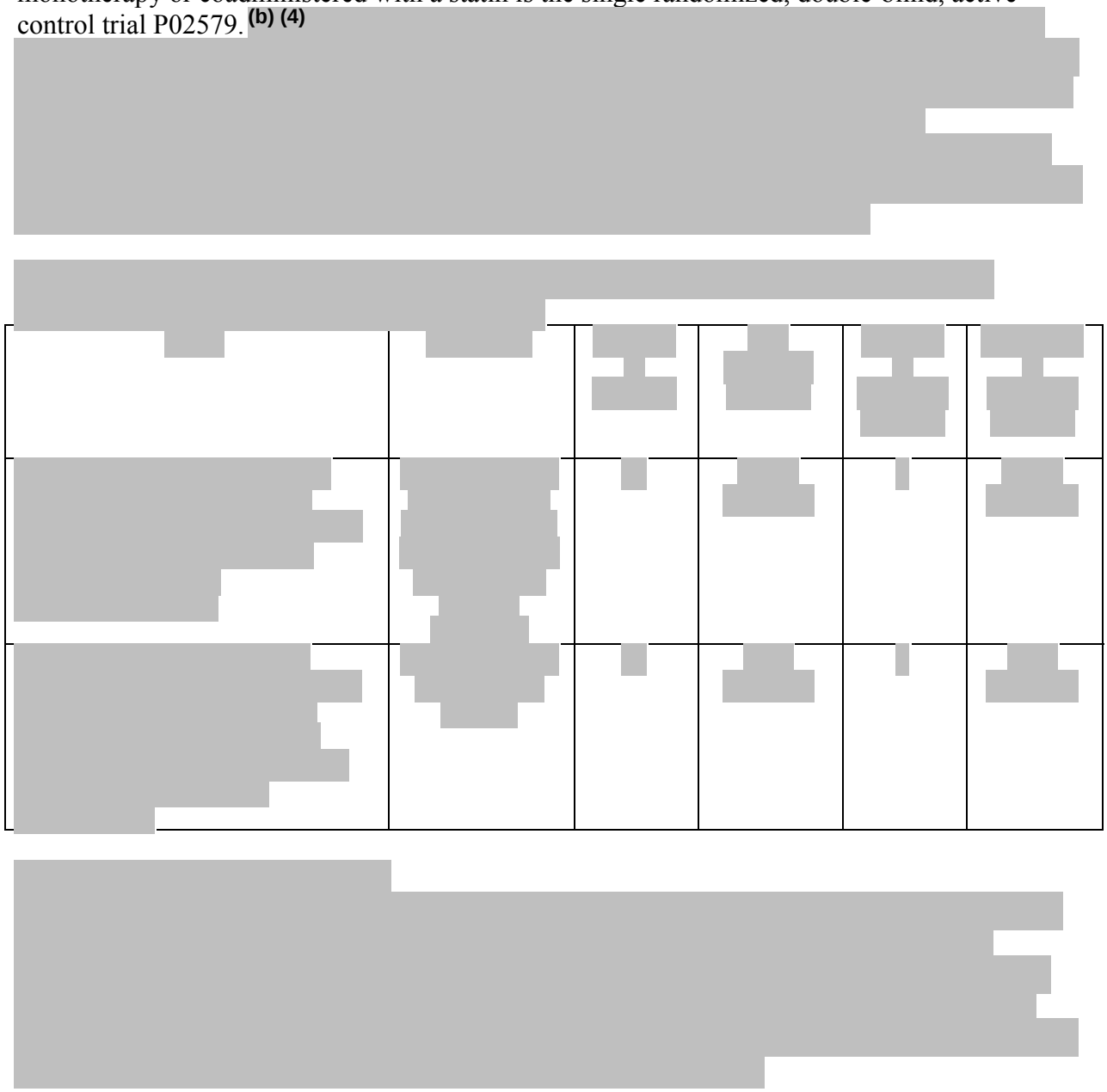
No new clinical pharmacology studies were conducted to support this current application regarding pediatric subjects. However, a Phase 1 clinical pharmacology trial P00774, in which pharmacokinetics of ezetimibe in adolescent subjects ≥10 to ≤18 years was measured, was submitted as part of the original ezetimibe and ezetimibe/simvastatin applications and is relevant to this current submission. Study P00774 was an 8-day, single-center, multiple-dose, open-label, parallel-group study in healthy, adolescent male and female subjects conducted to evaluate the pharmacokinetics and safety/tolerability of ezetimibe in adolescent children and serve as the basis for appropriate dose selection and inclusion of children with familial homozygous and heterozygous hypercholesterolemia in clinical safety and efficacy trials. Eighteen subjects with an age range of ≥10 to ≤18 years were enrolled and completed the study. Study P00774 demonstrated that the absorption, metabolism and pharmacokinetics of ezetimibe were similar in adolescents (10 to 18 years) and adults. In this study, two out of the 18 subjects enrolled (11%) reported treatment emergent adverse events, including headache (2/18; 11%), nausea (1/18, 6%), and vomiting (1/18, 6%). The adverse events reported by both subjects were considered by the Investigator as possibly related to treatment. Each adverse event in this study resolved without sequelae. All other safety assessments for subjects were within the normal ranges during the trial. There were no serious or significant adverse events or deaths reported in this study.

Table 4.4.1 Clinical Pharmacology Trial Submitted in the Original Ezetimibe and Ezetimibe/Simvastatin NDA That Included Pediatric Subjects

Study	Treatment	Number of Pediatric Subjects	Age range of Pediatric Subjects
P00774 a: Evaluation of the Pharmacokinetics and Safety of Multiple-Dose SCH 58235 (Ezetimibe) in Healthy Adolescent Volunteers	Ezetimibe 10 mg once daily for 7 days	18	≥10 to ≤18 years

5 Sources of Clinical Data

The pivotal study for the pediatric development program for ezetimibe administered as monotherapy or coadministered with a statin is the single randomized, double-blind, active control trial P02579. (b) (4)



(b) (4)

(b) (4)

(b) (4)

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5.1 Tables of Clinical Studies

Table 5.1 List of Clinical Studies

Type of Study	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
P02579	Measure efficacy and safety in pediatric subjects ≥10 years and ≤17 years of age with heterozygous familial hyper-choles-terolemia	3 Step trial: Step 1 and 2: randomized, double-blind, controlled, parallel-group. Step 3: open-label	Step 1: 6 treatment groups: EZ 10 mg/day plus simva 10 mg/day PO; EZ 10 mg/day plus simva 20 mg/day PO; EZ 10 mg/day plus simva 40 mg/day PO; EZ –matching placebo plus simva 10 mg/day PO; EZ –matching placebo plus simva 20 mg/day PO; EZ – matching placebo plus simva 40 mg/day PO. Step 2: 2 treatment groups: EZ 10 mg/day plus simva 40 mg/day PO; EZ-matching placebo plus simva 40 mg/day PO. Step 3: open label EZ 10 mg/day	Step 1: 248 Step 2: 240 Step 3: 228	Adolescent (≥10 and ≤17 years of age) boys and girls (postmenarc hal only), Tanner Stage II or higher, body weight at least 40 kg and above the 10th percentile with hetero-zygous familial Hypercholes terolemia.	Step 1: 6 weeks Step 2: 27 weeks additional Step 3: 20 weeks additional

5.2 Review Strategy

All reviewers conducted independent reviews, but collaborated on areas of controversy and individual questions. Please refer to the review of Joy Mele M.S., FDA statistical reviewer, for the efficacy statistical review.

5.3 Discussion of Individual Studies

This sNDA is based on Study P02579. The detailed review is included in the main body of this document.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

(b) (4)

hyperlipidemia.

Homozygous Familial Hypercholesterolemia (HoFH)
VYTORIN is indicated for the reduction of elevated total-C and LDL-C in adult and adolescent (10 to 17 years of age) patients with homozygous familial hypercholesterolemia, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

6.1.1 Methods

The clinical data used in the efficacy review (b) (4) are as follows:

- **Protocol P02579** is a randomized, double-blind, controlled, parallel-group, multicenter, phase 3 study to evaluate the efficacy and safety of the coadministration of EZ 10 mg/day plus simva 10 mg/day, 20 mg/day, or 40 mg/day vs simva 10 mg/day, 20 mg/day, or 40 mg/day as monotherapy on LDL-C reduction for up to one year in 248 adolescent (age ≥10 and ≤17 years) boys and post-menarchal (at least 1 year after first period) girls with HeFH.

The single pediatric study reviewed in this document (Study P02579) was designed by MSP Singapore Company to address written requests for both Zetia alone and Vytorin.

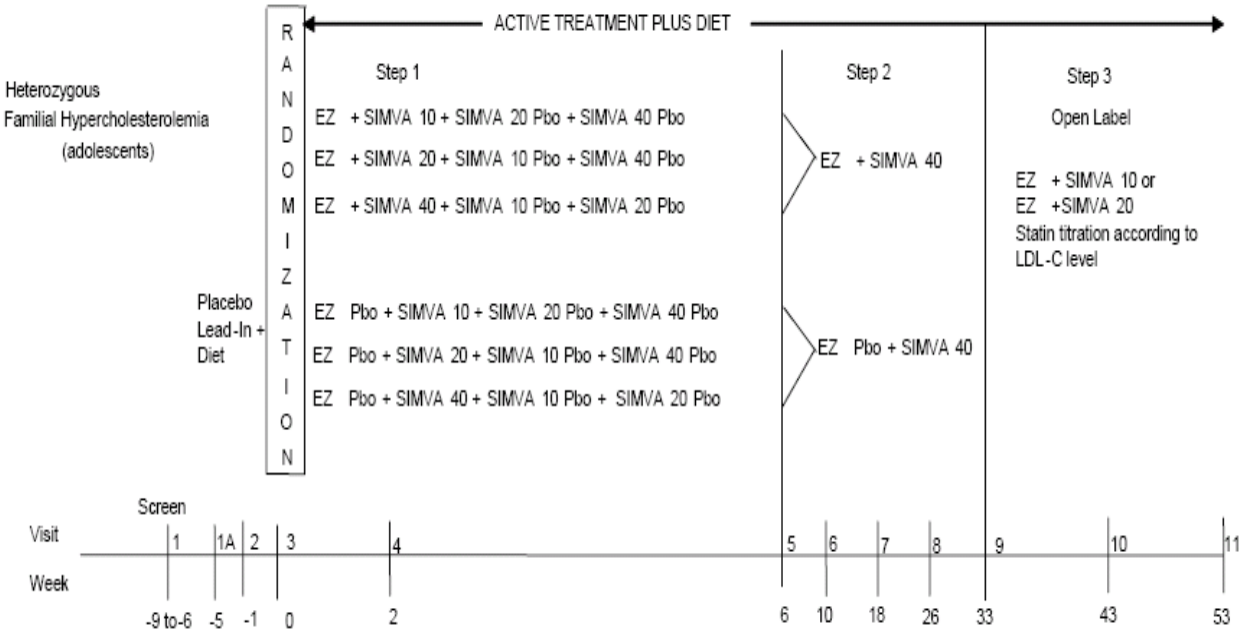
The written request asked for a three-period, efficacy and safety study of ezetimibe combined with an approved statin for the treatment of heterozygous familial hypercholesterolemia (HeFH) in adolescents with HeFH who have failed dietary intervention per guidelines of the American Academy of Pediatrics:

- Period One: Six-week, randomized, double-blind, parallel dose group study. Dose groups are to include approved (for heterozygous familial hypercholesterolemia) pediatric doses of the selected statin given as monotherapy or with ezetimibe. For example, if the selected statin has doses of 10 mg, 20 mg, and 40 mg approved for use in adolescents, there are to be six dose groups in the study: statin 10 mg plus placebo, statin 20 mg plus placebo, statin 40 mg plus placebo, statin 10 mg plus ezetimibe 10 mg, statin 20 mg plus ezetimibe 10 mg, and statin 40 mg plus ezetimibe 10 mg. The study is to include at least 180 randomized subjects, and at least 30 subjects randomized per Step One treatment group. After completion of Step One, patients will then enter:

- Period Two: Twenty-seven-week, double-blind, parallel group study of the maximum approved (for heterozygous familial hypercholesterolemia) pediatric dose of the selected statin, given with ezetimibe 10 mg or matching placebo. Patients will then enter:
- Period Three: Twenty-week, open-label, extension study of ezetimibe 10 mg given in combination with the selected statin, with titration of the statin dose to low-density lipoprotein cholesterol (LDL-C) goal (by National Cholesterol Education Program guidelines).

The trial was conducted, as shown in Figure 6.1.1, with three periods (or steps) as requested.

Figure 6.1.1 Trial Design



Source: Figure 1 of applicant's study report

Diagnosis and Criteria for Inclusion:
Adolescent boys and girls with HeFH were to be selected for the study.
Key Entry Criteria:

1. Adolescents (age ≥10 to ≤17 years) of either sex and of any race, Tanner Stage II or higher, body weight at least 40 kg and above 10th percentile (using accepted standards). Girls were to be postmenarchal, defined as at least 1 year after first menstrual period and having had at least 3 menstrual periods.
2. Subjects meeting at least one of the following clinical criteria:
    a. Genotype-confirmed HeFH with written documentation of the genetic diagnosis prior to or at the time of Screening, and LDL-C >159 mg/dL to <400 mg/dL.
    b. LDL-C values >159 mg/dL to <400 mg/dL with at least one biological parent with genotype-confirmed HeFH and a historical untreated LDL-C of >159 mg/dL.

c. LDL-C values >159 mg/dL to <400 mg/dL with at least one biological parent with an untreated LDL-C value of at least 210 mg/dL not associated with a disorder known to produce secondary elevation of LDL-C.
d. LDL-C values >189 mg/dL to <400 mg/dL and a family history of hypercholesterolemia consistent with dominant autosomal transmission.
e. LDL-C values >159 mg/dL to <400 mg/dL with tendinous xanthomas, not associated with a disorder known to produce secondary elevation of LDL-C.

3. Fasting plasma triglyceride level that was ≤350 mg/dL at Visit 1 and Visit 2.
4. Subjects were to have been on a diet in accordance with AAP guidelines for at least 13 weeks prior to the qualifying lipid determination at Visit 2 (Week -1).
5. Clinical laboratory tests (complete blood count [CBC], blood chemistries, and urinalysis) were to be within normal limits (except as noted in Item Nos. 6 and 7 below) or clinically acceptable to the investigator and sponsor.
6. Liver function tests, ALT (SGPT) and AST (SGOT), were to be ≤1.5 times the upper limit of normal (ULN) using the central laboratory reference range.
7. CPK determination was to be ≤1.5 times the upper limit of normal using the central laboratory reference range.
8. Subjects were to be free of any clinically significant disease (other than hypercholesterolemia) that would interfere with the study evaluations.

All efficacy data for this review were obtained from the sponsor's submitted supplemental NDA, which may be accessed through the FDA Electronic Document Room path \\CDSESUB1\NONECTD\N21445\S_020\2007-12-14.

6.1.2 Demographics

According to the written request the trial was to include adolescents (boys and postmenarchal girls, ages ≥ 10 years and ≤ 17 years, Tanner stage ≥ II) with heterozygous familial hypercholesterolemia (HeFH) who had failed dietary intervention per guidelines of the American Academy of Pediatrics. A reasonable balance of gender (no fewer than 30% of one gender) was to be attained at randomization. The study was to include at least 180 randomized subjects, and at least 30 subjects randomized per Step One treatment group.

A total of 248 adolescent subjects, 10 to 17 years of age, were enrolled and received randomized treatment assignment. Two of these girls (subjects 15/925 and 22/943) did not have both at least one baseline and at least one postbaseline lipid determination and thus could not be analyzed in the ITT population. Therefore the ITT data set included 246 subjects (104 girls and 142 boys). Boys and postmenarchal girls, ages ≥ 10 years and ≤ 17 years, Tanner stage ≥ II were enrolled. 106 females (42.7%) and 142 males (57.3%) were randomized. The median age for boys was 14 years and 15 years for girls. All subjects were of Tanner stage 2 or above. The clinical study report included information on the representation of pediatric patients of ethnic and racial minorities according to the categories and designations in the pediatric Written Request: 81.6% of the cohort were classified as White; 4% Asian; 1.7% Black; 0% "American Indian or Alaskan

Native" or as "Native Hawaiian or Other Pacific Islander"; multi-racial 13.2%. Ethnicity: 13.8% Hispanic/Latino; 86.3% Not Hispanic/Latino.

Table 6.1.2.1: Baseline Demographic Characteristics in Protocol No. P02579

	Pooled EZ/simva n=126	Pooled Simva n=122	EZ/simva 10/10 n=43	EZ/simva 10/20 n=40	EZ/simva 10/40 n=43	Simva 10 n=40	Simva 20 n=40	Simva 40 n=42
Sex (n,%)								
Female	53 (42)	53 (43)	18 (42)	17 (43)	18 (42)	17 (43)	18 (45)	18 (43)
Male	73 (58)	69 (57)	25 (58)	23 (58)	25 (58)	23 (58)	22 (55)	24 (57)
Race (n,%)								
White	105 (83)	98 (80)	37 (86)	32 (80)	36 (84)	34 (85)	32 (80)	32 (76)
Non-White	21 (17)	24 (20)	6 (14)	8 (20)	7 (16)	6 (15)	8 (20)	10 (24)
Asian	5 (4)	4 (3)	0	2 (5)	3 (7)	1 (3)	3 (8)	0
Black/African American	3 (2)	1 (1)	1 (2)	1 (3)	1 (2)	1 (3)	0	0
American Indian or Alaskan Native	0	0	0	0	0	0	0	0
Native Hawaiian or Pacific Islander	0	0	0	0	0	0	0	0
Multiracial	13 (10)	19 (16)	5 (12)	5 (13)	3 (7)	4 (10)	5 (13)	10 (24)
Ethnicity (n,%)								
Hispanic or Latino	17 (13)	17 (14)	5 (12)	6 (15)	6 (14)	5 (13)	6 (15)	6 (14)
Not Hispanic or Latino	109 (87)	105 (86)	38 (88)	34 (85)	37 (86)	35 (88)	34 (85)	36 (86)
Age (yrs)								
Mean (SD)	14.0 (1.9)	14.3 (1.8)	14.1 (1.8)	14.0 (2.0)	14.0 (2.0)	14.5 (1.8)	14.1 (2.1)	14.4 (1.5)
Median	14.0	14.0	14.0	14.0	14.0	15.0	14.0	15.0
Range	10 - 17	10 - 17	10 - 17	10 - 17	10 - 17	11 - 17	10 - 17	11 - 17
Age (n,%)								
10 - 17	126 (100)	122 (100)	43 (100)	40 (100)	43 (100)	40 (100)	40 (100)	42 (100)
Weight (kg)								
Mean (SD)	58.07 (12.91)	61.17 (15.77)	59.55 (13.30)	56.02 (10.73)	58.50 (14.35)	63.66 (15.35)	56.23 (13.68)	63.51 (17.23)
Median	56.90	57.10	59.00	54.95	55.70	63.55	52.00	57.05
Range	34.2 - 113.5	36.5 - 111.5	40.2 - 113.5	36.8 - 92.9	34.2 - 110.7	36.5 - 96.0	38.8 - 111.5	41.3 - 111.1
Height (cm)								
	Pooled EZ/simva n=126	**Pooled Simva n=122**	**EZ/simva 10/10 n=43**	**EZ/simva 10/20 n=40**	**EZ/simva 10/40 n=43**	**Simva 10 n=40**	**Simva 20 n=40**	**Simva 40 n=42**
Mean (SD)	162.21 (9.66)	164.72 (9.88)	162.33 (9.69)	161.80 (9.41)	162.48 (10.06)	165.12 (10.38)	163.05 (9.85)	165.92 (9.44)
Median	162.20	163.55	163.40	162.65	162.20	163.85	162.95	164.45
Range	134.2 - 190.9	141.2 - 190.9	140.1 - 179.5	134.2 - 179.5	137.2 - 190.9	141.2 - 190.9	147.5 - 186.5	149.8 - 189.6
BMI								
Mean (SD)	21.94 (3.70)	22.39 (4.71)	22.48 (3.91)	21.33 (3.14)	21.96 (3.97)	23.09 (4.05)	20.98 (3.45)	23.05 (5.96)
Median	21.45	21.30	22.30	21.20	21.20	22.95	20.55	20.90
Range	16.2 - 38.7	15.6 - 42.8	16.9 - 38.7	16.2 - 29.7	16.8 - 35.9	15.6 - 32.9	16.5 - 32.1	16.2 - 42.8

BMI = Body Mass Index; cm = Centimeters; kg = Kilograms; SD = Standard Deviation; yrs = Years
Source: Applicant's Table 12, pg 94/3968

The racial components of "multiracial" were not captured during the study. No subject reported himself/herself as "American Indian or Alaskan Native" or as "Native Hawaiian or Other Pacific Islander" during the trial.

Table 6.1.2.2: Baseline Demographic Age in Protocol No. P02579

P02579
All Randomized Subjects

Summary of Demographic Age Data For Step 1 and Step 2

	Pooled EZ/Simva n=126	Pooled Simva n=122	EZ 10mg + Simva 10mg n=43	EZ 10mg + Simva 20mg n=40	EZ 10mg + Simva 40mg n=43	Simva 10mg n=40	Simva 20mg n=40	Simva 40mg n=42
Age (n,%)								
10	5 (4)	2 (2)	1 (2)	2 (5)	2 (5)	0	2 (5)	0
11	9 (7)	7 (6)	2 (5)	3 (8)	4 (9)	3 (8)	3 (8)	1 (2)
12	17 (13)	11 (9)	7 (16)	6 (15)	4 (9)	2 (5)	4 (10)	5 (12)
13	17 (13)	22 (18)	8 (19)	3 (8)	6 (14)	9 (23)	6 (15)	7 (17)
14	21 (17)	20 (16)	4 (9)	7 (18)	10 (23)	5 (13)	8 (20)	7 (17)
15	27 (21)	25 (20)	11 (26)	9 (23)	7 (16)	7 (18)	6 (15)	12 (29)
16	17 (13)	20 (16)	6 (14)	6 (15)	5 (12)	9 (23)	4 (10)	7 (17)
17	13 (10)	15 (12)	4 (9)	4 (10)	5 (12)	5 (13)	7 (18)	3 (7)

The baseline demographics show that the entry criteria specified by the pediatric written request were met.

Table 6.1.2.3: Baseline Values for Lipid Variables

		Pooled EZ/simva n=126	Pooled Simva n=122	EZ/simva 10/10 n=43	EZ/simva 10/20 n=40	EZ/simva 10/40 n=43	Simva 10 n=40	Simva 20 n=40	Simva 40 n=42
Calculated LDL-C Class	**<160 (SI: < 4.1)**	**0**	**6 (5)**	**0**	**0**	**0**	**0**	**4 (10)**	**2 (5)**
	≥160 (SI: ≥4.1)	126 (100)	116 (95)	43 (100)	40 (100)	43 (100)	40(100)	36 (90)	40 (95)
	≥190 (SI: ≥4.9)	99 (79)	87 (71)	35 (81)	26 (65)	38 (88)	30 (75)	27 (68)	30 (71)
Calculated LDL-C	**n**	**126**	**122**	**43**	**40**	**43**	**40**	**40**	**42**
(US: mg/dL)	Mean	225.2	218.6	225.6	212.8	236.4	230.4	211.5	214
	SD	41.7	44.1	43.5	37.9	40.8	48	44.8	37.9
	Median	217.8	207	213.5	210.8	240	216	197.3	208.5
	Min	160.5	148.5	167	160.5	169	165.5	148.5	158.5
	Max	351	336	336	297	351	336	329	323
HDL-C	**n**	**126**	**122**	**43**	**40**	**43**	**40**	**40**	**42**
(US: mg/dL)	Mean	46	45.8	43.7	48.7	45.9	45.8	46.1	45.4
	SD	9.7	8.8	7.9	11.4	9.2	8.9	8.8	8.9
	Median	45	45.5	44	46.5	45	45.3	45.8	45.5
	Min	25.5	25	25.5	33.5	28.5	29.5	28	25
	Max	92.5	71	64	92.5	63.5	71	68	67.5
Total Cholesterol	**n**	**126**	**122**	**43**	**40**	**43**	**40**	**40**	**42**
(US: mg/dL)	Mean	291.7	284.5	290.1	281.5	302.8	296.1	278.7	279.1
	SD	44.7	45.6	47.9	38.7	45	49.1	46.3	40.1
	Median	282	271	278	275.3	307	284.5	263.8	269.5
	Min	221	204.5	221	221.5	233	225	204.5	218.5
Triglycerides	**n**	**126**	**122**	**43**	**40**	**43**	**40**	**40**	**42**
(US: mg/dL)	Mean	102.5	100.7	104.5	99.6	103.2	99.5	105.2	97.7
	SD	46.7	42.9	50.6	47.5	42.6	34.5	52.1	41.1
	Median	89	88	88.5	86.3	95	87	88	90.5
	Min	35	40.5	46	48	35	40.5	58	51.5
	Max	250.5	328	243	250.5	234	190	328	267.5

Source: Applicant's Table 13, pg 96/3968

The EZ/simva 10/40 mg treatment group had higher mean baseline levels of LDL-C, TC, non-HDL-C, and Apo B compared with the simva 40 mg monotherapy treatment group; the differences were statistically significant.

According to the applicant, the differences between EZ/Simva 10/40 mg and Simva 40 mg monotherapy with respect to mean baseline levels of LDL-C, TC, non-HDL-C, and Apo B were taken into account in the efficacy analyses. The pre-specified analysis in the Data Analysis Plan for LDL-C, TC, non-HDL-C, and Apo B at Step 1 was using an ANOVA model with fixed effects for simvastatin dose (simvastatin: 10, 20 and 40 mg), treatment (ezetimibe, placebo), simvastatin dose by treatment interaction, and sex. The difference between the treatment groups (pooled as well as pairwise comparisons) was statistically significant with respect to the reduction of LDL-C, TC, non-HDL-C and Apo B. The difference was still statistically significant after incorporating baseline LDL-C, TC, non-HDL-C, or Apo B as a covariate in the ANOVA model. The applicant notes that the baseline LDL-C, TC, non-HDL-C and Apo B were well balanced between EZ/Simva 10/40 group and Simva 40 group for Step 2 analyses. The FDA statistical reviewer notes that the efficacy analysis model did not adjust for baseline LDL but used percent change from baseline which was felt to be enough of an adjustment.

Table 6.1.2.4: Baseline Cardiovascular History

	EZ/simva 10/10 n=43	EZ/simva 10/20 n=40	EZ/simva 10/40 n=43	Simva 10 n=40	Simva 20 n=40	Simva 40 n=42
Cardiac Disorders	0	3 (8)	1 (2)	1 (3)	2 (5)	1 (2)
Congenital, Familial And Genetic Disorders	0	0	0	0	0	1 (2)
Investigations	2 (5)	1 (3)	2 (5)	1 (3)	1 (3)	1 (2)
Surgical and Medical Procedures	0	0	0	0	1 (3)	0
Vascular Disorders	1 (2)	0	0	0	0	0

Source: Applicant's Table 14, pg 99/3968

Table 6.1.2.5: Summary of Baseline Cardiovascular Risk Factors

	Pooled EZ/simva, n=126	Pooled Simva, n=122	EZ/simva 10/10 n=43	EZ/simva 10/20 n=40	EZ/simva 10/40 n=43	Simva 10 n=40	Simva 20 n=40	Simva 40 n=42
NCEP Risk Category								
CHD								
No	126 (100)	122 (100)	43 (100)	40 (100)	43 (100)	40 (100)	40 (100)	42 (100)
Other Forms of Atherosclerosis[a]								
No	126 (100)	122 (100)	43 (100)	40 (100)	43 (100)	40 (100)	40 (100)	42 (100)
Diabetes								
No	126 (100)	122 (100)	43 (100)	40 (100)	43 (100)	40 (100)	40 (100)	42 (100)
Cardiac Risk Related Questions								
Any Cigarette Smoking in the Past Month								
Yes	1 (1)	12 (10)	1 (2)	0	0	5 (13)	4 (10)	3 (7)
No	125 (99)	110 (90)	42 (98)	40 (100)	43 (100)	35 (88)	36 (90)	39 (93)
Family History of Premature CHD[b]								
Yes	50 (40)	46 (38)	16 (37)	13 (33)	21 (49)	13 (33)	15 (38)	18 (43)
No	76 (69)	76 (62)	27 (63)	27 (68)	22 (51)	27 (68)	25 (63)	24 (57)
Hypertension[c]								
No	126 (100)	122 (100)	43 (100)	40 (100)	43 (100)	40 (100)	40 (100)	42 (100)
HDL-C Value								
< 40 mg/dL	27 (21)	25 (20)	11 (26)	5 (13)	11 (26)	9 (23)	7 (18)	9 (21)
40 - 49 mg/dL	61 (48)	58 (48)	24 (56)	18 (45)	19 (44)	16 (40)	21 (53)	21 (50)
50 - 59 mg/dL	29 (23)	31 (25)	7 (16)	13 (33)	9 (21)	11 (28)	10 (25)	10 (24)
≥ 60 mg/dL	9 (7)	8 (7)	1 (2)	4 (10)	4 (9)	4 (10)	2 (5)	2 (5)

CHD = Coronary Heart Disease; HDL-C = High Density Lipoprotein Cholesterol; NCEP = National Cholesterol Education Program
a: Peripheral Artery Disease, Abdominal Aortic Aneurysm, Symptomatic Carotid Artery Disease, TIA, Stroke.
B: CHD in male first-degree relative < 55 years old. CHD in female first-degree relative < 65 years old.
C: BP >140/90 mmHg or on antihypertensive medication.
Source: Applicant's Table 15, pg 100/3968

Overall, the 6 treatment groups were well-balanced regarding baseline demographic characteristics, cardiovascular history, cardiovascular risk factors, and general histories. The EZ/simva 10/40 mg treatment group did have slightly higher mean baseline levels of LDL-C, TC, non-HDL-C, and Apo B compared with the simva 40 mg monotherapy treatment group.

6.1.3 Patient Disposition

A total of 342 subjects were enrolled in the study and screened for eligibility for randomized treatment assignment. Of these, 94 subjects (27%) discontinued before receiving randomized treatment assignment. Failure to meet protocol eligibility criteria was the primary reason for which subjects were not assigned randomized treatment, accounting for 74 of the 94 enrolled but not randomized subjects. A total of 248 (73%) subjects (106 girls and 142 boys) continued in the Randomization/Active Treatment Phase. A total of 7 subjects discontinued Step 1, 13 subjects discontinued Step 2, and 6 subjects discontinued Step 3. A total of 241 subjects completed Step 1, 227 subjects completed Step 2, and 222 (222/248, 89.5%) subjects completed Step 3. There were a total of 26 patients who dropped out of the study with no reason predominating.

Table 6.1.3.1: Disposition of Subjects in Step 1

Disposition	EZ/simva 10/10	EZ/simva 10/20	EZ/simva 10/40	Simva 10	Simva 20	Simva 40
Randomized	43 (100)	40 (100)	43 (100)	40 (100)	40 (100)	42 (100)
Discontinued Treatment Phase	0	1 (3)	2 (5)	1 (3)	1 (3)	2 (5)
Adverse Event	0	1 (3)	1 (2)	0	0	1 (2)
Lost to Follow-Up	0	0	0	0	0	1 (2)
Subject Did Not Wish to Continue for Reasons Unrelated to Assigned Study Treatment	0	0	1 (2)	0	1 (3)	0
Non-Compliance With Protocol	0	0	0	1 (3)	0	0
Completed Treatment Phase	43 (100)	39 (98)	41 (95)	39 (98)	39 (98)	40 (95)

Source: Applicant's Table 9, pg 89/3968

Table 6.1.3.2 Disposition of Subjects in Step 2

Disposition	EZ/simva 10/40	Simva 40
Randomized	122 (100)	118 (100)
Discontinued Treatment Phase	8 (7)	5 (4)
Adverse Event	2 (2)	0
Laboratory Adverse Events	3 (2)	1 (1)
Lost to Follow-Up	1 (1)	0
Subject Did Not Wish to Continue for Reasons Unrelated to Assigned Study Treatment	1 (1)	3 (3)
Non-Compliance With Protocol	1 (1)	1 (1)
Completed Treatment Phase	114 (93)	113 (96)

Source: Applicant's Table 10, pg 89/3968

Table 6.1.3.3 Disposition of Subjects in Step 3

Disposition	Long-Term Experience EZ/simva
Treated	227 (100)
Discontinued Treatment Phase	5 (2)
Subject Did Not Wish to Continue for Reasons Unrelated to Assigned Study Treatment	3 (1)
Subject Moved or Relocated	1 (<1)
Non-Compliance With Protocol	1 (<1)
Completed Treatment Phase	222 (98)

Source: Applicant's Table 11, pg 90/3968

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy variable was percent change from Baseline in LDL-C at Week 6 (Step 1) comparing the pooled EZ/simva arms against the pooled simvastatin arms as specified in the written request. The primary analysis was performed using an ANOVA model with terms for statin dose, treatment, statin dose by treatment interaction and covariates as proposed in the written request. Gender was named as a covariate in the protocol. The primary comparison of the

pooled "ezetimibe plus simvastatin" versus "simvastatin monotherapy" groups was performed using this model with a 2-tailed test at the 5% significance level. The poolability across the doses of simva (10 to 40 mg) was assessed using the test of interaction. A test for interaction for treatment by simvastatin dose yielded a non-significant p>0.7 suggesting that pooling across dose was acceptable. The primary analysis included all randomized subjects i.e. "intent-to-treat" (ITT) population. Subjects who had at least one baseline and one on-treatment LDL-C value were included in the analysis. The intent-to-treat population consisted of 246 of the 248 randomized patients. Significance on the primary analysis was required to do further analyses of secondary endpoints.

The results for the pooled groups in the Intent-to-Treat subject population at Week 6 are shown in Table 6.1.4 for the primary efficacy variable. The difference between the Pooled EZ/simva treatment group and the Pooled Simva monotherapy treatment group was approximately −15%, which was statistically significant (p<0.01) and likely clinically meaningful.

Table 6.1.4 Mean Percent Change in LDL-C from Baseline to Week 6 (Step 1 endpoint)

	Pooled Simva n=120	**Pooled EZ/simva** n=126	**p-value**
Baseline			
Mean Value in mg/dL (SE)	219 (4)	225 (4)	0.27
Endpoint			
Mean Value in mg/dL (SE)	144 (4)	114 (4)	<0.01
Mean Change from Baseline (SE)	-75 (3)	-111 (3)	<0.01
Mean % Change from Baseline (SE)	-34 (1)	-49 (1)	<0.01
Difference in mean percent changes from Baseline: Pooled EZ/simva – Pooled Simva (95% confidence limits)	-15 (-18, -12)		

Note: Mean and standard errors in this table are least-square means and standard errors based on ANOVA model that extracts effects due to treatment (EZ 10 mg, placebo), dose (simva 10 mg, 20 mg, and 40 mg), treatment by dose interaction, and sex effects.
SE = Standard Error
Source: Applicant's Table 18

6.1.5 Analysis of Secondary Endpoints(s)

Endpoints from Baseline to Step 1 Endpoint (Week 6)-Pooled Data

The key secondary efficacy variables included percent changes from Baseline to 6 weeks (end of Step 1) in TC, non-HDL-C, Apo B, HDL-C, TG, LDL-C:HDL-C ratio, and TC:HDL-C ratio. The results for the pooled groups in the Intent-to-Treat subject population at Week 6 are shown in Table 6.1.5.1 for some of the secondary efficacy variables. Multiplicity with regard to the multiple secondary endpoints was addressed using Hochberg's procedure. An ANOVA model was used for all secondary endpoints except triglycerides (TG) where a non-parametric model was used. The applicant states that due to the large variability associated with TG noted in the literature, a non-parametric evaluation using ANOVA on the ranks extracting effects due to treatment (EZ, placebo) and gender were performed.

Table 6.1.5.1 Mean Percent Change in Lipid Parameters from Baseline to Week 6 (Step 1 endpoint)

	Pooled Simva n=120	**Pooled EZ/simva** n=126	**Difference in mean percent changes from Baseline: Pooled EZ/simva – Pooled Simva (95% CI)**	**p-value**
Total Cholesterol Mean % Change from Baseline (SE)	-26 (1)	-38 (1)	-12 (-15, -9)	<0.01
HDL Mean % Change from Baseline (SE)	+6.5 (1)	+6.6 (1)	+0.1 (-3, +3)	0.95
Apo B Mean % Change from Baseline (SE)	-27 (1)	-39 (1)	-12 (-15, -9)	<0.01
Non-HDL-C Mean % Change from Baseline (SE)	-33 (1)	-47 (1)	-14 (-17, -11)	<0.01
TG Median % Change from Baseline (SD)	-12 (31)	-17 (30)	-2 (-9, +4)	0.05

The treatment differences seen with TC, non-HDL, and Apo B were statistically significant and likely clinically meaningful. The treatment differences seen with TG and HDL were not statistically significant.

Endpoints from Baseline to Step 1 Endpoint (Week 6)-Individual Dose Data

Since the overall treatment effect was significant, results between individual treatment groups were analyzed in pairwise manner, as follows:

• EZ/simva 10/10 mg vs simva 10 mg monotherapy;

• EZ/simva 10/20 mg vs simva 20 mg monotherapy;
• EZ/simva 10/40 mg vs simva 40 mg monotherapy.
The incremental mean percent changes observed in the pairwise analyses were -16.34%, -15.19%, and -13.55%, respectively, and each result was statistically significant (p<0.01) (Table 6.1.5.2).

Table 6.1.5.2 Mean Percent Change in LDL-C from Baseline to Step 1 (Week 6) Endpoint: EZ/Simva Compared With Simvastatin Individual Treatment Groups

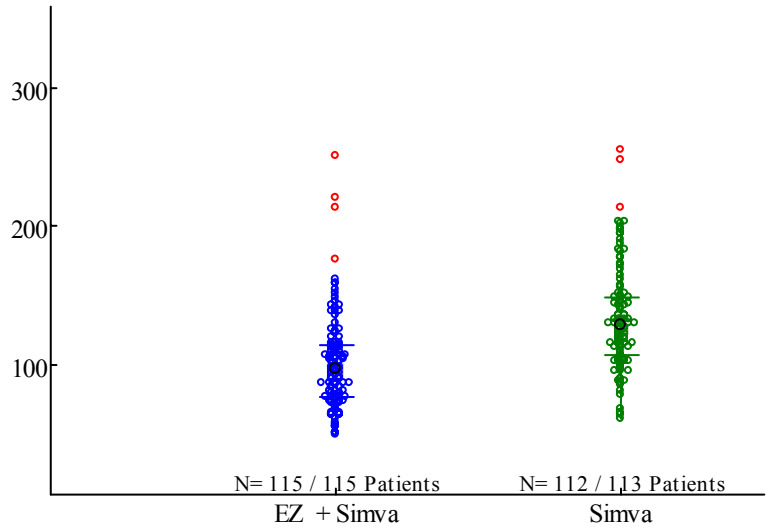
	EZ/SIM 10/10 (n=43) Mean % Change from Baseline	**SIM 10 (n=39)** Mean % Change from Baseline	**Difference in mean % Changes from Baseline (95%CI)**	**p-value**
LDL	-47% (2)	-30% (2)	-16% (-22%, -10%)	<0.01
	EZ/SIM 10/20 (n=40)	**SIM 20 (n=39)**	**Trt Diff (95%CI)**	**p-value**
LDL	-50% (2)	-34% (2)	-15% (-21%, -9%)	<0.01
	EZ/SIM 10/40 (n=43)	**SIM 40 (n=42)**	**Trt Diff (95%CI)**	**p-value**
LDL	-52% (2)	-39% (2)	-14% (-19%, -8%)	<0.01

The treatment-mediated reduction in LDL-C concentration was seen at Week 2 in each of the 6 treatment groups and was maintained through the duration of Step 1 for each group.

Endpoints from Baseline to Step 2 Endpoint (Week 33)
Results of the efficacy analysis of treatment with EZ/simva 10/40 mg vs. simva 40 mg as monotherapy in reducing LDL-C from Baseline to the Step 2 Endpoint (Week 33) showed that mean percent change of approximately −54% was evident in the EZ/simva 10/40 mg treatment group compared with approximately −38% in the simva 40 mg monotherapy treatment group. The difference between the EZ/simva 10/40 mg treatment group and the simva 40 mg monotherapy treatment group was approximately −16% (95% CI: -19 to -11%), which was statistically significant (p<0.01).

A boxplot of Week 33 LDL data by pooled treatment group (EZ/simva vs simva) is shown in Figure 6.1.5.1. The outliers are presented in red and are approximately the same in both groups. The data distributions for both groups differ in that the EZ/simva cluster has more subjects with an LDL < 200 mg/dL than the simva monotherapy cluster.

Figure 6.1.5.1 Boxplot of Week 33 LDL-C Data by Treatment Group



Source: Figure courtesy of Joy Mele, M.S., FDA biostatistician

Results of the efficacy analysis of treatment with EZ/simva 10/40 mg vs. simva 40 mg as monotherapy in reducing TC, non-HDL-C, Apo B, TG, LDL-C:HDL-C ratio, and TC:HDL-C ratio from Baseline to the Step 2 Endpoint (Week 33) is shown in Table 6.1.5.3 below. The differences between the EZ/simva 10/40 mg treatment group and the simva 40 mg monotherapy treatment group were statistically significant ($p<0.01$) for each TC, non-HDL-C, Apo B, TG, LDL-C:HDL-C, and TC:HDL-C but was not statistically significant for HDL-C. As seen in the Week 6 data, the treatment differences at Week 33 with LDL, TC, non-HDL, and Apo B were statistically significant and likely clinically meaningful.

Table 6.1.5.3 Mean Percent Change in Lipid Variables from Baseline to Step 2 (Week 33) Endpoint, Intent-to-Treat Subject Population

	n Simva 40 mg, EZ/simva 10/40 mg	Mean % Change From Baseline Simva 40 mg	Mean % Change From Baseline EZ/simva 10/40 mg	Between Group Difference	p-value
TC	120, 126	-29.25	-42.45	-13.19	<0.01
non-HDL-C	120, 126	-35.73	-51.31	-15.57	<0.01
Apo B	118, 122	-27.88	-42.64	-14.76	<0.01
HDL-C	120, 126	3.68	4.67	1.0	0.58
TG[a]	120, 126	-13.04	-20.00	-9.51	<0.01
LDL-C:HDL-C	120, 126	-39.48	-55.47	-15.99	<0.01
TC:HDL-C	120, 126	-30.94	-44.43	-13.49	<0.01

a: Median percent change from Baseline was analyzed for TG.

LDL Goals at Week 33

For the number and proportion of subjects reaching goals for LDL-C from baseline to Step 2 endpoint (Week 33) three different standards of LDL-C goals were examined:

- AAP Ideal Goal: <110 mg/dL (Table 6.1.5.4);
- AAP Acceptable Goal: <130 mg/dL (Table 6.1.5.5);
- American Heart Association (AHA) Guideline Goal (Table 6.1.5.6):
  - If cardiovascular (CV) risk factors <2, then LDL-C goal is <130 mg/dL;
  - If CV risk factors ≥2, then LDL-C goal is <100 mg/dL.

Results of the efficacy analysis demonstrated that a larger proportion of subjects receiving treatment with EZ/simva 10/40 mg compared with simva 40 mg monotherapy attained the LDL-C concentration from Baseline to the Step 2 Endpoint (Week 33) for each of the three different goals examined ($p<0.01$). Furthermore, at each intermediate time point of treatment, Week 10, Week 18, Week 26, and Week 33, a larger proportion of subjects receiving treatment with EZ/simva 10/40 mg compared with simva 40 mg monotherapy attained each of the three different goals for LDL-C concentration ($p < 0.01$).

Table 6.1.5.4 Number (and Percentage) of Subjects Reaching NCEP Goal for LDL-C from Baseline to Step 2 (Week 33) Endpoint, Intent-to-Treat Subject Population for AAP Ideal Goal

	Simva 40 n=120	EZ/simva 10/40 n=126	p-value	EZ/simva 10/40– simva 40	
				Point Estimate	(95% CI)
Week 10	41 (34)	87 (69)	<0.01	35%	(23%, 48%)
Week 18	30 (25)	76 (60)	<0.01	35%	(24%, 47%)
Week 26	35 (29)	76 (60)	<0.01	31%	(19%, 43%)
Week 33	30 (25)	78 (62)	<0.01	37%	(25%, 48%)
Endpoint	32 (27)	79 (63)	<0.01	36%	(24%, 48%)

Note: AAP Ideal Goal: LDL-C goal is <110 mg/dL. AAP = American Academy of Pediatrics; CI = Confidence Interval; LDL-C = Low Density Lipoprotein Cholesterol; NCEP = National Cholesterol Education Program
Source Data: Applicant's Table 38

Table 6.1.5.5 Number (and Percentage) of Subjects Reaching NCEP Goal for LDL-C From Baseline to Step 2 (Week 33) Endpoint, Intent-to-Treat Subject Population for AAP Acceptable Goal

	Simva 40 n=120	EZ/simva 10/40 n=126	p-value	EZ/simva 10/40– simva 40	
				Point Estimate	(95% CI)
Week 10	67 (56)	105 (83)	<0.01	28%	(16%, 39%)
Week 18	62 (52)	98 (78)	<0.01	26%	(15%, 38%)
Week 26	65 (54)	98 (78)	<0.01	24%	(12%, 35%)
Week 33	61 (51)	96 (76)	<0.01	25%	(14%, 37%)
Endpoint	64 (53)	97 (77)	<0.01	24%	(12%, 35%)

Note: AAP Acceptable Goal: LDL-C goal is <130 mg/dL.
AAP = American Academy of Pediatrics; CI = Confidence Interval; LDL-C = Low Density Lipoprotein Cholesterol; NCEP = National Cholesterol Education Program
Source: Applicant's Table 39

Table 6.1.5.6 Number (and Percentage) of Subjects Reaching AHA Goal for LDL-C From Baseline to Step 2 (Week 33) Endpoint, Intent-to-Treat Subject Population

	Simva 40 n=120	EZ/simva 10/40 n=126	p-value	EZ/simva 10/40– simva 40	
				Point Estimate	(95% CI)
Week 10	63 (53)	95 (75)	<0.01	23%	(11%, 36%)
Week 18	57 (48)	92 (73)	<0.01	26%	(14%, 37%)
Week 26	61 (51)	93 (74)	<0.01	23%	(11%, 35%)
Week 33	56 (47)	92 (73)	<0.01	26%	(15%, 38%)
Endpoint	59 (49)	93 (74)	<0.01	25%	(13%, 36%)

Note: For AHA Goal: CV risk factors <2, then LDL-C goal is <130 mg/dL; CV risk factors ≥2, then LDL-C goal is <100 mg/dL.
AHA = American Heart Association; CI = Confidence Interval; CV = Cardiovascular; LDL-C = Low Density Lipoprotein Cholesterol
Source: Applicant's Table 39

Endpoints from Baseline to Step 3 Endpoint (Week 53)

During Step 3 each continuing subject was to receive open-label treatment with EZ/simva 10/10 mg or EZ/simva 10/20 mg at the investigator's discretion depending on the LDL-C levels, with the opportunity for the investigator to increase the dose up to EZ/simva 10/40 mg or titrate the dose downward. Step 3 was 20 weeks in duration, starting at Week 33 and ending at Week 53. Mean percent changes from Baseline to the end of Step 3 in LDL-C, TC, non-HDL-C, HDL-C, LDL-C: HDL-C and TC: HDL-C, and the median percent change from Baseline to the end of Long-Term Coadministration in TG are summarized in (Table 6.1.5.7).

Table 6.1.5.7 Summary Statistics at Step 3 (Week 53) Endpoint

	Baseline			Week 53					
	n	Actual Mean	(SE)	n	Actual Mean	(SE)	Change Mean	(SE)	% Change Mean	(SE)
LDL-C	246	222.10	(2.75)	200	112.44	(2.76)	-109.9	(3.02)	-49.13	(1.09)
TC	246	288.34	(2.89)	200	175.93	(2.90)	-112.3	(3.15)	-38.54	(0.91)
Non-HDL-C	246	242.46	(2.91)	200	129.18	(2.93)	-113.4	(3.14)	-46.42	(1.07)
HDL-C	246	45.88	(0.59)	200	46.75	(0.71)	1.10	(0.51)	3.32	(1.16)
TG[a]	246	88.50	(44.91)	200	75.50	(37.00)	-13.50	(44.84)	-16.63	(43.50)
LDL-C:HDL-C	246	5.06	(0.09)	200	2.55	(0.08)	-2.55	(0.09)	-49.60	(1.29)
TC:HDL-C	246	6.55	(0.10)	200	3.93	(0.09)	-2.64	(0.10)	-39.34	(1.14)

HDL-C = High Density Lipoprotein Cholesterol; LDL-C = Low Density Lipoprotein Cholesterol; non- HDL-C = High Density Lipoprotein Cholesterol; SD = Standard
Deviation; SE = Standard Error; TC = Total Cholesterol; TG = Triglycerides
a: Median values and Standard Deviation (SD) are provided for TG
Source: Applicant's Table 41

The incrementally greater reduction in LDL-C after treatment with EZ/simva compared with simvastatin monotherapy was maintained throughout the duration of the 53 week study.

The secondary endpoints specified in the written request included the following:

- LDL % change from baseline at Week 6 comparing each EZ/simva arm to simvastatin at the matching simvastatin dose level
- Treatment comparisons for % change from baseline for LDL, total cholesterol (TC) and apolipoprotein B (apo B) at 33 weeks
- Proportion of patients reaching LDL goal by Week 33

The applicant performed all the requested analyses.

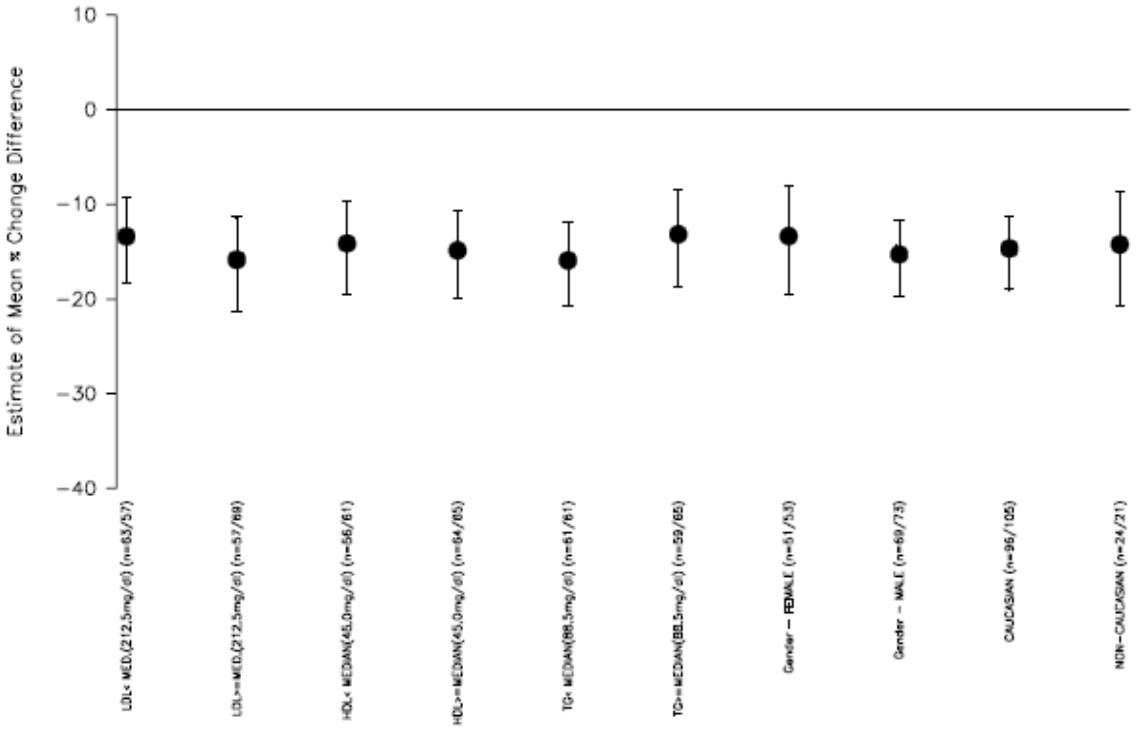
6.1.6 Other Endpoints

None

6.1.7 Subpopulations

Analyses based on gender and race and baseline TG, LDL and HDL were planned and conducted by the applicant. The results show consistency of the treatment effect across these predefined subgroups with a greater drop in LDL for EZ/simva over simvastatin alone (Figure 6.1.7).

Figure 6.1.7 Graph of LDL percent change from baseline treatment difference by subgroups



Point estimate and 95% confidence interval of the difference between mean percent change from Baseline of Pooled EZ/simva compared with Pooled Simva in LDL-C at Step 1 Endpoint in various subgroups of the population defined by baseline characteristics: Intent-to-Treat Data Set
Figure 3 extracted from page 111 of the study report

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The mean percent changes from Baseline to Week 6 in the lipid variables LDL-C, TC, non-HDL-C, Apo B and HDL-C, and median percent change from Baseline for TG are presented in Table 6.1.8.

Table 6.1.8 Response to EZ plus Simvastatin Coadministration in Adolescent Subjects with HeFH (Mean % Change from Untreated Baseline) at Week 6, Step 1 Endpoint

Treatment	N	LDL-C	TC	Non-HDL-C	Apo B	TG[a]	HDL-C
Pooled EZ/simva (All Ezetimibe/Simvastatin Doses)[b]	126	-49.45	-38.23	-46.84	-38.92	-16.56	6.58
Pooled Simva (All Simvastatin Doses)[b]	120	-34.43	-26.28	-32.68	-26.69	-12.28	6.47
Ezetimibe/Simvastatin by Dose							
10/10 mg	43	-46.71	-37.13	-44.48	-36.74	-17.57	3.79
10/20 mg	40	-49.52	-37.17	-47.14	-39.41	-17.05	9.55
10/40 mg	43	-52.14	-40.40	-48.90	-40.62	-13.43	6.39
Simvastatin by Dose							
10 mg	39	-30.37	-23.06	-27.92	-23.18	-3.85	2.71
20 mg	39	-34.33	-26.18	-33.34	-27.39	-12.50	9.68
40 mg	42	-38.59	-29.60	-36.77	-29.49	-20.32	7.03

Note: Baseline on no lipid lowering drug
Apo B = Apolipoprotein B; HDL-C = High Density Lipoprotein Cholesterol; LDL-C = Low Density Lipoprotein Cholesterol; non- HDL-C = non High Density Lipoprotein Cholesterol; TC = Total Cholesterol; TG = Triglycerides
a: For triglycerides, median % change from Baseline
b: EZ/simva doses pooled (10/10, 10/20, and 10/40 mg) significantly reduced LDL-C, TC, non-HDL-C, and Apo B, compared to simva dose pooled (10, 20, and 40 mg).
Source: Applicant's Table 42

In a pediatric population with HeFH, EZ/simva individual dose groups of 10/10, 10/20, and 10/40 mg had a significantly greater reduction in LDL-C, TC, non-HDL-C, ApoB, LDL-C:HDL-C ratio, and TC:HDL-C ratio at Week 6 compared with the corresponding individual dose groups of simva monotherapy 10, 20, and 40 mg.

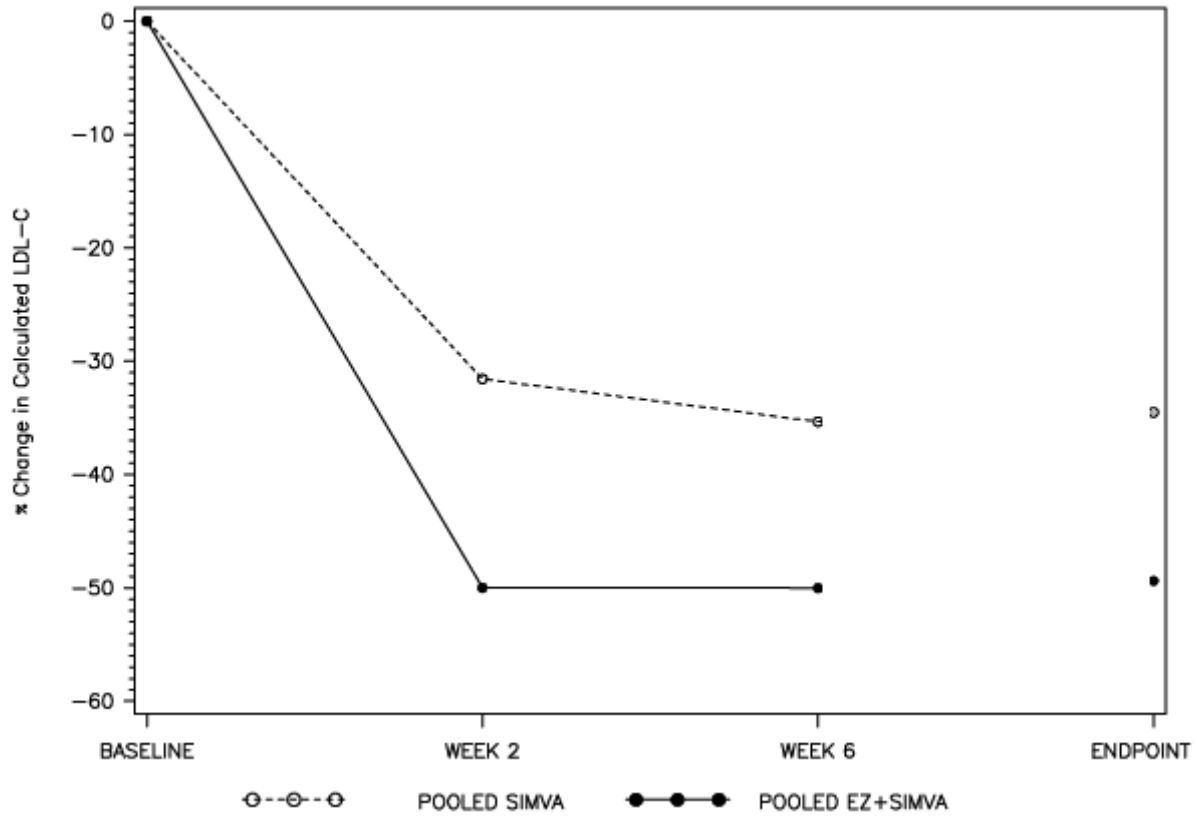
(b) (4)

(b) (4)

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The incrementally greater reduction in LDL-C after treatment with EZ/simva compared with simvastatin monotherapy was apparent at Week 2 and maintained through the end of Step 1 (Figure 6.1.9). The efficacy of EZ/simva for LDL-C reduction was also maintained throughout the duration of the 53 week study.

Figure 6.1.9 Mean Percent Change in LDL-C Across Time From Baseline to Week 6 in the Two Pooled Treatment Groups



Source: Applicant's Figure 2; pg 105/3968

6.1.10 Additional Efficacy Issues/Analyses

None

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

Study P02579 is the study used to evaluate safety.

7.1.2 Adequacy of Data

P02579 was adequately powered for its intended primary efficacy endpoint of LDL-C lowering of the pooled EZ/simva arms against the pooled simva arms. As per the Pediatric Written Request, an adequate number of adolescent subjects with HeFH were exposed to the drugs. Duration of exposure and drug dosage was adequate to assess most safety issues. Both males and females were adequately represented but there was limited demographic subsets as ≥ 80% of subjects were White and approximately 85% of subjects were not Hispanic or Latino.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

This submission involved only one study so pooling data across studies to estimate and compare incidence is not relevant for this submission.

For the efficacy evaluation, the poolability across the doses of simva (10 to 40 mg) was assessed using the test of interaction. A test for interaction for treatment by simvastatin dose yielded a non-significant p>0.7 suggesting that pooling across dose was acceptable.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Please refer to Section 6.1.2 for the demographics of the target population. The majority of the subjects had been on prior statin therapy. Thus, this population's safety experiences may be somewhat different than the experiences of a group of statin-naive adolescents.

During the double-blind, randomized treatment phase of the trial from Baseline to the end of Step 2, 109 subjects (87%) assigned to receive EZ/simva 10/40 mg and 105 subjects (86%) assigned to receive simva 40 mg monotherapy were exposed to the drug for at least 183 days (at least 6 months) (Table 7.2.1.1). During Long-Term Coadministration 115 subjects (48%) were

exposed to EZ plus simva for at least 183 days (at least 6 months) and 24 subjects (10%) were exposed to EZ plus simva for at least 366 days (at least 12 months) (Table 7.2.1.2).

During Step 1, the mean exposure for EZ/simva 10/10 mg was 40.1 days, with a maximum exposure of 49 days; the mean exposure for EZ/simva 10/20 mg was 39.2 days, with a maximum exposure of 49 days; and the mean exposure for EZ/simva 10/40 mg was 40.5 days, with a maximum exposure of 48 days. The mean exposure for simva 10 mg monotherapy was 39.7 days, with a maximum exposure of 49 days; the mean exposure for simva 20 mg monotherapy was 40.6 days, with a maximum exposure of 56 days; and the mean exposure for simva 40 mg monotherapy was 40.3 days, with a maximum exposure of 50 days.

During Step 2, the mean exposure for EZ/simva 10/40 mg was 202.2 days, with a maximum exposure of 250 days, and the mean exposure for simva 40 mg monotherapy was 208.2 days, with a maximum exposure of 242 days.

During Step 3, the mean exposure for EZ 10 mg plus simva coadministration was 228.2 days, with a maximum exposure of 395 days.

Table 7.2.1.1 Extent of Exposure From First Day of Administration Through the End of Step 1 (Week 6)

Duration (day)	EZ/simva 10/10 mg n=43	EZ/simva 10/20 mg n=40	EZ/simva 10/40 mg n=43	Simva 10 mg n=40	Simva 20 mg n=40	Simva 40 mg n=42
Received any treatment						
≥1	43 (100)	40 (100)	43 (100)	39 (98)	40 (100)	42 (100)
≥14	43 (100)	40 (100)	42 (98)	39 (98)	40 (100)	42 (100)
>28	43 (100)	38 (95)	41 (95)	37 (93)	39 (98)	41 (98)
>56	0	0	0	0	1 (3)	0

Source: Applicant's Table 48

Table 7.2.1.2 Extent of Exposure from First Day of Administration Through the End of Step 2 (Week 33)

	EZ/simva 10/40 mg n=126	Simva 40 mg n=122
Received Any Treatment (n,%)		
≥1 days	126 (100)	121 (99)
≥14 days	125 (99)	121 (99)
>28 days	122 (97)	119 (98)
>56 days	120 (95)	117 (96)
>98 days	117 (93)	116 (95)
>154 days	116 (92)	112 (92)
≥183 days (Approximately 6 months)	**109 (87)**	**105 (86)**
>207 days	85 (67)	92 (75)
≥366 days (Approximately 12 months)	**0**	**0**
Statistics (Day)		
n	126	121
Mean	202.2	208.2
SD	48.6	41.1
Median	218	221
Min	13	15
Max	250	242

Source: Applicant's Table 49

Table 7.2.1.3 Extent of Exposure from First Day of Administration Through the End of (Long-Term Coadministration (Week 53)

	EZ 10 mg + Simva n=238
Received Any Treatment (n,%)	
≥1 days	238 (100)
≥14 days	237 (100)
>28 days	235 (99)

>56 days	232 (97)
>98 days	223 (94)
>140 days	139 (58)
>154 days	117 (49)
≥183 days (Approximately 6 months)	**115 (48)**
>207 days	114 (48)
>266 days	113 (47)
>336 days	78 (33)
≥366 days (Approximately 12 months)	**24 (10)**
>385 days	3 (1)

Source: Applicant's Table 50

7.2.2 Explorations for Dose Response

See Sections 6.1.8. and 7.5.1.

7.2.3 Special Animal and/or In Vitro Testing

No new animal or *in vitro* data was submitted with this sNDA.

7.2.4 Routine Clinical Testing

All laboratory tests were routed to the central laboratory. Subjects were required to fast for 12 hours prior to any laboratory tests.

An abbreviated safety panel was done at Weeks -1, 2, 10, 18, 26, and 43, and included the following tests: albumin, glucose, alkaline phosphatase, SGPT/ALT, SGOT/AST, serum creatinine, CPK, GGTP, and total bilirubin. Indirect bilirubin was triggered in the event that total bilirubin was elevated.

An extended safety panel was done at Weeks -9 to -6, 0, 6, 33, and 53 and included the tests performed for the Abbreviated Safety Panel plus the ones listed below. Urinalysis was performed at Weeks -9 to -6, 0, 33, and 53.

- Hematology, including differential, WBC, platelet count, hemoglobin, and hematocrit;
- Blood chemistries, including total protein, albumin, calcium, inorganic phosphorus, fasting glucose, BUN, uric acid, total bilirubin, alkaline phosphatase, SGPT/ALT, SGOT/AST, serum creatinine, serum electrolytes (Na, K, Cl), creatinine phosphokinase (CPK), and gammaglutamyl transpeptidase (GGTP);
- Urinalysis. Gross urinalysis evaluation included specific gravity, pH, blood, ketones, protein, and glucose. A microscopic examination included WBC and RBC.

Other safety evaluations included:

- Physical examinations;
- Assessment of sexual maturation (including assessments of height, sexual maturation, steroid hormone synthesis, and changes in menstrual cycles in girls);
- Assessment of adverse events (including pancreatitis, statin-related AEs, and thrombocytopenia and by-time assessment of the frequency of AEs); and
- Clinical assessments (including angioedema).

Adverse events were evaluated by treatment group at the end of Step 1 (Week 6), Step 2 (Week 33), and Long-Term Coadministration, Step 3 (Week 53) (for safety reporting, beginning of Long-Term Coadministration was Baseline for subjects assigned to receive EZ/simva coadministration at Randomization; beginning of Long-Term Coadministration was start of Step 3 for subjects assigned to receive simva monotherapy at Randomization).

The reports of AEs were examined over time using time periods of roughly equal duration. AEs were examined from Baseline to the end of Step 2 (Week 33) using 3 periods of approximately 11 weeks each. AEs were examined from the beginning to the end of Long-Term Coadministration using periods of approximately 13 weeks each.

7.2.5 Metabolic, Clearance, and Interaction Workup

No new information in this area was submitted for this application

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Drug specific safety concerns evaluated:

• Liver function test abnormalities (Week -9 to -6, -1, 0, 2, 6, 10, 18, 26, 33, 43, 53)
• Linear growth (Week -9 to -6, 0, 33, 53)
• Sexual maturation (Tanner staging) (Week -9 to -6, 33, 53)
• Steroid hormone biosynthesis (Week 0, 33, 53) Hormone assessment includes DHEAS, cortisol, FSH, LH levels, estradiol (measured in girls only) and testosterone (measured in boys only).
• Angioedema AEs (Week -1, 0, 2, 6, 10, 18, 26, 33, 43, 53)
• Pancreatitis AEs (Week -1, 0, 2, 6, 10, 18, 26, 33, 43, 53); lipase and amylase not drawn
• Statin-related concerns, e.g., myopathy, rhabdomyolysis, and drug interactions (Week -1, 0, 2, 6, 10, 18, 26, 33, 43, 53)

7.3 Major Safety Results

7.3.1 Deaths

No subject died while enrolled in the trial.

7.3.2 Nonfatal Serious Adverse Events

There were more subjects in the EZ/simva coadministration group compared to simva monotherapy group in Step 1 and Step 2 for whom a serious adverse event was reported, but the number of subjects with SAEs was small.

Table 7.3.2.1 Serious Adverse Events Reported from First Day of Administration Through the End of Step 1 (Week 6)

	EZ/simva 10/10 mg n=43	EZ/simva 10/20 mg n=40	EZ/simva 10/40 mg n=43	Simva 10 mg n=40	Simva 20 mg n=40	Simva 40 mg n=42
Subjects Reporting Any Adverse Event	1 (2)	0	0	0	0	0
General Disorders and Administration Site Conditions	1 (2)	0	0	0	0	0
Pyrexia	1 (2)	0	0	0	0	0

Source: Applicant's Table 58

Table 7.3.2.2 Serious Adverse Events Reported from First Day of Administration Through the End of Step 2 (Week 33)

	EZ/simva 10/40 mg n=126	Simva 40 mg n=122
Subjects Reporting Any Adverse Event	4 (3)	1 (1)
General Disorders and Administration Site Conditions	1 (1)	0
Pyrexia	1 (1)	0
Infections and Infestations	2 (2)	0
Arthritis bacterial	1 (1)	0
Tonsillitis	1 (1)	0
Injury, Poisoning and Procedural Complications	0	1 (1)
Accidental overdose	0	1 (1)
Musculoskeletal and Connective Tissue Disorders	1 (1)	0
Tendonitis	1 (1)	0
Nervous System Disorders	1 (1)	0
Encephalopathy	1 (1)	0

Source: Applicant's Table 59

Table 7.3.2.3 Serious Adverse Events Reported from First Day of Administration Through the End of Long- Term Coadministration (Week 53)

	EZ 10 mg + Simva n=238
Subjects Reporting Any Adverse Event	6 (3)
Infections and Infestations	4 (2)
Arthritis bacterial	1 (<1)
Pilonidal cyst	1 (<1)
Subcutaneous abscess	1 (<1)
Tonsillitis	1 (<1)
Injury, Poisoning and Procedural Complications	1 (<1)
Overdose	1 (<1)
Musculoskeletal and Connective Tissue Disorders	1 (<1)
Tendonitis	1 (<1)
Nervous System Disorders	1 (<1)
Encephalopathy	1 (<1)

Source: Applicant's Table 60

7.3.3 Dropouts and/or Discontinuations

A total of 9 subjects were discontinued from the study at the end of Week 33 due to adverse events: 7 subjects (6%), ezetimibe/simvastatin 10/40 mg coadministration and 2 subjects (2%), simvastatin 40 mg monotherapy group. The number of discontinuations were small but were numerically larger for EZ/simva for ALT increased, CPK increased, muscle spasms, and myalgia.

Table 7.3.3.1 Adverse Events Leading to Discontinuation Reported from First Day of Administration Through the End of Step 1 (Week 6)

	EZ/simva 10/10 mg n=43	EZ/simva 10/20 mg n=40	EZ/simva 10/40 mg n=43	Simva 10 mg n=40	Simva 20 mg n=40	Simva 40 mg n=42
Subjects Reporting Any Adverse Event	**0**	**1 (3)**	**1 (2)**	**0**	**0**	**1 (2)**
Gastrointestinal Disorders	**0**	**0**	**1 (2)**	**0**	**0**	**1 (2)**
Abdominal pain	0	0	0	0	0	1 (2)
Nausea	0	0	1 (2)	0	0	0
Musculoskeletal and Connective Tissue Disorders	**0**	**1 (3)**	**0**	**0**	**0**	**0**
Muscle spasms	0	1 (3)	0	0	0	0

Source: Applicant's Table 61

Table 7.3.3.2 Adverse Events Leading to Discontinuation Reported from First Day of Administration Through the End of Step 2 (Week 33)

	EZ/simva 10/40 mg n=126	Simva 40 mg n=122
Subjects Reporting Any Adverse Event	**7 (6)**	**2 (2)**
Gastrointestinal Disorders	**1 (1)**	**1 (1)**
Abdominal pain	0	1 (1)
Nausea	1 (1)	0
Investigations	**3 (2)**	**1 (1)**
Alanine aminotransferase increased	2 (2)	1 (1)
Blood creatine phosphokinase increased	1 (1)	0
Musculoskeletal and Connective Tissue Disorders	**3 (2)**	**0**
Muscle spasms	1 (1)	0
Myalgia	2 (2)	0

Source: Applicant's Table 62

Table 7.3.3.3 Adverse Events Leading to Discontinuation Reported from First Day of Administration Through the End of Long-Term Coadministration (Week 53)

	EZ 10 mg + Simva n=238
Subjects Reporting Any Adverse Event	**7 (3)**
Gastrointestinal Disorders	**1 (<1)**
Nausea	1 (<1)
Investigations	**3 (1)**
Alanine aminotransferase increased	2 (1)
Blood creatine phosphokinase increased	1 (<1)
Musculoskeletal and Connective Tissue Disorders	**3 (1)**
Muscle spasms	1 (<1)
Myalgia	2 (1)

Source: Applicant's Table 63

The 2 subjects who discontinued due to ALT increased are discussed in Section 7.5.5 and Appendix 9.2. The table below provides additional information on the 3 subjects (all females, 2 on EZ/simva 40 mg and 1 on EZ/simva 20 mg) who discontinued treatment due to muscular-related adverse events.

Table 7.3.3.4 Subjects Who Were Discontinued due to Muscular-Related Adverse Events

Center/ Subject	Gender/ Age in yrs/Race	Treatment	Adverse Event	Study Day Comments (Days Following End of Treatment in Parentheses)	Narrative
49/1004*	F/17/White	EZ/simva 10/40 mg	Myalgia	15-16 48-81 91-105 (4)	Myalgia was reported as an AE on Day 15, resolving on Day 16. The AE was mild in severity, possibly related to treatment, and required interruption. On Day 48 myalgia was reported again as a mild AE, requiring interruption of treatment and resolving on Day 81. On Day 91 it was increased to moderate, possibly related to treatment, and required discontinuation. The AE was resolved on Day 105, four days after the end of treatment.
24/948*	F/15/White	EZ/simva 10/40 mg	Myalgia	81-82 88-89	Myalgia was reported as an AE on Day 81, resolving on Day 82. The AE was mild in severity, possibly related to treatment, and required interruption. On Day 88 myalgia was reported again as a mild AE, resolving on Day 89. The AE was possibly related to treatment and required interruption and discontinuation.
03/941	F/16/White	EZ/simva 10/20 mg	Muscle Spasm	3-3 10-10 11-86(70)	Muscular cramp in both legs was reported as an AE on Day 3. The AE was moderate in severity, possibly related to the study drug, and required no action. A moderate cramp in left leg recurred on Day 10, requiring the interruption of treatment and resolving on the same day. Muscular cramp in both legs was reported as an AE on Day 11. The AE was moderate in severity, possibly related to the study drug, and required discontinuation. The event resolved on Day 86, 70 days after the end of treatment.

*Refer to Appendix 9.2 for more detailed subject narrative

Study Treatment Interruption Due to Adverse Events

A total of twelve subjects (10%) from the coadministration therapy group and 11 subjects (9%) on simva monotherapy interrupted treatment during Step 1 of the study due to adverse events. None of the adverse events leading to interruption was reported for more than one subject, except for nausea, which was reported for two subjects in the simva 10 mg monotherapy group.

A total of 23 subjects (18%) from the coadministration therapy group and 18 subjects (15%) from the monotherapy group interrupted treatment at the end of Step 2 (Week 33) due to adverse events. Adverse events experienced by more than 1 subject that was more frequent in the combination therapy arm include diarrhea, nausea, gastroenteritis, CPK increased, myalgia, and dizziness.

Twenty-four subjects (10%) interrupted treatment due to AEs at the end of the Long-Term Coadministration due to adverse events. AEs that occurred in >1 subject include diarrhea, nausea, gastroenteritis, influenza, tonsillitis, CPK increased, myalgia, dizziness, and headache.

7.3.4 Significant Adverse Events

Significant adverse events are discussed throughout this safety section.

- A total of 9 subjects were discontinued from the study at the end of Week 33 due to adverse events: 7 subjects (6%), ezetimibe/simvastatin 10/40 mg coadministration and 2 subjects (2%), simvastatin 40 mg monotherapy group. The number of discontinuations were small but were numerically larger for EZ/simva for ALT increased, CPK increased, muscle spasms, and myalgia.
- The number of subjects who had CPK values that were ≥3xULN from Baseline to the end of Week 33 were numerically larger in the EZ/simva 10/40 group (9, 7%) as compared to the simva 40 mg group (2, 2%). During the trial there were no subjects with CPK elevations ≥5xULN with "associated muscle symptoms." There were 2 subjects with transient CPK elevations ≥10xULN without "associated muscle symptoms", both of these subjects were in the EZ/simva 10/20 group.

7.3.5 Submission Specific Primary Safety Concerns

During the trial there were no reports of angioedema, rhabdomyolysis, myopathy, pancreatitis, hepatitis, jaundice, clinical signs of liver dysfunction, cholecystectomies, or cholecystitis.

Hepatic
The number of subjects who had ALT or AST values that were ≥3xULN on at least two consecutive occasions from Baseline to the end of Week 33 was small overall and very slightly larger in the EZ/simva group (4, 3% vs. 2, 2%). The Sponsor used the following algorithm with three criteria to identify cases of subjects with consecutive measurements of ALT and/or AST ≥3xULN:
(1) Two consecutive measurements for ALT and/or AST ≥3xULN; or
(2) A single, last measurement ≥3xULN; or
(3) A measurement ≥3xULN followed by a measurement <3xULN that was taken more than 2 days after the last dose of study medication.

At the end of Step 2/Week 33, only two subjects (14/916 and 24/950) had consecutive documented ALT and/or AST levels ≥3xULN while on treatment. Two subjects had ALT and/or

AST levels ≥3xULN at the last on-treatment observation with a follow-up occurring more than 2 days after the end of treatment (10/043 and 44/121). Two subjects (31/967 and 52/163) had an elevated AST and/or ALT level ≥3xULN at the end of Step 2 that was not consecutive as documented by the next levels observed during Step 3.

The outcomes of the six subjects meeting the criteria for two consecutive postbaseline values of ALT and/or AST elevations > 3X ULN in Step 1 and 2 and the one individual in Step 3 are outlined in Table 7.3.5.1, below:

Table 7.3.5.1 Subjects Meeting Criteria for ALT or AST ≥3xULN on at least two consecutive occasions from Baseline to the end of Week 53

Center/ Subject	Treatment at Onset of AST/ALT Elevation	Normalization On Study Drug	Normalization Off Study Drug	Algorithm Criterion for ALT/AST elevation	Study Drug Status/
44/121[a] M/16/W	EZ 10mg/ Simva 20mg Step 1		(AST ≥ 3X ULN) (peak AST= 3.4xULN). Total Bilirubin normal but CK increased. Returned to within reference range within 3 weeks after study drug discontinuation	AST/ #3	Discontinued Study Drug
14/916 F/17/W	EZ 10mg/ Simva 40mg Step 2		(ALT ≥ 3X ULN) (peak ALT= 3.9xULN, TBili 1.9xULN, DBili 1.25 x ULN, IBili 1.45 x ULN) Returned close to normal within 4 days of study drug discontinuation. See Section 7.4.2 for further details.	ALT / #1	Discontinued Study Drug
31/967[b] F/12/ Multiracial	EZ 10mg/ Simva 40mg Step 2	Isolated ALT and AST ≥3X ULN on Day 232. Peak ALT= 4.7xULN; peak AST= 8.6xULN. ALT near normal on Day 239 and normal on Day 259. Normal AST on Day 239. Continued Study. Total Bilirubin normal but CK increased.		AST/ #3	Study Drug Continued
10/043 M/15/W	Simva 40mg Step 2		ALT 3X ULN [Day 120 (12.6 x ULN) and Day 135(5xULN) with normal T Bili and elevated CK], 9 days	ALT/ #3	Discontinued Drug

Center/ Subject	Treatment at Onset of AST/ALT Elevation	Normalization On Study Drug	Normalization Off Study Drug	Algorithm Criterion for ALT/AST elevation	Study Drug Status/
			after discontinuing therapy. Normalized by Day 169, 43 days after last dose of study drug. AST ≥3X ULN (6 x ULN) on Day 120, and decreased to <3X ULN by Day 135, 9 days after discontinuing therapy. Normalized by Day 169, 43 days after last dose of study drug.		
24/950 F/17/W	Simva 40mg Step 2	ALT (ALT ≥ 3X ULN) (7 x ULN) on Day 186 and 193(5xULN). TBili and CK normal. Returned to ≥1X ULN and < 2X ULN by Day 207. AST (AST ≥ 3X ULN) (5.2 x ULN) on Day 186. Declining by Day 193 and returned to near reference range by Day 207. AST normal by Day 214. Near normal levels when received co-administration therapy around Day 239. Last values on Day 317 (day 79 of co-administration) has normal AST level and near normal ALT level		ALT/ #1	Continued in trial after elevations of ALT and AST
52/163[b] M/12/W	EZ/Simva 10/40 mg Step 2		ALT elevated to 3.2 x ULN on Day 246, his last visit in Step 2. The next observation on Day 253, the first visit of Step 3, ALT levels had returned to <3xULN.	ALT/ #3	
55/969 F/14/W	EZ 10mg/ Simva 10 mg		(ALT ≥ 3X ULN) Values were normal through Day 16-302 of	ALT/ #3	Discontinued Drug

Center/ Subject	Treatment at Onset of AST/ALT Elevation	Normalization On Study Drug	Normalization Off Study Drug	Algorithm Criterion for ALT/AST elevation	Study Drug Status/
	Step 3		Study. Abnormal (ALT ≥3X ULN) (3.7 x ULN) value was observed 1 day following end of study drug treatment. Normal TBili and CK. At last contact, day 380, 8 days after last dose of study drug, ALT level had resolved to near reference range.		

[a] Subject 44/121 was observed to have had elevated ALT ≥3xULN according to criterion #3 during Step 1. The subject was discontinued from the trial in Step 1. The subject did not enter Step 2 and consequently did not receive ezetimibe 10/40 mg.
[b] Subject triggered the algorithm, criterion #3 with a last observation for ALT and/or AST in Step 2 that was ≥3xULN. However, the first observation from ALT or AST in Step 3 was not elevated.
See Table 7.4.2.3 in Section 7.4 for additional details

Nine subjects had ALT increased reported as an adverse event (6 subjects [5%] assigned ezetimibe/simvastatin 10/40 mg and 3 subjects [2%] assigned simvastatin 40 mg monotherapy) from Baseline to the end of Week 33. Investigators reported AST increased as adverse event for three subjects: two subjects assigned to receive ezetimibe/simvastatin 10/40 mg and one subject assigned to receive simvastatin 40 mg monotherapy. There were 2 additional subjects for whom ALT increased was reported as an AE during Long-Term Coadministration (Weeks 34-53).

Musculoskeletal
The number of subjects who had CPK values that were ≥3xULN from Baseline to the end of Week 33 were numerically larger in the EZ/simva 10/40 group (9, 7%) as compared to the simva 40 mg group (2, 2%). During the trial there were no subjects with CPK elevations ≥5xULN with "associated muscle symptoms." There were 2 subjects with transient CPK elevations ≥10xULN without "associated muscle symptoms", both of these subjects were in the EZ/simva 10/20 group. Six subjects had blood creatine phosphokinase (CPK) increased reported as an adverse event (4 subjects [3%] assigned ezetimibe/simvastatin 10/40 mg and two subjects [2%] assigned simvastatin 40 mg monotherapy) from Baseline through the end of Week 33. Investigators reported myalgia as an adverse event for eight subjects (7 subjects [6%] assigned to ezetimibe/simvastatin 10/40 mg and 1 subject [1%] assigned simvastatin 40 mg monotherapy) from Baseline through the end of Week 33. The reports of myalgia were considered mild or moderate in severity. There were no new reports of myalgia as an adverse event during Long-Term Coadministration (Weeks 34-53). None of the reports of myalgia was associated with elevated CPK. Three subjects (2%) from were discontinued from the study due to adverse events related to musculoskeletal function (myalgia or muscle spasm). All 3 subjects were female and were on EZ/simva (2 on 10/40; 1 on 10/20 mg).

Elevations in AST/ALT and CPK are discussed in Section 7.4.2.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

End of Step 1 (Week 6)
A summary of treatment-emergent adverse events reported for ≥5% of subjects from the first day of administration through the end of Step 1 (Week 6) is presented in Table 7.4.1.1. The percentage cutoff for these displays was chosen to capture AEs reported for at least 2 subjects to ensure better representation of the characteristics of the whole subject population rather than reports by individual subjects.

There were no consistent differences in the percentages of subjects with AEs in the body system/organ classes for the six treatment groups. The five body system/organ classes for which adverse events were more frequently reported (i.e., the highest percentage in any of the treatment groups) are listed below:

- Gastrointestinal disorders: (7% EZ/simva 10/10 mg coadministration vs 18% simva 10 mg monotherapy; 18% EZ/simva 10/20 mg coadministration vs 8% simva 20 mg monotherapy; and 7% EZ/simva 10/40 mg coadministration vs 7% simva 40 monotherapy);
- Infections and Infestations: (19% vs 18%; 30% vs 18%; and 19% vs 19%);
- Investigations: (7% vs 10%; 18% vs 8%; and 12% vs 5%);
- Musculoskeletal and Connective Tissue Disorders" (5% vs 5%; 13% vs 10%; and 2% vs 5%);
- Nervous System Disorders: (2% vs 5%; 10% vs 8%; and 7% vs 12%).

AEs that occurred more frequently in the EZ/simva group vs simva monotherapy group were diarrhea, seasonal allergy, tonsillitis, ALT increased, and pharyngolaryngeal pain. AEs that occurred more frequently in the simva group vs EZ/ simva group were headache and menstrual discomfort.

Table 7.4.1.1 Treatment-Emergent Adverse Events Reported for at Least 5% of Subjects from First Day of Administration Through the End of Step 1 (Week 6)

	EZ/simva 10/10 mg n=43	EZ/simva 10/20 mg n=40	EZ/simva 10/40 mg n=43	Simva 10 mg n=40	Simva 20 mg n=40	Simva 40 mg n=42
Subjects Reporting any Adverse Event	**18 (42)**	**27 (68)**	**18 (42)**	**20 (50)**	**18 (45)**	**21 (50)**
Cardiac Disorders						
Palpitations	0	0	2 (5)	0	0	0
Gastrointestinal Disorders						
Diarrhoea	1 (2)	4 (10)	1 (2)	1 (3)	1 (3)	0
Dyspepsia	0	0	0	2 (5)	0	0
Nausea	0	1 (3)	1 (2)	2 (5)	0	0
Vomiting	1 (2)	1 (3)	1 (2)	2 (5)	1 (3)	0
General Disorders and Administration Site Conditions						
Pyrexia	0	0	0	2 (5)	0	1 (2)
Immune System Disorders						
Seasonal allergy	0	1 (3)	2 (5)	0	0	0
Infections and Infestations						
Influenza	4 (9)	1 (3)	2 (5)	1 (3)	2 (5)	2 (5)
Nasopharyngitis	2 (5)	5 (13)	3 (7)	4 (10)	2 (5)	4 (10)
Sinusitis	0	1 (3)	0	2 (5)	0	0
Tonsillitis	0	2 (5)	1 (2)	0	0	1 (2)
Upper respiratory tract infection	0	0	2 (5)	1 (3)	1 (3)	0
Investigations						
Alanine aminotransferase increased	0	3 (8)	0	0	0	0
Dehydroepiandrosterone increased	0	1 (3)	2 (5)	2 (5)	2 (5)	0
Nervous System Disorders						
Headache	0	4 (10)	1 (2)	1 (3)	2 (5)	5 (12)
Reproductive System and Breast Disorders						
Menstrual discomfort	0	0	0	2 (5)	0	1 (2)
Respiratory, Thoracic and Mediastinal Disorders						
Pharyngolaryngeal pain	1 (2)	3 (8)	1 (2)	0	0	0

Source: Applicant's Table 51

Investigators reported ALT increased as adverse event for three subjects (8%) assigned to receive EZ/simva 10/20 mg coadministration and AST increased for one subject (3%) assigned to receive simva 20 mg monotherapy at the end of Step 1. Clinically significant cases of ALT and/or AST elevations are discussed in Section 7.4.2.

Four subjects had "blood creatine phosphokinase increased" reported as an adverse event (one subject in each of the 3 EZ/simva coadministration groups and one subject in the simva 20 mg monotherapy group) at the end of Step 1. These subjects are discussed in Section 7.4.2.

Seven subjects reported DHEA increase; 3 subjects were in the EZ/simva group and 4 subjects were in the simva only group. Each report was mild in severity, designated unrelated to treatment by the investigator and required no action. There were no other adverse event reports associated with steroid hormones.

Sixteen subjects (8 in EZ/simva and 8 in simva) had Musculoskeletal and Connective Tissue Disorders at the end of Step 1. All of the reports of Musculoskeletal and Connective Tissue Disorders were considered mild in severity. All of the reports of myalgia occurred in the EZ/simva group [3, (7%)] as compared to the simva group (0).

End of Step 2 (Week 33)

Treatment-emergent adverse events were reported for 83% of subjects assigned to receive EZ/simva 10/40 mg coadministration therapy (105/126) and for 84% subjects assigned to simva 40 mg monotherapy (103/122). The five body system/organ classes for which adverse events were more frequently reported (i.e., the highest percentage in any of the treatment groups) are listed below:

- Gastrointestinal disorders (25% EZ/simva 10/40 mg coadministration vs 19% simva 40 mg monotherapy);
- Infections and Infestations (46 vs 41%);
- Investigations (19% vs 13%);
- Musculoskeletal and Connective Tissue Disorders" (13% vs 16%);
- Nervous System Disorders" (21% vs 19%).

The most common adverse events (reported for at least 5% of subjects in either treatment group) were as follows:

- Abdominal pain (5% of subjects assigned EZ/simva 10/40 mg vs 2% of subjects assigned simva 40 mg monotherapy);
- Diarrhea (7% vs 2%);
- Nausea (6% vs 3%);
- Vomiting (4% vs 5%);
- Influenza (6% vs 10%);
- Nasopharyngitis (21% vs 22%);
- Sinusitis (5% vs 4%);
- ALT increase (5% vs 2%);
- Myalgia (6% vs 1%);
- Headache (13% vs 13%);
- Cough (3% vs 7%);
- Pharyngolaryngeal pain (5% vs 2%);
- Acne (3% vs 7%).

A summary of all treatment-emergent adverse events reported for ≥5% of subjects in either of the two treatment groups from the first day of administration through the end of Week 33 is presented in Table 7.4.1.2. GI symptoms (abdominal pain, nausea, diarrhea), ALT increased, pharyngolaryngeal pain, and myalgia occurred more frequently with EZ/simva vs simva monotherapy.

Table 7.4.1.2 Treatment-Emergent Adverse Events Reported for at Least 5% of Subjects from First Day of Administration through the End of Step 2 (Week 33)

	EZ/simva 10/40 mg n=126	Simva 40 mg n=122
Subjects Reporting any Adverse Event	**105 (83)**	**103 (84)**
Gastrointestinal Disorders		
Abdominal pain	6 (5)	3 (2)
Diarrhoea	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		
Alanine aminotransferase increased	6 (5)	3 (2)
Musculoskeletal and Connective Tissue Disorders		
Myalgia	7 (6)	1 (1)
Nervous System Disorders		
Headache	16 (13)	16 (13)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	4 (3)	8 (7)
Pharyngolaryngeal pain	6 (5)	3 (2)
Skin and Subcutaneous Tissue Disorders		
Acne	4 (3)	9 (7)

Source: Applicant's Table 52

Nine subjects had ALT increased reported as an adverse event (6 subjects [5%] assigned EZ/simva 10/40 mg and 3 subjects [2%] assigned simva 40 mg monotherapy) at the end of Step 2. Investigators reported AST increased as an adverse event for three subjects: two subjects assigned to receive EZ/simva 10/40 mg and one subject assigned to receive simva 40 mg monotherapy. Clinically significant cases of ALT and/or AST elevations are described in Section 7.4.2. Three of these 9 subjects with AEs of ALT increased are the same three subjects reported during Step 1 for subjects receiving EZ/simva treatment; the events reported from Baseline to the end of Step 2 include those events that occurred from Baseline to the end of Step 1.

Six subjects had blood creatine phosphokinase (CPK) increased reported as an adverse event (4 subjects [3%] assigned EZ/simva 10/40 mg and two subjects [2%] assigned simva 40 mg monotherapy) at the end of Step 2. Clinically significant cases of CPK elevations are described in Section 7.4.2. Three of these 6 subjects with AEs of CPK increased are the same cases reported during Step 1 for subjects receiving EZ/simva treatment. Investigators reported myalgia as an adverse event for eight subjects (7 subjects [6%] assigned to EZ/simva 10/40 mg and 1 subject [1%] assigned simva 40 mg monotherapy) at the end of Step 2. Two of these 8 subjects with AEs are the same cases reported during Step 1 for subjects receiving EZ/simva treatment. All of the reports of myalgia were considered mild or moderate in severity. Three subjects (2%)

from the coadministration treatment group were discontinued from the study due to adverse events related to musculoskeletal function (see Section 7.3.3). These are the same 3 subjects who were discontinued prior to the end of Step 1 due to an AE related to musculoskeletal function.

End of Step 3 (Week 53)
Treatment-emergent adverse events were reported for 71% of subjects assigned to receive EZ 10 mg plus simva (168/238). The five body system/organ classes for which adverse events were more frequently reported (i.e., the highest percentage in any of the treatment groups) are listed below:

- Gastrointestinal System Disorders (17%);
- Infection and Infestations (42%);
- Injury, Poisoning, and Procedural Complications (14%);
- Investigations (14%);
- Nervous System Disorders (15%).

A summary of all treatment-emergent adverse events reported for ≥5% of subjects from the first day of administration through the end of Week 53 is presented in Table 7.4.1.3.

Table 7.4.1.3 Treatment-Emergent Adverse Events Reported by ≥5% of Subjects from First Day of Administration through the End of Long-Term Coadministration (Week 53)

	EZ 10 mg + Simva n=238
Subjects Reporting any Adverse Event	**168 (71)**
Infections and Infestations	
Influenza	20 (8)
Nasopharyngitis	40 (17)
Nervous System Disorders	
Headache	21 (9)

Source: Applicant's Table 53

Investigators reported ALT increased as an adverse event for eight (3%) subjects. Six of these 8 subjects have already been described during Step 1 or Step 2; these 6 subjects were each receiving EZ/simva treatment when ALT increased was reported and Long-Term Coadministration includes all coadministration treatment from Baseline to the end of the trial. Thus, there were 2 additional subjects for whom ALT increased was reported as an AE after Step 2 during Long-Term Coadministration.

Seven subjects (3%) had myalgia reported as an adverse event during Long- Term Coadministration. These 7 subjects have already been described during Step 1 or Step 2; they were each receiving EZ/simva treatment when myalgia was reported and Long-Term Coadministration includes all coadministration treatment from Baseline to the end of the trial. Clinically significant increases in CPK are described in Section 7.4.2.

7.4.2 Laboratory Findings

Hepatobiliary Function
Clinically important elevations in hepatic transaminase activity were defined by at least two consecutive values for ALT and/or AST activity that are ≥3xULN. In this study, subjects were considered to have presumed consecutive postbaseline elevations if they met one of the following criteria: (1) two consecutive measurements for ALT and/or AST ≥3xULN, (2) a single last measurement ≥3xULN, or (3) a measurement ≥3xULN followed by a measurement <3xULN that was taken more than 2 days after the last dose of study medication.

From Baseline to the end of Step 1, one subject treated with EZ/simva 10/20 mg met the criteria for consecutive/presumed consecutive ≥3xULN elevations in ALT and/or AST. The subject is described in Table 7.4.2.3.

From Baseline to the end of Step 2 (Week 33), subjects that met the criteria for consecutive ≥3xULN elevations in ALT and/or AST are summarized in Table 7.4.2.1. The number of subjects who had ALT or AST values that were ≥3xULN on at least two consecutive occasions from Baseline to the end of Week 33 was small overall and slightly larger in the EZ/simva group (4, 3% vs. 2, 2%). The subjects are described in Table 7.4.2.3.

Table 7.4.2.1 Number (%) of Subjects with Postbaseline Values for ALT and AST > ULN at the End of Step 2 (Week 33)

	EZ/simva 10/40 n=126		Simva 40 n=122	
Alanine Aminotransferase (Reference Range: 5–25 mU/mL)				
≥3xULN	4	(3)	2	(2)
≥3xULN, consecutive[a]	3	(2)	2	(2)
Aspartate Aminotransferase (Reference Range: 8–30 mU/mL)				
≥3xULN	2	(2)	2	(2)
≥3xULN, consecutive[a]	2	(2)	1	(1)
Alanine Aminotransferase and/or Aspartate Aminotransferase				
≥3xULN	5	(4)	2	(2)
≥3xULN, consecutive[a]	4	(3)	2	(2)

Note: Each subject listed in this table is presented only once, in the category of the highest activity level reported.
ULN = Upper Limit of Normal.
A: This category includes those subjects with (1) two consecutive measurements for ALT and/or AST ≥3xULN, (2) a single, last measurement ≥3xULN, or (3) a measurement ≥3xULN followed by a measurement <3xULN that was taken more than 2 days after the last dose of study medication
Source: Applicant's Table 66

During Long-Term Coadministration, subjects that had consecutive ≥3xULN elevations in ALT and/or AST are summarized in 7.4.2.2. Three out 238 subjects (1%) had ALT or AST values that were ≥3xULN on at least two consecutive occasions from Week 34 to the end of Week 53. The subjects are described in Table 7.4.2.3.

Table 7.4.2.2. Number (%) of Subjects with Postbaseline Values for ALT and AST > ULN at the End of Long-Term Coadministration (Week 53)

	EZ 10 mg + Simva n=238	
Alanine Aminotransferase (Reference Range: 5–25 mU/mL)		
≥3xULN	5	(2)
≥3xULN, consecutive[a]	2	(1)
Aspartate Aminotransferase (Reference Range: 8–30 mU/mL)		
≥3xULN	2	(1)
≥3xULN, consecutive[a]	1	(<1)
Alanine Aminotransferase and/or Aspartate Aminotransferase		
≥3xULN	6	(3)
≥3xULN, consecutive[a]	3	(1)

Note: Each subject listed in this table is presented only once, in the category of the highest activity level reported.
ULN = Upper Limit of Normal.
A: This category includes those subjects with (1) two consecutive measurements for ALT and/or AST ≥3xULN, (2) a single, last measurement ≥3xULN, or (3) a measurement ≥3xULN followed by a measurement <3xULN that was taken more than 2 days after the last dose of study medication
Source: Applicant's Table 67

Table 7.4.2.3 Listing of Subjects with Two Consecutive Postbaseline Values for ALT and/or AST ≥3xULN

Center/ Subject	Sex/ Age[a]/Race	Treatment	Observation (Elevated ALT/AST)	Baseline Value[b] (mU/mL)	Post-Baseline Value(s) (mU/mL)	Study Day (Days Following End of Treatment in Parentheses)	Comments
44/121	M/16/White	EZ/simva 10/20 mg	AST: elevation	24	**102** 68 23	47 (1) 51 (5) 63 (17)	On Day 47 (1), the subject was observed to have elevated AST. AST decreased at the next visit to less than 3xULN. AST returned to within the reference range within 3 weeks. CPK was reported as an AE on the same Day 47 (1), resolving on Day 62 (16). The AE required discontinuation. (This subject's CPK elevation is described in Table 72.)
14/916	F/17/White	EZ/simva 10/40 mg	ALT: AE, consecutive elevations	9	**84** **97** 30	185 192 200 (4)	ALT was reported as an AE of moderate intensity on Day 185. On Day 192 it was increased to severe, possibly related to treatment, and required discontinuation. On Day 200 (4), the last contact with the subject, ALT levels returned to values near the reference range and the AE was downgraded to mild and resolved.
31/967	F/12/Multiracial	EZ/simva 10/40 mg	ALT: AE, consecutive elevations	9	**117** 36 12	232 239 259	ALT was reported as an AE on Day 232, resolving on Day 239. The AE was mild in severity, unlikely related to treatment, and required no action. ALT decreased to a level near the reference range on Day 239 and to near baseline level by Day 259. The subject continued in the trial.
			AST: AE, elevation	14	**257** 24	232 239	AST was reported as an AE on Day 232, resolving on Day 239. The AE was mild in severity, unlikely related to treatment, and required no action. AST decreased to a level within the reference range, near baseline level by Day 239. The subject continued in the trial.

10/043	M/15/White	Simva 40 mg	ALT: AE, consecutive elevations	6	**316** **124** 23	120 135 (9) 169 (43)	ALT was reported as an AE on Day 120, resolving on Day 169. The AE was severe, probably related to treatment, and required treatment discontinuation. ALT decreased to levels within the reference range by Day 169 (43), which was the last contact with the subject.
			AST: elevations	16	**182** 59 21	120 135 (9) 169 (43)	AST was observed to be elevated on Day 120, coincident with the elevations of ALT. AST returned to levels near the reference range on Day 135 (9). AST decreased to levels within the reference range by Day 169 (43), which was the last contact with the subject.
24/950	F/17/White	Simva 40 mg	ALT: consecutive elevations	22	**175** **125** 57	186 193 207	ALT was elevated ≥3xULN on two consecutive measurements on Day 186 and Day 193. The subject's ALT level returned to <2xULN by Day 207 and remained ≥1xULN and <2xULN for the remainder of the subject's participation in the trial. After the consecutive observations of elevated ALT, the subject continued in the trial.
			AST: elevation	16	**156** 82 31	186 193 207	AST was elevated ≥3xULN on Day 186. The subject's AST level returned to levels near the reference range by Day 193 and remained within the reference range for the rest of the subject's participation in the trial. After the observation of elevated AST, the subject continued in the trial.
55/969	F/14/White	EZ 10 + simva	ALT: AE, elevations	8	**92** 42	373 (1) 380 (8)	ALT was reported as an AE on Day 373 (1) and was considered to be ongoing following the last contact with the subject on Day 380 (8). The AE was moderate in severity, probably related to treatment, and required further laboratory monitoring. At the last contact with the subject on Day 380 (8), ALT levels had resolved to near the reference range.

Note: Subject 52/163 (M/12/White) had elevated ALT at the last regularly scheduled visit of Step 2 on Day 246. The subject continued in the trial. At the next observation on Day 253, ALT had returned to within the normal range. However, the algorithm for supporting listing for Step 2 includes subject 52/163 as part of the listing of subjects having elevated ALT at the end of the Step or Trial. Because further observations indicated that the subject had a transient ALT elevation, the subject is not considered to have met the criteria for consecutive elevations of ALT and is not included in this comprehensive listing of ALT/AST elevations.
AE = Adverse Event; ALT/AST = Alanine Aminotransferase and Aspartate Aminotransferase; CPK = Creatine Phosphokinase; F = Female; M = Male; ULN = Upper Limit of Normal.
A: Age is in years.
B: Reference ranges: ALT: 5-25 mU/mL ; /AST: 8-30 mU/mL
Source: Applicant's Table 68

Additional measurements used to monitor the effects of active treatment on liver function included GGT, alkaline phosphatase, and total bilirubin. The number and proportion of subjects with values above the upper limit of the reference ranges for GGT, alkaline phosphatase, and total bilirubin was small and similar in Step 1, Step 2, and Long-Term Coadministration. However, there was one subject who discontinued secondary to elevated ALT (and total bilirubin) that warrants further description:

Center: P02579-0014 **Sex:** Female **Subject:** 0916 **Age:** 17 years
Treatment and Regimen Assigned & Received:
Step 1: Ezetimibe 10 mg + Simvastatin 20 mg
Step 2: Ezetimibe 10 mg + Simvastatin 40 mg
Step 3: N/A
Summary: A 17-year-old White female subject initiated pre-randomization phase in study on 12 OCT 2005. The subject's medical history was significant for hypercholesterolemia (cholesterol 257 mg/dL [normal range: 125-170 mg/dL], on 12 OCT 2005), tiredness, intermittent epistaxis, intermittent nausea, intermittent vomiting, and intermittent diarrhea. Previous medications at pre-

randomization time included simvastatin (40 mg/QD, from OCT 2004 [exact date unknown] to 11 OCT 2005, hypercholesterolemia). On 12 OCT 2005, laboratory results revealed an elevation of total bilirubin (see Table below for display of lab values). On that date, laboratory values were as follows: ALT 10 mU/mL, (normal range: 5-25 mU/mL), AST 12 mU/mL, (normal range: 8-30 mU/mL), and total bilirubin 1.6 mg/dL, (normal range: 0.10-1.10 mg/mL). Single-blind placebo lead-in phase was initiated 26 OCT 2005. Study drug (bottles A and B) was interrupted on 27 OCT 2005 due to the event of mild gastroenteritis with mild nausea and mild vomiting. Study drug was resumed on 29 OCT 2005. On 05 DEC 2005, the subject was randomized and double-blind active treatment phase (ezetimibe vs. placebo) with simvastatin various doses (Step 1) was initiated on the same day. On that date, mild elevated total bilirubin was noted. Laboratory values were as follows: ALT 9 mU/mL, AST 11 mU/mL, and total bilirubin 2.31 mg/dL. On 13 DEC 2005, elevated total bilirubin improved (total bilirubin was 1.93 mg/mL, on 14 DEC 2005) and the investigator considered the event to be resolved. Double-blind active treatment phase with simvastatin 40 mg (Step 2) was initiated on 16 JAN 2006. On that date, total bilirubin elevation recurred. Laboratory values were as follows: ALT 8 mU/mL, AST 8 mU/mL, and total bilirubin 2.68 mg/mL. On 15 FEB 2006, elevation of total bilirubin increased in intensity and became moderate (total bilirubin of 3.1 mg/mL). On 12 APR 2006, the elevation of total bilirubin decreased in intensity and became mild (total bilirubin of 1.87 mg/mL). The subject received treatment with acetaminophen/codeine/ibuprofen from 09 MAY 2006 to 18 MAY 2006 and amoxicillin/clavulanic acid from 09 MAY 2006 to 13 MAY 2006 due to mild sinusitis which occurred on 05 MAY 2006 and resolved on 10 MAY 2006. On 07 JUN 2006, moderate elevation of ALT was noted. On that date, laboratory results were as follows: ALT 84 mU/mL, AST 36 mU/mL, and total bilirubin 1.84 mg/mL. Another blood test was performed on 14 JUN 2006 and revealed a severe elevation of ALT. Laboratory results were as follows: ALT 97 mU/mL, AST 44 mU/mL, and total bilirubin 2.1 mg/mL. Study drug (bottles A and B) was discontinued due to the event of elevated ALT; the last dose of study drug was taken on 18 JUN 2006. On 22 JUN 2006, increased total bilirubin improved and was considered to be resolved per the investigator, and elevation of ALT was considered to be mild. Laboratory results were as follows: ALT 30 mU/mL, AST 16 mU/mL, and total bilirubin 1.36 mU/mL. The investigator considered the event of increased total bilirubin (episode from 15 FEB 2006 to 11 APR 2006) and the events of elevated ALT to be possibly related to study drug. After closure of the database, the study was unblinded and the subject was found to have received ezetimibe 10 mg and simvastatin 20 mg during Step 1; and ezetimibe 10 mg and simvastatin 40 mg during Step 2.

Table 7.4.2.4 Lab Values for Subject 014-000916 F/17/W

Date	Week	Alk Phos Normal range: (32-330)	GGT Normal Range (5-29)	AST Normal Range (8-30)	ALT Normal Range (8-30)	T Bili Normal Range (0.1-1.1)	Ind Bili Normal Range (0.1-1.1)	Dir Bili Normal Range (0-0.4)
10/12/05	Baseline	52	8	12	10	**1.6**	**1.29**	0.31
11/23/05	Baseline	53	7	9	7	**1.37**	**1.12**	0.25
12/05/05	Baseline	53	8	11	9	**2.31**	**2.05**	0.26
12/14/05	2	52	7	15	13	**1.93**	**1.73**	0.2
1/16/06	6	50	8	8	8	**2.68**	**2.11**	**0.57**
2/15/06	10	48	7	10	11	**3.1**	**2.5**	**0.6**

4/12/06	18	52	8	12	16	**1.87**	**1.45**	**0.42**
5/9/06	Treatment with acetaminophen/codeine/ibuprofen from 09 MAY 2006 to 18 MAY 2006 and amoxicillin/clavulanic acid from 09 MAY 2006 to 13 MAY 2006 due to mild sinusitis							
6/07/06	26	55	21	**36**	**84**	**1.84**	**1.43**	**0.41**
6/14/06	26	53	29	**44**	**97**	**2.1**	**1.63**	**0.47**
6/18/06	LAST DOSE OF STUDY DRUG TAKEN							
6/22/06	26	50	23	16	30	**1.36**	1.03	0.33

Bolded values in red are > ULN

This subject had abnormal bilirubin levels at baseline which would be consistent with Gilbert's anomaly, with elevated unconjugated bilirubin due to a genetic defect in UDPglucuronidase activity. Increases in bilirubin did not correspond with increases in liver transaminases. Liver transaminase elevations occurred after addition of acetaminophen/codeine/ibuprofen and amoxicillin/clavulanic acid to her medication regimen. Lab tests returned to baseline within a week of stopping ezetimibe/simvastatin and acetaminophen/codeine/ibuprofen.

Creatine Phosphokinase

Clinically important elevations in creatine phosphokinase activity were defined by CPK ≥5xULN with "associated muscle symptoms" or persistent CPK elevations ≥10xULN with or without muscle symptoms. The following adverse event preferred terms comprised the possible associated muscle symptoms: back pain, back pain aggravated, cramps extremities, cramps legs, muscle disorder, muscle necrosis, muscle weakness, muscle weakness aggravated, musculoskeletal pain, myalgia, myalgia aggravated, myopathy, myopathy aggravated, and rhabdomyolysis. The adverse event was considered associated with the high CPK value if it occurred within 7 days of the CPK measurement.

From Baseline to the end of Step 1 (Week 6), subjects that met the criteria for consecutive ≥3xULN elevations in CPK are summarized in Table 7.4.2.5. A small number of subjects had CPK ≥3xULN, ≥5xULN, or ≥10xULN during the 6 weeks from Baseline to the end of Step 1. The proportion of subjects with elevated CPK values was numerically higher in the EZ/simva group (4, 3%) as compared to the simva group (2, 2%). During the trial there were no subjects with CPK values ≥5xULN with "associated muscle symptoms." One subject, on EZ/simva 20 mg, had CPK ≥10xULN from Baseline to the end of Step 1 and is described in Table 7.4.2.8.

Table 7.4.2.5 Number (%) of Subjects with Postbaseline Values for CPK > ULN at the End of Step 1 (Week 6)

	EZ/simva 10/10 n=43		EZ/simva 10/20 n=40		EZ/simva 10/40 n=43		Simva 10 n=40		Simva 20 n=40		Simva 40 n=42	
CPK (Reference Range - Female: 20–120 mU/mL, Male: 30-180 mU/mL)												
≥3xULN to <5xULN	0		0		2	(5)	0		1	(3)	0	
≥5xULN to <10xULN	1	(2)	0			0	0		1	(3)	0	
≥10xULN	0		1	(3)		0	0		0		0	

Note: Each subject listed in this table is presented only once, in the category of the highest activity level reported.
ULN = Upper Limit of Normal.
Source: Applicant's Table 69

From Baseline to the end of Step 2 (Week 33), subjects that met the criteria for ≥3xULN elevations in CPK are summarized in Table 7.4.2.6. A small number of subjects were observed to have CPK ≥3xULN, ≥5xULN, or ≥10xULN during the 33 weeks from Baseline to the end of Step 2. The number of subjects who had CPK values that were ≥3xULN from Baseline to the end of Week 33 were numerically larger in the EZ/simva 10/40 group (9, 7%) as compared to the simva 40 mg group (2, 2%). The same subject that had CPK ≥10xULN from Baseline to the end of Step 1 is captured in this report from Baseline to the end of Step 2 in Table 7.4.2.5 and is described in Table 7.4.2.8.

Table 7.4.2.6 Number (%) of Subjects with Postbaseline Values for CPK > ULN at the End of Step 2 (Week 33)

	EZ/simva 10/40 n=126		Simva 40 n=122	
CPK (Reference Range - Female: 20–120 mU/mL, Male: 30-180 mU/mL)				
≥3xULN to <5xULN	5	(4)	1	(1)
≥5xULN to <10xULN	2	(2)	1	(1)
≥10xULN	2	(2)	0	

Note: Each subject listed in this table is presented only once, in the category of the highest activity level reported.
ULN = Upper Limit of Normal.
Source Data: Applicant's Table 70

During Long-Term Coadministration subjects that met the criteria for consecutive ≥3xULN elevations in CPK are summarized in Table 7.4.2.7. A small number of subjects were observed to have CPK ≥3xULN, ≥5xULN, or ≥10xULN from Baseline to the end of Long-Term Coadministration. A total of two subjects had CPK ≥10xULN during Long-Term Coadministration and are described in Table 7.4.2.8.

Table 7.4.2.7 Number (%) of Subjects with Postbaseline Values for CPK > ULN at the End of Long-Term Coadministration (Week 53)

	EZ 10 mg + Simva n=238	
CPK (Reference Range - Female: 20–120 mU/mL, Male: 30-180 mU/mL)		
≥3xULN to <5xULN	5	(2)
≥5xULN to <10xULN	3	(1)
≥10xULN	2	(1)

Note: Each subject listed in this table is presented only once, in the category of the highest activity level reported.
ULN = Upper Limit of Normal.
Source: Applicant's Table 71

Table 7.4.2.8 Subjects with Any Postbaseline Value for CPK ≥ 10 x ULN or Any Postbaseline Value ≥ 5 x ULN with Reported Associated Muscle Symptoms

Center/ Subject	Gender /Age[a]/ Race	Treat-ment	Observation Comments (Elevated CPK)	Baseline Value[b] (mU/mL)	Post-Base-line Value (mU/m	Study Day	Comments

					L)		
31/967*	F/12/ Multi-racial	EZ/simva 10/20 mg	CPK≥10xULN	50	19,530 122 76	232 239 259	CPK was reported as an AE on Day 232. The AE was severe in intensity and required that study medication be temporarily interrupted. No behaviors, activities, or circumstances associated with the elevated CPK measurement were noted by the investigator. CPK decreased to a level within the reference range on Day 239 and the AE was resolved. Study medication was resumed on Day 239. The subject continued in the trial and CPK remained within the reference range for the remainder of the subject's participation in the trial.
44/121*	M/16/ White	EZ/simva 10/20 mg	CPK ≥10xULN	161	360 3666 1612 214	16 47(1) 51(5) 63(17)	On Day -42, creatine phosphokinase (CPK) level was 141 mU/mL. From Day -19 to Day -1, the subject experienced mild lower back bruise for which treatment with acetaminophen was taken on Day -19 and Day -18. On Day 1, the subject was randomized and double-blind active treatment phase (EZ vs. placebo) with simva various doses (Step 1) was initiated on the same day. On Day 16 CPK level was 260 mU/mL. On Day 43, treatment with clindamycin (topical) was initiated, and triamcinolone (intradermal) was taken only on Day 43, due to mild acne. From Day 27 to Day 29, the subject had a moderate viral infection for which treatment with acetaminophen was taken on the same dates. On Day 47 (1), elevated CPK level was noted. CPK was 3666 mU/mL. No symptoms were reported at this time. CPK was reported as an AE on Day 47 (1) of mild intensity, resolving on Day 62 (16). The AE required discontinuation. On the same Day 47 (1), the subject was observed to have elevated AST (Table 7.4.2.4). CPK was elevated above the baseline value on Day 16. CPK was elevated on Day 47 (1) when study drug was discontinued. CPK returned to near baseline values by Day 63 (17).

CPK = Creatine Phosphokinase; ULN = Upper Limit of Normal. AE = Adverse Event; CPK = Creatine Phosphokinase; F = Female; M = Male; ULN = Upper Limit of Normal.
a: Age is in years. b: Reference ranges: CPK = Female: 20–120 mU/mL, Male: 30-180 mU/mL
Source: Applicant's Table 72
*Refer to Appendix 9.2 for additional information

7.4.3 Vital Signs

Blood pressure, pulse rate, and oral body temperature evaluations revealed no clinically significant changes and remained within the range observed for healthy male and female subjects. Any clinically significant changes that were noted on the follow-up physical examinations are reported as adverse events.

7.4.4 Electrocardiograms (ECGs)

No clinically significant changes were observed between treatment and baseline values in any of the ECG parameters evaluated.

7.4.5 Special Safety Studies

Growth and Sexual Maturation: Steroid Hormone Levels
Estradiol in Females
Each baseline and endpoint steroid hormone level for each subject was assigned a grade according to prespecified ranges. Shift tables were used to examine a change in the number of subjects with steroid hormones levels within a grade from Baseline to Endpoint. Possible effects of treatment on hormone levels were examined by shifts in the number of subjects with steroid hormones levels within a grade from Baseline to the end of Step 2 for each treatment group and from Baseline to the end of Long-Term Coadministration. The majority of subjects demonstrated steroid hormone levels within the normal ranges. In addition, for each hormone examined, subjects had the same endpoint grade as the baseline grade. There were no apparent differences between the two treatment groups at the end of Step 2 or change in trends during Long-Term Coadministration.

Specifically, 98% of the female subjects in each treatment group demonstrated levels within the normal range from Baseline to the end of Step 2. Ninety-nine percent (91/92) of female subjects treated with either EZ/simva 10/40 mg or simva 40 mg monotherapy started with estradiol in Grade 1 (7 – 150 pg/mL) at Baseline and 98% (90/92) had estradiol in Grade 1 at the Step 2 Endpoint.

During Long-Term Coadministration 98% of female subjects had normal estradiol levels, with most subjects (90/91) starting with estradiol in Grade 1 and 89/91 subjects having estradiol in Grade 1 at the end of Long-Term Coadministration.

Testosterone in Males

With regard to testosterone in male subjects, there was no significant difference between the two treatment groups as shown in the tables below:

Table 7.4.5.1 Summary of Testosterone Grade Changes from Baseline to End of Step 2 (Week 33) in Male Subjects

Treatment	Baseline Testosterone Grade	No. of Baseline With Testosterone Grade	Endpoint Evaluation of Testosterone Grade		
			0	1	2
EZ/simva 10/40 mg (n=73)	1	60	0	58 (95)	2 (3)
	2	1	0	0	1 (2)
	Total	61	0	58 (95)	3 (5)
Simva 40 mg (n=69)	1	56	0	55 (89)	1 (2)
	2	6	0	2 (3)	4 (7)
	Total	62	0	57 (92)	5 (8)
Total		123	0	115	8

Note: For each lab test, only subjects with a baseline value and at least one postbaseline value are included in this summary table.
Testosterone grade: 0: <LLN; 1 LLN – ULN; 2: >ULN
Testosterone normal Range 10–16 years of age: 0.0–5.5 nmol/mL; after 20 OCT 2005: 15–18: 1.0– 8.4 nmol/mL. The range changed during the trial (20 OCT 2005) to correspond to the increasing age of the subject population. There were no male subjects younger than 15 years of age with testosterone observations after 20 OCT 2005.
Source: Applicant's Table 75

Table 7.4.5.2 Summary of Testosterone Grade Changes from Baseline to End of Long-Term Coadministration (Week 53) in Male Subjects

Treatment	Baseline Testosterone Grade	No. of Baseline With Testosterone Grade	Endpoint Evaluation of Testosterone Grade		
			0	1	2
EZ 10 mg + Simva (n=139)	1	114	0	109 (90)	5 (4)
	2	7	0	1 (1)	6 (5)
	Total	121	0	110 (91)	11 (9)
Total		121	0	110	11

Note: For each lab test, only subjects with a baseline value and at least one postbaseline value are included in this summary table.
Testosterone grade: 0: <LLN; 1 LLN – ULN; 2: >ULN
Testosterone normal Range 10–16 years of age: 0.0–5.5 nmol/mL; after 20 OCT 2005: 15–18: 1.0– 8.4 nmol/mL. The range changed during the trial (20 OCT 2005) to correspond to the increasing age of the subject population. There were no male subjects younger than 15 years of age with testosterone observations after 20 OCT 2005.
Source: Applicant's Table 76

Cortisol, DHEA, FSH, and LH

Cortisol levels from baseline to endpoint, as well as maximum and minimum levels, were consistent between the EZ/simva 40 mg and the simva 40 mg group. 91% (105/116) of subjects on EZ/simva had normal cortisol levels at the beginning of the study and 92% (107/116) had normal cortisol levels at the end of Step 2. 88% (98/112) of subjects on simva had normal cortisol levels at the beginning of the study and 88% (99/112) had normal cortisol levels at the end of Step 2. A similar high percentage of normal values at beginning and end of Step 2 were seen for DHEA, FSH, and LH.

Overall, treatment had no effect on steroid hormone levels.

Height (Stadiometric Linear Growth)
Percent change in height from Baseline to the end of Step 2 and to the end of Long-Term Coadministration was used to evaluate linear growth of subjects during the trial. Overall, the majority of the subjects in both treatment groups experienced a 0 to 10% increase in height during the 33 weeks from Baseline to the end of Step 2: 88% of subjects treated with EZ/simva 10/40 mg compared with 87% of subjects treated with simva 40 mg monotherapy. The remainder of subjects in each treatment group was observed to have a -10% to 0% change in height from Baseline to Step 2: 12% of subjects treated with EZ/simva 10/40 mg compared with 13% of subjects treated with simva 40 mg monotherapy. The distribution of subjects at the end of Step 2 according to the percent change from Baseline in height is summarized in Table 7.4.5.3.

Table 7.4.5.3 Height Distribution of Percent Change from Baseline to End of Step 2 (Week 33)

Percent Change From Baseline	EZ/simva 10/40 mg n=126 Missing values = 10	Simva 40 mg n=122 Missing values = 10
< -30%	0	0
-30% to < -10%	0	0
-10% to <0%	14 (12)	15 (13)
0% to < 10%	102 (88)	97 (87)
10% to < 30%	0	0
≥30%	0	0

Source: Applicant's Table 77

Overall, the majority of the subjects experienced a 0 to 10% increase in height during Long-Term Coadministration: 94% of subjects treated with EZ + simva in Long-Term Coadministration. The remaining 6% of subjects were observed to have a -10% to 0% change in height. The distribution of subjects during Long-Term Coadministration according the percent change from Baseline in height is summarized in Table 7.4.5.4.

Table 7.4.5.4 Height: Distribution of Percent Change from Baseline to End of Long-Term Coadministration (Week 53)

Percent Change From Baseline	EZ 10 + simva n=238 Missing values = 11	
< -30%	0	
-30% to < -10%	0	
-10% to <0%	14	(6)
0% to < 10%	213	(94)
10% to < 30%	0	
≥30%	0	

Source: Applicant's Table 78

There were no reports of adverse events associated with height. The apparent decrease in height in 6-13% of subjects throughout the duration of the trial likely represents an error in height measurements.

Sexual Maturation Measured by Tanner Staging

Tanner Staging was used to evaluate changes in sexual maturation during the trial. Shift tables below describe the results for Tanner Staging from Baseline to the end of Step 2 (Week 33) (girls: Table 7.4.5.5 and boys: Table 7.4.5.6) and to the end of Long-Term Coadministration (Week 53) (girls: Table 7.4.5.7 and boys: Table 7.4.5.8), for both male and female subjects. The results demonstrate that treatment had no detectable effect on sexual maturation as measured by Tanner Staging. All subjects, male and female, maintained or progressed in Tanner Staging during the trial, as would be expected in a normal pool of adolescent subjects.

Table 7.4.5.5 Summary of Tanner Staging Changes from Baseline to End of Step 2 (Week 33) in Female Subjects

Treatment	Baseline Evaluation of Tanner Staging	No. of Baseline Evaluation of Tanner Staging	Endpoint Evaluation of Tanner Staging				
			I	II	III	IV	V
EZ/simva 10/40 mg (n=53)	III	11	0	0	2 (4)	9 (19)	0
	IV	21	0	0	0	13 (28)	8 (17)
	V	15	0	0	0	0	15 (32)
	Total	47	0	0	2 (4)	22 (47)	23 (49)
Simva 40 mg (n=53)	III	4	0	0	1 (2)	3 (7)	0
	IV	22	0	0	0	13 (28)	9 (20)
	V	20	0	0	0	0	20 (44)
	Total	46	0	0	1 (2)	16 (35)	29 (63)
Total		93	0	0	3	38	52

Source: Applicant's Table 79

Table 7.4.5.6 Summary of Tanner Staging Changes from Baseline to End of Step 2 (Week 33) in Male Subjects

Treatment	Baseline Evaluation of Tanner Staging	No. of Baseline Evaluation of Tanner Staging	Endpoint Evaluation of Tanner Staging				
			I	II	III	IV	V
EZ/simva 10/40 mg (n=73)	II	22	0	12 (17)	9 (13)	1 (1)	0
	III	19	0	0	6 (9)	13 (19)	0
	IV	15	0	0	0	12 (17)	3 (4)
	V	13	0	0	0	0	13 (19)
	Total	69	0	12 (17)	15 (22)	26 (38)	16 (23)
Simva 40 mg (n=69)	II	16	0	8 (12)	7 (11)	1 (2)	0
	III	16	0	0	2 (3)	13 (20)	1 (2)
	IV	20	0	0	0	14 (22)	6 (9)
	V	13	0	0	0	0	13 (20)
	Total	65	0	8 (12)	9 (14)	28 (43)	20 (31)
Total		134	0	20	24	54	36

Source: Applicant's Table 80

Table 7.4.5.7 Summary of Tanner Staging Changes from Baseline to End of Long-Term Coadministration (Week 53) in Female Subjects

Treatment	Baseline Evaluation of Tanner Staging	No. of Baseline Evaluation of Tanner Staging	Endpoint Evaluation of Tanner Staging				
			I	II	III	IV	V
EZ + simva n=99	III	15	0	0	1 (1)	13 (14)	1 (1)
	IV	43	0	0	0	22 (24)	21 (23)
	V	34	0	0	0	0	34 (37)
	Total	92	0	0	1 (1)	35 (38)	56 (61)
Total		92	0	0	1	35	56

Source: Applicant's Table 81

Table 7.4.5.8 Summary of Tanner Staging Changes from Baseline to End of Long-Term Coadministration (Week 53) in Male Subjects

Treatment	Baseline Evaluation of Tanner Staging	No. of Baseline Evaluation of Tanner Staging	Endpoint Evaluation of Tanner Staging				
			I	II	III	IV	V
EZ + simva n=139	II	40	0	11 (8)	20 (15)	6 (4)	3 (2)
	III	35	0	0	5 (4)	27 (20)	3 (2)
	IV	34	0	0	0	20 (15)	14 (10)
	V	26	0	0	0	0	26(19)
	Total	135	0	11 (8)	25 (19)	53 (39)	46 (34)
Total		135	0	11	25	53	46

Source: Applicant's Table 82

Menstrual Cycle

Each subject was to record the start date of each menstrual cycle during the trial. From the consecutive start dates, a duration of each cycle for each subject was calculated. The median and mean menstrual cycle durations were determined for each subject. For each treatment group, EZ/simva 10/40 mg and simva 40 mg monotherapy, a mean of the median menstrual cycle duration from Baseline to the end of Step 2 (Week 33) was evaluated. The median values were evaluated due to variability in the menstrual cycle duration for adolescent girls and the missing reports of start dates for each cycle.

There were no apparent differences in the average median duration of menstrual cycles from Baseline to the end of Step 2 (Week 33) for adolescent girls between subjects in the EZ/simva 10/40 mg treatment group compared with subjects in the simva 40 mg monotherapy group (Table 7.4.5.9). An evaluation of the median cycle durations during the trial also revealed that there were no apparent changes in the median menstrual cycle in adolescent girls treated with either EZ/simva 10/40 mg or simva 40 mg monotherapy duration during the trial.

Table 7.4.5.9 Summary Statistics of Menstrual Cycle Duration from Baseline to the End of Step 2 (Week 33)

	n	Lower Quartile	Median	Upper Quartile	Mean	SD
EZ/simva 10/40 mg	52	29	31	35	35.02	11.04
Simva 40 mg	51	29	30.5	41	36.57	13.12

Note: Quartile, Median, and Mean values are presented in days.
SD = Standard Deviation
Source: Applicant's Table 83

There were no reports of clinically significant findings related to menstruation during the trial. The following subjects had adverse events related to menses:

- Dysmenorrhea: Subjects 22/944, 4/934, 49/998, and 10/1009;
- Menstrual discomfort: Subjects 49/912, 49/918, 49/908, and 49/906;
- Menstrual irregularity: Subject 29/963.

One of these subjects was receiving EZ plus simva coadministration at the time of the reports (Subject 22/944). The others were receiving simva monotherapy at the time. Subject 29/963 report of "menstrual irregularity" did not resolve, but was considered ongoing. The other AEs related to menses resolved during the trial. Each adverse event was considered mild in severity. Overall, adolescent girls treated with either EZ/simva 10/40 mg or simva 40 mg monotherapy during the trial did not experience any changes in menstrual cycle characterization or duration.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

End of Step 1 (Week 6)

EZ/simva 10 mg vs simva 10 mg

Treatment-emergent adverse events were reported for 42% (18/43) of subjects assigned to the EZ/simva 10/10 mg group and for 50% (20/40) of subjects assigned to the simva 10 mg monotherapy group. Overall, adverse event profiles were similar for the two treatment groups receiving the coadministration of EZ/simva 10/10 mg and simva 10 mg monotherapy. The most common adverse events (reported for at least 5% of subjects in either treatment group) were as follows:

- Dyspepsia (0% of subjects assigned EZ/simva 10/10 mg vs 5% of subjects assigned simva 10 mg monotherapy);
- Nausea (0% vs 5%);
- Vomiting (2% vs 5%);
- Pyrexia (0% vs 5%);
- Influenza (9% vs 3%);
- Nasopharyngitis (5% vs 10%);
- Sinusitis (0% vs 5%);
- Dehydroepiandrosterone increased (0% vs 5%);
- Menstrual discomfort (0% vs 5%).

EZ/simva 20 mg vs simva 20 mg

Treatment-emergent adverse events were reported for 68% (27/40) of subjects assigned to the EZ/simva 20mg group and for 45% (18/40) of subjects assigned to the simva 20 mg monotherapy group. The most common adverse events (reported for at least 5% of subjects in either treatment group) were as follows:

- Diarrhea (10% of subjects assigned EZ/simva 10/20 mg vs 3% of subjects assigned simva 20 mg monotherapy);
- Influenza (3% vs 5%);
- Nasopharyngitis (13% vs 5%);
- Tonsillitis (5% vs 0%);
- ALT increased (8% vs 0%);
- Dehydroepiandrosterone increased (3% vs 5%);
- Headache (10% vs 5%);
- Pharyngolaryngeal pain (8% vs 0%).

Most of these adverse events were more frequent for the treatment group receiving the coadministration of EZ/simva 10/20 mg compared to simva 20 mg monotherapy.

EZ/simva 40 mg vs simva 40 mg

Treatment-emergent adverse events were reported for 42% (18/43) of subjects assigned to the EZ/simva 40 group and for 50% (21/42) of subjects assigned to the simva 40 monotherapy

group. Overall, adverse event profiles were similar for the two treatment groups receiving the coadministration of EZ/simva 10/40 mg and simva 40 mg monotherapy. The most common adverse events (reported for at least 5% of subjects in either treatment group) were as follows:

- Palpitations (5% of subjects assigned EZ/simva 10/40 mg vs 0% of subjects assigned simva 40 mg monotherapy);
- Seasonal allergy (5% vs 0%);
- Influenza (5% vs 5%);
- Nasopharyngitis (7% vs 10%);
- Upper respiratory tract infection (5% vs 0%);
- Dehydroepiandrosterone increased (5% vs 0%);
- Headache (2% vs 12%).

End of Step 2 (Week 33)
Treatment-emergent adverse events were reported for 83% (105/126) of subjects assigned to receive EZ/simva 10/40 mg coadministration therapy and for 84% (103/122) subjects assigned to simva 40 mg monotherapy. Adverse events of abdominal pain, diarrhea, nausea, ALT increased, myalgia and pharyngolaryngeal pain were more frequent for the treatment group receiving the coadministration of EZ/simva 10/40 mg vs simva 40 mg monotherapy. The most common adverse events (reported for at least 5% of subjects in either treatment group) were as follows:

- Abdominal pain (5% of subjects assigned EZ/simva 10/40 mg vs 2% of subjects assigned simva 40 mg monotherapy);
- Diarrhea (7% vs 2%);
- Nausea (6% vs 3%);
- Vomiting (4% vs 5%);
- Influenza (6% vs 10%);
- Nasopharyngitis (21% vs 22%);
- Sinusitis (5% vs 4%);
- ALT increase (5% vs 2%);
- Myalgia (6% vs 1%);
- Headache (13% vs 13%);
- Cough (3% vs 7%);
- Pharyngolaryngeal pain (5% vs 2%);
- Acne (3% vs 7%).

7.5.2 Time Dependency for Adverse Events

The reports of AEs were examined over time using time periods of roughly equal durations. AEs were examined from Baseline to the end of Step 2 (Week 33) using 3 periods of approximately 11 weeks each. AEs were examined to the end of Long-Term Coadministration using periods of approximately 13 weeks each. AEs were examined over time by three categories:

- **All:** AEs reported during a time period, which would include on-going AEs from earlier time periods;

- **First:** AEs reported during a time period, which would include AEs that are reported by a subject for the first time; this presentation excludes subsequent reports of a particular preferred term by an individual subject;
- **New:** AEs reported during a time period, which would include only AEs that have a start date in the time period.

In general, for **All**, **First**, and **New** AEs there were no significant differences in the reports between the two treatment groups from Baseline to the end of Step 2 over time. In the **All** Summary, diarrhea, myalgia, and pharyngolaryngeal pain were slightly more likely to occur in the first 12 weeks in the EZ 10/simva 40 group and headache was slightly more likely to occur in the first 12 weeks in the simva 40 group. Lab abnormalities such as increased ALT, AST, or CPK were distributed throughout the 3 time intervals. In the **First** Summary, diarrhea, myalgia, tonsillitis, pain in extremity, and pharyngolaryngeal pain were slightly more likely to occur in the first 12 weeks in the EZ 10/simva 40 group and headache and URI were slightly more likely to occur in the first 12 weeks in the simva 40 group. Lab abnormalities such as increased ALT, AST, or CPK were distributed throughout the 3 time intervals. Similarly, there were no significant changes in the pattern of **All**, **First**, and **New** AEs over time during the long-term experience.

7.5.3 Drug-Demographic Interactions

Treatment-emergent adverse events were examined in subgroup populations according to the following baseline characteristics: sex (boys vs girls) and race (White, Black, Asian vs Multiracial). The more commonly reported adverse events (those occurring in ≥5% of subjects in either of the two treatment groups for the overall population) were examined by sex (boys vs girls) and race (White, Black, Asian vs Multiracial).

For gender, the small numbers in each group (~20-25 for each of the 6 treatment groups for males and females, each) limits the analysis. In general, there were no clinically meaningful differences in the reporting of adverse events by sex at the end of Week 6, except for the treatment groups assigned to receive EZ/simva 10/40 mg coadministration therapy. In these treatment groups, adverse events were recorded for 28% of male subjects (7/25) and for 61% of female subjects (11/18). No clinically meaningful differences were reported at the end of Week 33 and Week 53.

The small sample size for the non-White populations makes any meaningful interpretation difficult. However, there were no obvious differences observed by race.

Increases in ALT/AST were generally similar across subgroups stratified by the baseline characteristics of gender and race.

7.5.4 Drug-Disease Interactions

All subjects in this study had Heterozygous Familial Hypercholesterolemia; no drug-disease interactions were reported.

7.5.5 Drug-Drug Interactions

No drug-interaction studies were conducted to support this current application regarding pediatric subjects.

In the P02579 trial there was an adverse event that, in this reviewer's opinion, is likely secondary to a drug-interaction (erythromycin).
Center: P02579-0010 **Sex:** Male **Subject:** 0043 **Age:** 15 years
Treatment and Regimen Assigned & Received:
Step 1: Placebo + Simvastatin 40 mg
Step 2: Placebo + Simvastatin 40 mg
Step 3: N/A
Discontinuation Due To Adverse Event: Elevated ALT
Summary: A 15-year-old White male subject initiated pre-randomization phase in study on 29 SEP 2005. The subject's medical history was significant for hypercholesterolemia (cholesterol 383 mg/dL [normal range: 125-170 mg/dL], on 29 SEP 2005), heartburn, and epistaxis. No concomitant medications at pre-randomization time were noted. On 29 SEP 2005, laboratory values were as follows: ALT 9 mU/mL, (normal range: 5-25 mU/mL), AST 15 mU/mL, (normal range: 8-30 mU/mL), GGT 12 mU/mL, (normal range: 5-29 mU/mL), and CPK 118 mU/mL, (normal range: 30-180 mU/mL). Single-blind placebo lead-in phase was initiated on 06 OCT 2005. On 19 OCT 2005, treatment with calcium carbonate was initiated due to heartburn. On 16 NOV 2005, the subject was randomized and double-blind active treatment phase (ezetimibe vs. placebo) with simvastatin various doses (Step 1) was initiated on the same day. On 16 NOV 2005, laboratory values were as follows: ALT 6 mU/mL, AST 16 mU/mL, GGT 13mU/mL, and CPK 104 mU/mL. Double-blind active treatment phase with simvastatin 40 mg (Step 2) was initiated on 05 JAN 2006. On 05 JAN 2006, laboratory values were as follows: ALT 15 mU/mL, AST 16 mU/mL, GGT 15 mU/mL, and CPK 115mU/mL. On 01 MAR 2006, the subject had moderate tonsillitis for which treatment with **erythromycin was taken from 02 MAR 2006 to 07 MAR 2006**. The study drug was not interrupted during the treatment with erythromycin (prohibited concomitant medication, per protocol). Tonsillitis resolved on 06 MAR 2006. On 15 MAR 2006, severe elevation of ALT was noted. On that date, laboratory results were as follows: ALT 316 mU/mL, AST 182 mU/mL, GGT 33 mU/mL, and CPK 183 mU/mL. Study drug was discontinued due to the event of elevated ALT; the last dose of study drug was taken on 21 MAR 2006. On 30 MAR 2006, laboratory results were as follows: ALT 124 mU/mL, AST 59 mU/mL, GGT 27 mU/mL, and CPK 103 mU/mL. The event of elevated ALT resolved on 03 MAY 2006. On that date, laboratory results were as follows: ALT 23 mU/mL, AST 21 mU/mL, GGT 15 mU/mL, and CPK 98mU/mL. The investigator considered the event of elevated ALT to be probably related to study drug. After closure of the database, the study was unblinded and the subject was found to have received a placebo and simvastatin 40 mg during Step 1 and 2.

7.5.6 Additional Safety Explorations

None

7.5.7 Human Carcinogenicity

Not applicable.

7.5.8 Human Reproduction and Pregnancy Data

No new studies regarding pregnancy or lactation were conducted to support this current application regarding pediatric subjects.

7.5.9 Pediatrics and Effect on Growth

There was no treatment effect on growth and sexual maturation or steroid hormone levels in the adolescent boys or girls. See Section 7.4.5 Special Safety Studies for details.

7.5.10 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were 14 subjects who reported a drug overdose. Summaries are provided in Table 7.5.9. No action was required as a result of any of the reports of accidental overdose.

Table 7.5.10 Drug Overdose

Center/ Randomization #	Age/Gender/ Race	Comment
04/0002	M/15/W	Took double dose of ezetimibe for 10 days- no AE was reported
04/0022	M/14/W	On 25 MAY 2006, the subject took three tablets of each study medication (bottles A [ezetimibe vs. placebo] and B [simvastatin]) by mistake. No adverse event related to the overdose was reported. All laboratory results were within normal ranges.
08/0033	M/10/W	Double-blind active treatment phase with simvastatin 40 mg (Step 2) was initiated on 14 DEC 2005. From 06 APR 2006 to 12 APR 2006 and from 30 MAY 2006 to 01 JUN 2006, the subject took one extra dose for both treatments, A and B. No adverse event related to the overdose was noted. All laboratory results remained within normal ranges.
08/0036	M/13/A	Double-blind active treatment phase with simvastatin 40 mg (Step 2) was initiated on 17 DEC 2005. From 06 APR 2006 to 14 APR 2006, the subject took one extra dose of both treatments A (ezetimibe vs. placebo) and B (simvastatin). All laboratory results remained within normal ranges.
09/0049	M/15/M	Open label active treatment phase (Step 3) was initiated on 24 JUL 2006; the subject had received ezetimibe 10 mg and simvastatin 20 mg. From 28 AUG 2006 to 01 OCT 2006, ezetimibe 20 mg was taken by mistake. At the same period of time, from 28 AUG 2006 to 03

		OCT 2006, the subject missed 37 doses of simvastatin. No adverse event related to the overdose of ezetimibe was reported. All laboratory results remained within normal ranges.
09/0055	M/15/M	Double-blind active treatment phase with simvastatin 40 mg (Step 2) was initiated on 30 JAN 2006. From 07 JUL 2006 to 18 JUL 2006, the subject took one extra dose of both treatments A (ezetimibe vs. placebo) and B (simvastatin). No adverse event related to the overdose was noted. On 07 AUG 2006, laboratory results showed mild elevation of ALT (27 mU/mL) and TSH (5.2 µIU/mL); all other laboratory results remained within normal ranges.
09/0153	M/17/M	On 22 MAR 2006, the subject was randomized and double-blind active treatment phase (ezetimibe vs. placebo) with simvastatin various doses (Step 1) was initiated on the same day. On that date, laboratory results were as follows: alanine aminotransferase (ALT 17 mU/mL, normal range: 5-25 mU/mL), CPK 144 mU/mL, and potassium (4.6 mmol/L, normal range: 3.5-5.0 mmol/L). From 17 APR 2006 to 21 APR 2006, the subject took extra doses of both treatments A (ezetimibe vs. placebo) and B (simvastatin). Double-blind active treatment phase with simvastatin 40 mg (Step 2) was initiated on 03 MAY 2006. On that date, laboratory results showed mild elevation of ALT (26 mU/mL) and potassium (5.1 mmol/L); all other laboratory results remained within normal ranges. From 15 MAY 2006 to 21 MAY 2006, the subject again took extra doses of both treatments A and B. On 26 JUL 2006, laboratory results showed mild elevation of ALT 52 mU/mL and CPK 186 mU/mL; all other laboratory results remained within normal ranges.
10/0160	M/13/W	Double-blind active treatment phase with simvastatin 40 mg (Step 2) was initiated on 01 JUN 2006. On 28 AUG 2006, CPK value was 238 mU/mL and ALK-P value was 342 mU/mL. From 15 SEP 2006 to 30 SEP 2006, the subject took two tablets daily by mistake from each bottle A (ezetimibe vs. placebo) and B (simvastatin). No adverse event related to the overdose was reported. On 21 OCT 2006, except for CPK (219 mU/mL) and ALK-P (344 mU/mL), all other laboratory results were within normal ranges.
10/0167	M/10/W	Open label active treatment phase (Step 3) was initiated on 19 JAN 2007; the subject had received ezetimibe 10 mg and simvastatin 20 mg. From 19 APR 2007 to 17 MAY 2007, the subject took 40 mg of simvastatin instead of 20 mg. No adverse event related to the overdose was noted.
10/0996	F/14/W	Double-blind active treatment phase with simvastatin 40 mg (Step 2) was initiated on 16 MAR 2006. From 12 AUG 2006 to 14 AUG 2006, the subject took two tablets daily of treatment A (ezetimibe vs. placebo); and from 12 AUG 2006 to 16 AUG 2006, the subject took two tablets daily of treatment B (simvastatin). Open label active treatment phase (Step 3) was initiated on 23 SEP 2006; the subject had received ezetimibe 10 mg and simvastatin 40 mg. From 13 OCT 2006 to 17 OCT 2006, the subject took 20 mg of ezetimibe instead of 10 mg; and from 13 OCT 2006 to 21 OCT 2006, the subject took 80 mg of simvastatin instead of 40 mg. No adverse event related to the overdoses was noted. All laboratory results remained within normal ranges.
10/1009	F/16/W	From 15 MAR 2007 to 07 APR 2007, the subject was considered to have taken 40 mg of simvastatin instead of 20 mg. According to the

		subject the bottle of simvastatin 20 mg fell and some of the tablets were lost. The subject confirmed that she did not overdose on study drug. The subject completed the study; the last dose of study drug was taken on 02 MAY 2007. No adverse event related to the suspected overdose was noted.
11/0040	M/15/W	On 07 NOV 2005, the subject was randomized and double-blind active treatment phase (ezetimibe vs. placebo) with simvastatin various doses (Step 1) was initiated on the same day. From 10 DEC 2005 to 13 DEC 2005, the subject took two tablets of treatment A (ezetimibe vs. placebo) and six tablets of treatment B (simvastatin). No adverse event related to the overdose was reported.
15/0101	F/15/W	Open label active treatment phase (Step 3) was initiated on 09 SEP 2006; the subject had received ezetimibe 10 mg and simvastatin 10 mg. On 24 JAN 2007, at the day of final study visit, by mistake the subject continued to take ezetimibe 10 mg/QD in addition to simvastatin 20 mg/QD.
15/0152	M/13/W	Double-blind active treatment phase with simvastatin 40 mg (Step 2) was initiated on 05 APR 2006. On 05 APR 2006, the subject took three tablets of treatment A (ezetimibe vs. placebo) instead of one. On 08 MAY 2006, the subject took two tablets of treatment A. No adverse event related to the overdoses was reported. All laboratory results remained within normal ranges.

Reports of overdose from postmarketing reports is provided in Section 8.

No new studies evaluating drug abuse were conducted to support this current application regarding pediatric subjects.

No new studies regarding rebound following withdrawal were conducted to support this current application regarding pediatric subjects.

7.6 Additional Submissions

Not applicable.

8 Postmarketing Experience

MSP stated that they searched the Worldwide Adverse Experience System (WAES) database from 13 DEC 2004 through 31 AUG 2007 for pediatric reports from healthcare providers, agencies and consumers with ezetimibe as the primary suspect therapy. The reports were separated into 4 groups depending on age and treatment:

- reports received for ezetimibe in patients 10 to 17 years old;
- reports received for ezetimibe/simvastatin in patients 10 to 17 years old;
- reports received for ezetimibe in patients 9 years and under; and
- reports received for ezetimibe/simvastatin in patients 9 years and under.

A total of 39 pediatric reports for ezetimibe or ezetimibe/simvastatin were identified, with 80 adverse experiences. Of these 39 reports, 21 cases with ezetimibe in the 10 to 17 years of age

group, 6 cases were with ezetimibe/simvastatin in the 10 to 17 years of age group, 10 cases with ezetimibe in the 9 years and under age group receiving ezetimibe, and 2 cases with ezetimibe/simvastatin in the 9 years and under age group.

In the 10 to 17 years of age group receiving ezetimibe, there were 3 serious and 18 non-serious cases identified. Of the 3 serious cases with ezetimibe in the 10 to 17 years of age group, there were 4 serious adverse experiences (2 expected events, 2 unexpected events): 1 prescribed overdose (E), 1 hypophosphatemia (U), 1 hyponatremia (U), and 1 overdose (E). Associated with these serious adverse events were 4 non-serious experiences: 1 high density lipoprotein decreased (E), 2 drug administration error (E), and 1 alopecia (U).

One serious unexpected case with ezetimibe in the 10 to 17 years of age group is described further:

- (Case ID 0505USA00621): A pharmacist reported a 13-year-old male patient experienced hyponatremia and hypophosphatemia and was hospitalized after 2 weeks of therapy with 10 mg ezetimibe. Ezetimibe was discontinued. No further information about this case was provided.

Of the 18 non-serious cases with ezetimibe in the 10 to 17 years of age group, there were 30 adverse experiences (15 expected events, 15 unexpected events): 1 mood altered (U), 1 eosinophil percentage increased (U), 1 abdominal pain (E), 1 red blood cell sedimentation rate increased (U), 1 arthralgia (E), 2 disturbance in attention (U), 1 restlessness (U), 1 rash (E), 1 drug interaction (E), 1 performance status decreased (U), 1 speech disorder (U), 2 high density lipoprotein decreased (U), 1 headache (E), 4 myalgias (E), 4 blood creatine phosphokinase increased (E), 1 drug ineffective (E), 1 hypercholesterolemia (U), 1 hypertriglyceridemia (U), 2 epicondylitis (U), 1 vitamin A decreased (U), and 1 incorrect drug dosage form administered (E).

In the 10 to 17 years of age group receiving ezetimibe/simvastatin, there were 2 serious cases and 4 non-serious cases. Of the 2 serious cases, there were 5 serious adverse experiences (3 expected events, 2 unexpected events): 1 muscle spasms (U), 1 rhabdomyolysis (E), 1 influenza like illness (U), and 2 prescribed overdoses (E). Associated with these serious reports, there was 1 non-serious adverse experience: 1 amenorrhea (U).

One serious unexpected case with ezetimibe/simvastatin in the 10 to 17 years of age group is described further.

- (Case ID 0703USA05218): A 17-year-old male patient taking one half a tablet daily for 9 months, who experienced muscle spasms, rhabdomyolysis and influenza illness. No other information about this case was available.

Of the 4 non-serious cases with ezetimibe/simvastatin in the 10 to 17 years of age group, there were 5 adverse experiences all of which were considered expected: 1 blood creatine phosphokinase increased (E), 1 myalgia (E), 1 nausea (E), 1 abdominal pain (E), and 1 therapeutic response unexpected (E).

In the 9 year old and under group receiving ezetimibe, there were 7 serious cases and 3 non-serious cases. Of the 7 serious cases, there were 13 serious adverse experiences (10 expected events, 3 unexpected events): 4 overdose (E), 1 accidental exposure (E), 2 prescribed overdoses (E), 1 abdominal pain upper (E), 1 back pain (E), 1 skin tightness (U), 1 sleep disorder (U), 1 circulatory collapse (U) and 1 gastrointestinal pain (E). Associated with these serious adverse events, there were 9 non-serious experiences: 3 accidental exposures (E), 3 no adverse effects (E), 1 dyspepsia (E), 1 papilledema (U), and 1 inappropriate schedule of drug administration (E).

Of the 3 non-serious cases with ezetimibe in the 9 year old and under group, there were 5 adverse experiences (4 expected events, 1 unexpected events): 1 fatigue (E), 1 malaise (E), 1 hepatic function abnormal (E), 1 flushing (U) and 1 hepatic enzyme increased (E).

In the 9 year old and under group receiving ezetimibe/simvastatin, there were 2 serious cases. Of the 2 serious cases, there were 2 serious expected adverse experiences: 1 accidental overdose (E) and 1 prescribed overdose (E). Associated with these serious reports, there were 2 non serious adverse experiences: 2 headaches (E).

9 Appendices

9.1 Literature Review/References

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9.2 Subject Narratives

Discontinuations for Muscular-Related Adverse Reactions
Center: P02579-0049 **Sex:** Female **Subject:** 1004 **Age:** 17 years
Treatment and Regimen Assigned & Received:
Step 1: Ezetimibe 10 mg + Simvastatin 40 mg
Step 2: Ezetimibe 10 mg + Simvastatin 40 mg
Step 3: N/A
Discontinuation Due To Adverse Event: Intermittent headache, muscle ache legs
Summary: A 17-year-old White female subject initiated pre-randomization phase in study on 31 JAN 2006, for efficacy, safety, and tolerability of ezetimibe in coadministration with simvastatin in the therapy of adolescents with HeFH. The subject's medical history was significant for hypercholesterolemia (cholesterol 259 mg/dL [normal range: 125-170 mg/dL], on 31 JAN 2006) and psychological support for the death of her father in 2001. Concomitant medications at pre-randomization time included ethinylestradiol/ norgestrel (oral contraception). Single-blind placebo lead-in phase was initiated on 07 FEB 2006. On 14 FEB 2006, the subject had a mild sport accident (no detail provided). From 14 FEB 2006 to 20 FEB 2006, the subject experienced mild headache which required no additional therapy. On 21 MAR 2006, the subject was randomized and double-blind active treatment phase (ezetimibe vs. placebo) with simvastatin various doses (Step 1) was initiated on the same day. On that date, CPK was 43 mU/mL, (normal range: 20-120 mU/mL). On 04 APR 2006 and 05 APR 2006, the subject complained of intermittent headache and legs muscle ache for which study drug (bottles A and B) was interrupted on the same dates. On 04 APR 2006, CPK was 79 mU/mL. From 15 APR 2006 to 30 APR 2006, the subject had a mild influenza for which treatment with acetaminophen was taken from 15 APR 2006 to 20 APR 2006. Last dose date of Step 1 was on 04 MAY 2006. Double-blind active treatment phase with simvastatin 40 mg (Step 2) was initiated on 07 MAY 2006. On 05 MAY 2006, CPK was 68 mU/mL. On 07 MAY 2006, the subject began to complain of mild legs muscle ache and mild intermittent headache. Study drug (bottles A and B) was interrupted due to the events of myalgia and headache on 06 JUN 2006. On 06 JUN 2006, CPK was 74 mU/mL. Myalgia resolved on 09 JUN 2006. Study drug was resumed on 17 JUN 2006. On 19 JUN 2006, the subject complained of moderate legs muscle ache. Study drug (bottles A and B) was discontinued due to the events of legs muscle ache and intermittent headache; the last dose of study drug was taken on 29 JUN 2006. The events of headache resolved on 29 JUN 2006 and myalgia resolved on 03 JUL 2006. On 12 JUL 2006, CPK was 77 mU/mL. During the study, all other laboratory results remained within normal ranges. The investigator considered the events of intermittent headache and legs muscle ache (two episodes) to be possibly related to study drug. After closure of the database, the study was unblinded and the subject was found to have received ezetimibe 10 mg and simvastatin 40 mg during Step 1 and Step 2.

Center: P02579-0024 **Sex:** Female **Subject:** 0948 **Age:** 15 years
Treatment and Regimen Assigned & Received:
Step 1: Ezetimibe 10 mg + Simvastatin 20 mg
Step 2: Ezetimibe 10 mg + Simvastatin 40 mg
Step 3: N/A
Discontinuation Due To Adverse Event: Right lower leg muscle ache

Summary: A 15-year-old White female subject initiated pre-randomization phase in study on 20 JAN 2006, for efficacy, safety, and tolerability of ezetimibe in coadministration with simvastatin in the therapy of adolescents with HeFH. The subject's medical history was significant for hypercholesterolemia (cholesterol 289 mg/dL [normal range: 125-170 mg/dL], on 20 JAN 2006). No concomitant medications at pre-randomization time were noted. Single-blind placebo lead-in phase was initiated on 01 FEB 2006. On 15 MAR 2006, the subject was randomized and double-blind active treatment phase (ezetimibe vs. placebo) with simvastatin various doses (Step 1) was initiated on the same day. Double-blind active treatment phase with simvastatin 40 mg (Step 2) was initiated on 25 APR 2006. On 04 MAY 2006, the subject experienced mild right lower leg pain. Study drug (bottles A and B) was interrupted on that date. The leg pain resolved on 04 MAY 2006. Study drug was resumed on 23 MAY 2006. On 03 JUN 2006, the subject complained of mild right lower leg muscle ache. Study drug (bottles A and B) was interrupted on that date. Leg muscle ache resolved on 04 JUN 2006 and study drug was resumed on the same day. On 10 JUN 2006, mild right lower leg muscle ache recurred. Study drug (bottles A and B) was interrupted on that date. Muscle ache resolved on 11 JUN 2006. Study drug was resumed on 21 JUN 2006. Study drug was discontinued due to the event of right lower leg muscle ache; the last dose of study drug was taken on 17 JUL 2006. During the study, creatine phosphokinase levels remained within normal ranges. The investigator considered the events of leg pain and leg muscle ache to be possibly related to study drug. After closure of the database, the study was unblinded and the subject was found to have received ezetimibe 10 mg and simvastatin 20 mg during Step 1; and ezetimibe 10 mg and simvastatin 40 mg during Step 2.

Discontinuations for ALT Increased
Center: P02579-0010 **Sex:** Male **Subject:** 0104 **Age:** 12 years
Treatment and Regimen Assigned & Received:
Step 1: Ezetimibe 10 mg + Simvastatin 20 mg
Step 2: Ezetimibe 10 mg + Simvastatin 40 mg
Step 3: N/A
Adverse Event Of Special Interest: Elevated ALT
Discontinuation Due To Adverse Event: Elevated ALT
Summary: A 12-year-old White male subject initiated pre-randomization phase in study on 25 NOV 2005, for efficacy, safety, and tolerability of ezetimibe in coadministration with simvastatin in the therapy of adolescents with HeFH. The subject's medical history was significant for hypercholesterolemia (cholesterol 390 mg/dL [normal range: 125-170 mg/dL], on 25 NOV 2005). No concomitant medications at pre-randomization time were noted. On 25 NOV 2005, laboratory values were as follows: ALT 21 mU/mL, (normal range: 5-25 mU/mL) and AST 13 mU/mL, (normal range: 8-30 mU/mL). Single-blind placebo lead-in phase was initiated 05 DEC 2005. On 05 JAN 2006, ALT value was 35 mU/mL. On 24 JAN 2006, the subject was randomized and double-blind active treatment phase (ezetimibe vs. placebo) with simvastatin various doses (Step 1) was initiated on the same day. On that date, ALT was 24 mU/mL and AST 15 mU/mL. From 26 FEB 2006 to 03 MAR 2006, the subject had a mild cold, no therapy was taken. Double-blind active treatment phase with simvastatin 40 mg (Step 2) was initiated on 06 MAR 2006. On that date, elevation of ALT was noted. Laboratory values were as follows: ALT 55 mU/mL and AST 34 mU/mL. Per the investigator, ALT elevation was considered severe. On 13 MAR 2006, ALT value was 62 mU/mL and AST 30 mU/mL. On 20 MAR 2006,

the subject began to experience a moderate tonsillitis for which treatment with acetaminophen/ibuprofen and amoxicillin/clavulanic acid was taken from 22 MAR 2006 to 29 MAR 2006. Tonsillitis resolved on 29 MAR 2006. Laboratory results were as follows: on 22 MAR 2006, ALT 69 mU/mL and AST 36 mU/mL; on 27 MAR 2006, ALT 82 mU/mL and AST 39 mU/mL; on 03 APR 2006, ALT 46 mU/mL and AST 27 mU/mL; on 12 APR 2006, ALT 61 mU/mL and AST 35 mU/mL; and on 26 APR 2006, ALT 47 mU/mL and AST 29 mU/mL. Study drug was discontinued due to the event of elevated ALT: the last dose of study drug was taken on 01 MAY 2006. On 04 MAY 2006, at the discontinuation visit assessment, the event of elevated ALT remained ongoing (ALT was 56 mU/mL and AST 31 mU/mL). The investigator considered the event of elevated ALT to be probably related to study drug. After closure of the database, the study was unblinded and the subject was found to have received ezetimibe 10 mg and simvastatin 20 mg during Step 1; and ezetimibe 10 mg and simvastatin 40 mg during Step 2.

Center: P02579-0010 **Sex:** Male **Subject:** 0043 **Age:** 15 years
Treatment and Regimen Assigned & Received:
Step 1: Placebo + Simvastatin 40 mg
Step 2: Placebo + Simvastatin 40 mg
Step 3: N/A
Reason for Summary: Discontinuation Due To Adverse Event: Elevated ALT
Narrative Summary is in Section 7.5.5 Drug-Drug Interactions.

CPK Increased
Center: P02579-0031 **Sex:** Female **Subject:** 0967 **Age:** 12 years
Treatment and Regimen Assigned & Received:
Step 1: Ezetimibe 10 mg + Simvastatin 20 mg
Step 2: Ezetimibe 10 mg + Simvastatin 40 mg
Step 3: Ezetimibe 10 mg + Simvastatin 10 mg
Adverse Event Of Special Interest: Creatine phosphokinase increased
Summary: A 12-year-old Multiracial female subject initiated pre-randomization phase in study on 06 FEB 2006, for efficacy, safety, and tolerability of ezetimibe in co-administration with simvastatin in the therapy of adolescents with HeFH. The subject's medical history was significant for hypercholesterolemia (cholesterol 300 mg/dL [normal range: 125-170 mg/dL), on 06 FEB 2006), and goiter (2005, stable with normal thyroid function). On 06 FEB 2006, laboratory results were as follows: ALT 9 mU/mL, (normal range: 5-25 mU/mL), AST 14 mU/mL, (normal range: 8- 30 mU/mL), CPK 45 mU/mL, (normal range: 20-120 mU/mL), and thyroid stimulating hormone (TSH 2.7 µIU/mL, normal range: 0.3-5.0 µIU/mL). No concomitant medications at pre-randomization time were noted. Single-blind placebo lead-in phase was initiated on 10 FEB 2006. On 21 MAR 2006, the subject was randomized and double-blind active treatment phase (ezetimibe vs. placebo) with simvastatin various doses (Step 1) was initiated on the same day. On 21 MAR 2006, laboratory results were as follows: ALT 9 mU/mL, AST 14 mU/mL, and CPK 50 mU/mL. Double-blind active treatment phase with simvastatin 40 mg (Step 2) was initiated on 02 MAY 2006. On that date, laboratory results were as follows: ALT 15 mU/mL, AST 19 mU/mL, and CPK 48 mU/mL. On 18 SEP 2006, at visit assessment, laboratory results were as follows: ALT 18 mU/mL, AST 19 mU/mL, and CPK 67 mU/mL. Open label active treatment phase (Step 3) was initiated on 07 NOV 2006; the subject had

received ezetimibe 10 mg and simvastatin 10 mg. On that date, laboratory results revealed severe increased CPK (19530 mU/mL), increased ALT (117mU/mL), and increased AST (257 mU/mL). Elevation of ALT and AST was considered mild per the investigator. No concomitant medications were noted at this time. Study drug (bottles A and B) was interrupted on 10 NOV 2006. The events of increased CPK, increased ALT and increased AST resolved on 14 NOV 2006. On that date, laboratory results were as follows: ALT 36 mU/mL, AST 24 mU/mL, and CPK 122 mU/mL. Study drug was resumed on 17 NOV 2006. On 04 DEC 2006, laboratory results were as follows: ALT 12 mU/mL, AST 17 mU/mL, and CPK 76 mU/mL. On 15 JAN 2007, laboratory results were as follows: ALT 13 mU/mL, AST 23 mU/mL, and CPK 236 mU/mL. The subject completed the study; the last dose of study drug was taken on 26 MAR 2007. On 27 MAR 2007, laboratory results were as follows: ALT 11 mU/mL, AST 15 mU/mL, and CPK 54 mU/mL. The investigator considered the event of increased CPK to be possibly related to study drug and the events of increased ALT and increased AST to be unlikely related to study drug. After closure of the database, the study was unblinded and the subject was found to have received ezetimibe 10 mg and simvastatin 20 mg during Step 1; and ezetimibe 10 mg and simvastatin 40 mg during Step 2.

Center: P02579-0042 **Sex:** Female **Subject:** 1001 **Age:** 15 years
Treatment and Regimen Assigned & Received:
Step 1: Placebo + Simvastatin 20 mg
Step 2: Placebo + Simvastatin 40 mg
Step 3: Ezetimibe 10 mg + Simvastatin 10 mg
Adverse Event Of Special Interest: Blood creatine phosphokinase increased
Summary: A 15-year-old White female subject initiated pre-randomization phase in study on 28 DEC 2005, for efficacy, safety, and tolerability of ezetimibe in coadministration with simvastatin in the therapy of adolescents with HeFH. The subject's medical history was significant for hypercholesterolemia (cholesterol 300 mg/dL [normal range: 125-170 mg/dL), on 28 DEC 2005). On 28 DEC 2005, laboratory results and vital signs were as follows: CPK 57 mU/mL, (normal range: 20-120 mU/mL), TSH 2.7 µIU/mL, (normal range: 0.3-5.0 µIU/mL), weight 47 kg, height average 160 cm, blood pressure 110/70 mmHg, and pulse 85 bpm. No concomitant medications at pre-randomization time were noted. Single-blind placebo lead-in phase was initiated on 04 JAN 2006. On 08 FEB 2006, the subject was randomized and double-blind active treatment phase (ezetimibe vs. placebo) with simvastatin various doses (Step 1) was initiated on the same day. On 08 FEB 2006, laboratory results and vital signs were as follows: CPK 50 mU/mL, TSH 1.7 µIU/mL, weight 47.5 kg, height average 160.8 cm, blood pressure 105/75 mmHg, and pulse 76 bpm. From 27 JAN 2006 to 31 JAN 2006, the subject experienced a mild stress-related insomnia; no therapy was taken for this condition. From 24 FEB 2006 to 01 MAR 2006, the subject complained of moderate lumbar pain. Study drug (bottles A and B) was interrupted on 24 FEB 2006 and resumed on 02 MAR 2006. On 22 FEB 2006, CPK value was 82 mU/mL. Double-blind active treatment phase with simvastatin 40 mg (Step 2) was initiated on 22 MAR 2006. Open label active treatment phase (Step 3) was initiated on 27 SEP 2006; the subject had received ezetimibe 10 mg and simvastatin 10 mg. On 27 SEP 2006, laboratory results and vital signs were as follows: CPK 75 mU/mL, TSH 1.6 µIU/mL, weight 53 kg, height average 162.2 cm, blood pressure 110/75 mmHg, and pulse 88 bpm. From 04 DEC

2006 to 10 DEC 2006, the subject had a mild varicella, for which acetaminophen was taken only on 04 DEC 2006. The subject completed the study; the last dose of study drug was taken on 13 FEB 2007. On 14 FEB 2007, mild blood CPK increased and mild blood TSH increased were noted. On 14 FEB 2007, laboratory results and vital signs were as follows: CPK 252 mU/mL, TSH 12 µIU/mL, weight 52 kg, height average 162.8 cm, blood pressure 120/70 mmHg, and pulse 80 bpm. The other laboratory analyses were all normal. On 22 FEB 2007, CPK value (61 mU/mL) and TSH value (1.5 µIU/mL) were normal. The investigator considered the events of blood CPK increased and blood TSH increased to be possibly related to study drug. After closure of the database, the study was unblinded and the subject was found to have received a placebo and simvastatin 20 mg during Step 1; and a placebo and simvastatin 40 mg during Step 2.

Center: P02579-0044 **Sex:** Male **Subject:** 0121 **Age:** 16 years
Treatment and Regimen Assigned & Received:
Step 1: Ezetimibe 10 mg + Simvastatin 20 mg
Step 2: N/A
Step 3: N/A
Adverse Event Of Special Interest: Elevated creatine phosphokinase levels
Discontinuation Due To Adverse Event: Elevated creatine phosphokinase levels
Summary: A 16-year-old White male subject initiated pre-randomization phase in study on 08 DEC 2005, for efficacy, safety, and tolerability of ezetimibe in coadministration with simvastatin in the therapy of adolescents with HeFH. The subject's medical history was significant for hypercholesterolemia (cholesterol 302 mg/dL [normal range: 125-170 mg/dL], on 08 DEC 2005), drug allergies (amoxicillin, cefzole®), and acne. Concomitant medications at pre-randomization time included dycloxacillin (acne) and benzoyl peroxide/clindamycin (topical, acne). On 08 DEC 2005, CPK level was 141 mU/mL (normal range: 30-180 mU/mL). Single-blind placebo lead-in phase was initiated on 15 DEC 2005. From 28 DEC 2005 to 18 JAN 2006, the subject experienced mild lower back bruise for which treatment with acetaminophen was taken on 28 DEC 2005 and 29 DEC 2005. On 19 JAN 2006, the subject was randomized and double-blind active treatment phase (ezetimibe vs. placebo) with simvastatin various doses (Step 1) was initiated on the same day. On that date, CPK level was 161 mU/mL. On 03 FEB 2006, at visit 4, CPK level was 260 mU/mL. On 02 MAR 2006, treatment with clindamycin (topical) was initiated, and triamcinolone (intradermal) was taken only on 02 MAR 2006, due to mild acne. From 14 FEB 2006 to 16 FEB 2006, the subject had a moderate viral infection for which treatment with acetaminophen was taken on the same dates. On 06 MAR 2006, at visit 5, elevated CPK level was noted. CPK was 3666 mU/mL. No symptoms were reported at this time. Study drug (bottles A and B) was discontinued due to the event of elevated CPK; the last dose of study drug was taken on 05 MAR 2006. On 10 MAR 2006, CPK level was 1612 mU/mL. On 22 MAR 2006, CPK level was 214 mU/mL. On 13 APR 2006, at the last contact date, the event of elevated CPK remained ongoing. On that date, CPK level was 233 mU/mL. The investigator considered the event of elevated CPK levels to be possibly related to study drug. After closure of the database, the study was unblinded and the subject was found to have received ezetimibe 10 mg and simvastatin 20 mg during Step 1.

9.3 Labeling Recommendations

Please refer to the PLR labeling review for details on the proposed labeling changes for the Vytorin package insert. (b) (4)

8.4 Pediatric Use

The effects of ZETIA co-administered with simvastatin (n=126) compared to simvastatin monotherapy (n=122) have been evaluated in adolescent boys and girls with heterozygous familial hypercholesterolemia (HeFH). In a multicenter, double-blind, controlled study followed by an open-label phase, 142 boys and 106 postmenarchal girls, 10 to 17 years of age (mean age 14.2 years, 43% females, 82% Caucasians, 4% Asian, 2% Blacks, 13% multi-racial) with HeFH were randomized to receive either ZETIA co-administered with simvastatin or simvastatin monotherapy. Inclusion in the study required 1) a baseline LDL-C level between 160 and 400 mg/dL and 2) a medical history and clinical presentation consistent with HeFH. The mean baseline LDL-C value was 225 mg/dL (range: 161-351 mg/dL) in the ZETIA co-administered with simvastatin group compared to 219 mg/dL (range: 149-336 mg/dL) in the simvastatin monotherapy group. The patients received co-administered ZETIA and simvastatin (10 mg, 20 mg, or 40 mg) or simvastatin monotherapy (10 mg, 20 mg, or 40 mg) for 6 weeks, co-administered ZETIA and 40 mg simvastatin or 40 mg simvastatin monotherapy for the next 27 weeks, and open-label co-administered ZETIA and simvastatin (10 mg, 20 mg, or 40 mg) for 20 weeks thereafter.

The results of the study at Week 6 are summarized in Table 3. Results at Week 33 were consistent with those at Week 6.

Table 3
Mean Percent Difference at Week 6 Between the Pooled ZETIA Co-Administered with Simvastatin Group and the Pooled Simvastatin Monotherapy Group in Adolescent Patients with Heterozygous Familial Hypercholesterolemia

	Total-C	LDL-C	Apo B	Non-HDL-C	TG*	HDL-C
Mean percent difference between treatment groups	-12%	-15%	-12%	-14%	-2%	+0.1%
95% Confidence Interval	(-15%, -9%)	(-18%, -12%)	(-15%, -9%)	(-17%, -11%)	(-9%, +4%)	(-3%, +3%)

*For triglycerides, median % change from baseline

From the start of the trial to the end of Week 33, discontinuations due to an adverse reaction occurred in 7 (6%) patients in the ZETIA co-administered with simvastatin group and in 2 (2%) patients in the simvastatin monotherapy group.

During the trial, hepatic transaminase elevations (two consecutive measurements for ALT and/or AST ≥3 X ULN) occurred in four (3%) individuals in the ZETIA co-administered with simvastatin group and in two (2%) individuals in the simvastatin monotherapy group. Elevations of CPK (≥10 X ULN) occurred in two (2%) individuals in the ZETIA co-administered with simvastatin group and in zero individuals in the simvastatin monotherapy group.

In this limited controlled study, there was no significant effect on growth or sexual maturation in the adolescent boys or girls, or on menstrual cycle length in girls.

Co-administration of ZETIA with simvastatin at doses greater than 40 mg/day has not been studied in adolescents. Also, ZETIA has not been studied in patients younger than 10 years of age or in pre-menarchal girls.

Based on total ezetimibe (ezetimibe + ezetimibe-glucuronide), there are no pharmacokinetic differences between adolescents and adults. Pharmacokinetic data in the pediatric population <10 years of age are not available.

9.4 Advisory Committee Meeting

Not applicable.

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/s/

Eileen Craig
6/10/2008 06:51:25 AM
MEDICAL OFFICER

Eric Colman
6/10/2008 07:13:59 AM
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I agree with Dr. Craig's conclusions and regulatory recommendation