CLINICAL REVIEW

Application Type	NDA 21-176, NDA 21-141, IND 48,034
Submission Number	022
Submission Code	SE5
Letter Date	10 Dec 2008
Stamp Date	10 Dec 2008
PDUFA Goal Date	10 June 2009
Reviewer Name	Eileen Craig, MD
Review Completion Date	8 June 2009
Established Name	colesevelam hydrochloride
(Proposed) Trade Name	Welchol®
Therapeutic Class	Lipid-lowering agent
Applicant	Daiichi-Sankyo
Priority Designation	S
Formulation	Powder for oral suspension
Dosing Regimen	3.75 gram packet once daily or 1.87 (b)(4) gram packet twice daily
Indication	Primary Hyperlipidemia
Intended Population	Children 10 to 17 years of age

Table of Contents

1 Recommendations/Risk Benefit Assessment

Colesevelam hydrochloride (Welchol™) is a bile acid sequestrant for subjects with primary hyperlipidemia (Frederickson type IIa). In May 2000, Welchol was approved for adults as a lipid-lowering bile acid sequestrant in the dose strength of 625 mg (total daily dose of 3.8 g/day). Bile acid sequestrant drugs effect quite modest reductions in total and LDL-C, particularly in comparison to currently marketed doses of statins. Daiichi Sankyo Pharma Development (DSPD) is submitting this supplemental New Drug Application 21-176 (Study WEL-410) to provide data to support a proposed indication for Welchol as therapy in pediatric subjects with hyperlipidemia. DSPD is also seeking to fulfill the Pediatric Written Request and gain pediatric exclusivity. In August 2008, DSPD submitted NDA 22-362, an *in vitro* bioequivalency study, for the Welchol Powder for Oral Suspension dosage form. The Powder for Oral Suspension dosage form was designed to meet the Written Request requirement that a dosage form suitable for pediatric subjects be available. The PDUFA due date for this NDA is 6/15/09.

1.1 Recommendation on Regulatory Action

Approve, pending label negotiation and pending approval of a pediatric formulation for Welchol.

1.2 Risk Benefit Assessment

Brief Overview of Clinical Program

Study WEL-410 was an 8-week, multi-center, randomized, double-blind, placebo-controlled, parallel-group, pediatric study in diet-controlled heterozygous familial hypercholesterolemia (heFH) male and female subjects, 10 to 17 years of age, who were taking a stable dose of an FDA approved statin (atorvastatin, lovastatin, pravastatin, simvastatin) or who were naïve to lipid-lowering therapy. The 8-week double-blind study was followed by an 18-week, open-label treatment period to evaluate the safety profile of high-dose colesevelam HCl (3750 mg) as either combination therapy or monotherapy.

This study consisted of 3 periods as follows:
Period I – Stabilization (approximately 4 weeks): Period I was a single-blind stabilization period. All subjects received 6 placebo tablets daily. Subjects were either taking a stable dose of an FDA approved statin (atorvastatin, lovastatin, pravastatin, simvastatin) (24%) or were naïve to lipid-lowering therapy (76%).

Period II – Double-Blind Treatment (Day 1 to Week 8): Period II was an 8-week, randomized, double-blind, parallel-group, placebo-controlled treatment period. One hundred ninety-four subjects were assigned randomly in a 1:1:1 ratio to high-dose colesevelam HCl (3750 mg/day), low-dose colesevelam HCl (1875 mg/day), or placebo. At randomization, 63% of the subjects were male and 87% of the subjects were Caucasian. Subjects continued to take their prescribed statin or no statin if they were treatment naïve. Subjects were stratified by background statin therapy (atorvastatin, simvastatin, or other statin). One hundred eighty-six subjects completed

Period II: 62 (96.9%) subjects in the colesevelam HCl 3750 mg group, 60 (92.3%) subjects in the colesevelam HCl 1875 mg group, and 64 (98.5%) subjects in the placebo group.

Period III – Open-Label Treatment (Week 8 to Week 26): Period III was an 18-week, open-label treatment period to evaluate the safety profile of high-dose colesevelam HCl (3750 mg) as either combination therapy or monotherapy. All subjects were treated with colesevelam HCl 3750 mg/day. During this period, it was recommended to attempt to achieve a goal LDL-C of <110 mg/dL. Subjects taking only colesevelam HCl or placebo during Period II were eligible for initiation of statin treatment during Period III, as prescribed by the investigator, in addition to the colesevelam HCl. Subjects not achieving the LDL-C goal were eligible to receive an escalating dose of statin, at the discretion of the investigator, to the maximum recommended dose. However, few investigators optimized the statin therapy by escalating doses of statins or starting statins in this study. One hundred seventy-three (89.2%) subjects completed Period III: 60 (93.8%) subjects whose Period II treatment was colesevelam HCl 3750 mg, 54 (83.1%) subjects whose Period II treatment was colesevelam HCl 1875 mg, and 59 (90.8%) subjects whose Period II treatment was placebo.

The primary efficacy parameter was the percent change in LDL-C from study baseline to the end of the double-blind treatment period (Period II/Week 8). The secondary efficacy parameters included the following:

- Percent changes in total cholesterol (TC), HDL-C, non-high-density lipoprotein cholesterol (non-HDL-C), TG, apolipoprotein A-I (apo A-I), and apo B from study baseline to the end of double-blind treatment;
- Percent change in LDL-C from the start of Period III (Visit 5/Week 8) to the end of open-label treatment (Visit 7/Week 26);
- Percent changes in TC, HDL-C, non-HDL-C, TG, apo A-I, and apo B from the start of Period III to the end of open-label treatment;
- Percent change in LDL-C from study baseline (Visit 3/Day 1) to the end of open-label treatment (Visit 7/Week 26); and
- Percent changes in TC, HDL-C, non-HDL-C, TG, apo A-I, and apo B from study baseline to the end of open-label treatment.

Efficacy at Week 8:
The Least Squares (LS) mean percent change in LDL-C from study baseline to Week 8 with last observation carried forward (LOCF) was -10.0% for the colesevelam HCl 3750 mg group, -3.8% for the colesevelam HCl 1875 mg group, and 2.5% for the placebo group. The difference in LS mean percent change between the colesevelam HCl 3750 mg group and the placebo group was -12.5%, ($p < 0.0001$). The difference in LS mean percent change between the colesevelam HCl 1875 mg group and the placebo group was -6.3%, ($p=0.0307$). In the statin-naïve treatment group, colesevelam 3750 mg therapy provided 11.6% reduction in LDL-C ($p<0.0001$), 8.1% increase in HDL-C, and a 15.3% increase in TG. In the background-statin treatment group, colesevelam 3750 mg therapy provided a 5.4% reduction in LDL-C ($p=0.5$), 9.0% increase in HDL-C and a 26.7% increase in TG.

Total Cholesterol: The difference in LS mean percent change for between the colesevelam HCl 3750 mg group and the placebo group was -7.4% (p=0.0011).Triglyceride: There were no statistically significant treatment differences for either colesevelam HCl dose compared to placebo. HDL-C: The difference in LS mean percent change between the colesevelam HCl 3750 mg group and the placebo group was 6.1% (p=0.0081). Non-HDL-C: The difference in LS mean percent change between the colesevelam HCl 3750 mg group and the placebo group was -10.9% (p=0.0001). Apolipoprotein A-I: The difference in LS mean percent change between the colesevelam HCl 3750 mg group and the placebo group was 6.9% (p=0.0055). Apolipoprotein B: The difference in LS mean percent change between the colesevelam HCl 3750 mg group and the placebo group was -8.3% (p=0.0009). The addition of colesevelam 3750 mg did decrease the Apo B/Apo A-I ratio in both the statin and statin-naïve group.

In conclusion, colesevelam 3750 mg as monotherapy provides modest LDL-lowering efficacy. However, the limited additional LDL-lowering efficacy when colesevelam is added to a statin along with the substantial body of evidence that demonstrates that statin therapy lowers risk of myocardial infarction, cardiovascular death, stroke, and need for coronary revascularization procedures in adults, raises the issue of whether colesevelam 3750 mg should primarily be used in statin-intolerant children or in children who are on optimally-dosed statin and have not reached their LDL-C goal.

Safety
Safety assessments included adverse reactions, vital signs, physical examination results, serum pregnancy testing, Tanner staging, and clinical laboratory measurements (hematology, blood chemistry, urinalysis, hormones, lipid-soluble vitamins, hsCRP, prothrombin time, and partial thrombin-plastin time).

No subject died during Period II or III. In the placebo-controlled Period II, four (2.1%) subjects discontinued due to adverse reactions that occurred during Period II of the study: 1 (1.6%) subject in the colesevelam HCl 3750 mg group and 3 (4.6%) subjects in the colesevelam HCl 1875 mg group. All of the adverse reactions were considered to be related to study medication (fatigue, nausea, diarrhea, and decreased appetite). Four subjects discontinued due to adverse reactions (nausea, flatulence, nasopharyngeal cancer, and migraine) that occurred during Period III of the study. The adverse reactions of nausea and flatulence were considered to be related to study medication.

In Period II, the most frequently reported adverse reactions in the colesevelam HCl 3750 mg group were nasopharyngitis (6.3%), fatigue (3.1%), influenza (3.1%), and headache (3.1%). The most frequently reported adverse reactions in the colesevelam HCl 1875 mg group were nasopharyngitis (6.2%), fatigue (4.6%), headache (4.6%), and rhinitis (4.6%). The most frequently reported adverse reactions in the placebo group were ear infection (4.6%), nasopharyngitis (4.6%), and upper respiratory tract infection (4.6%). The most commonly reported adverse reactions (incidence ≥ 2%) in patients treated with colesevelam in the placebo-controlled trial regardless of causality were: nasopharyngitis, headache, fatigue, creatinine phosphokinase increase, rhinitis and vomiting. In the current Welchol label, in clinical trials in adults, the most common (incidence ≥2% and greater than placebo) adverse reactions with Welchol included constipation, dyspepsia, nausea, accidental injury, asthenia, pharyngitis, flu

syndrome, rhinitis, and myalgia. The most frequently reported adverse reactions during Period III were headache (7.6%), nasopharyngitis (5.4%), upper respiratory tract infection (4.9%), influenza (3.8%), and nausea (3.8%).

During Period II, 20 (10.3%) subjects experienced gastrointestinal adverse reactions: 4 (6.3%) subjects in the colesevelam HCl 3750 mg group, 9 (13.8%) subjects in the colesevelam HCl 1875 mg group, and 7 (10.8%) subjects in the placebo group. The most frequently reported adverse reactions were vomiting (2.1%), diarrhea (1.5%), dyspepsia (1.5%), and nausea (1.5%). During Period III, 24 (13.0%) subjects experienced gastrointestinal adverse reactions. The more frequently reported gastrointestinal disorders experienced during Period III include: 7 (3.8%) subjects had nausea, 6 (3.3%) subjects had abdominal pain, 2 (1.1%) subjects had diarrhea, and 2 (1.1%) subjects had dyspepsia.

In this limited controlled study, there were no significant effects on growth, sexual maturation, fat-soluble vitamin levels or clotting factors in the adolescent boys or girls. Because of the tablet size, dysphagia or esophageal obstruction have been observed during the Welchol post-approval use. In this study, there were no episodes of dysphagia, choking, choking sensation, esophageal obstruction, or foreign body trauma and no subject discontinued treatment because of the drug administration requirements of taking 6 tablets a day. In conclusion, no new safety issues were identified in this study in children and adolescents.

1.3 Recommendations for Postmarketing Risk Management Activities

FDA continues to receive colesevelam reports of difficulty swallowing tablets or sensation of tablets being “stuck” or “lodged” in the throat. There have been 71 reports received from the marketing date (5/2000) through 2007; 5 reports were received in 2007 and 24 reports in 2008. The Office of Surveillance and Epidemiology recommended on 5 Feb 09 that the firm continue to submit all suspected reports of dysphagia or esophageal obstruction associated with colesevelam as expedited (15-Day Alert) reports for an additional year.

1.4 Recommendations for other Post Marketing Study Commitments

None

2 Introduction and Regulatory Background

Colesevelam hydrochloride (Welchol™) is a bile acid sequestrant for subjects with primary hyperlipidemia (Frederickson type IIa). In May 2000, Welchol was approved for adults as a lipid-lowering bile acid sequestrant in the dose strength of 625 mg (total daily dose of 3.8 g/day). In January 2008, Welchol was approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. Daiichi Sankyo Pharma Development (DSPD) is submitting this supplemental New Drug Application 21-176 to provide data to support a proposed indication for Welchol as therapy in pediatric subjects with hyperlipidemia. DSPD is also seeking to fulfill the Pediatric Written Request and gain pediatric exclusivity.

In August 2008, DSPD submitted NDA 22-362, an *in vitro* bioequivalency study, for the Welchol Powder for Oral Suspension dosage form. The Powder for Oral Suspension dosage form was designed to meet the Written Request requirement that a dosage form suitable for pediatric subjects be available. The PDUFA due date for this NDA is 6/15/09.

2.1 Product Information

Colesevelam hydrochloride, WelChol®, is a non-absorbed, lipid-lowering polymer that binds bile acids in the intestine, impeding their reabsorption. Bile acid sequestrants (BAS) deplete hepatic cholesterol pools (cholesterol is the precursor for bile acids) and induce a compensatory increase in the expression of LDL-receptors on hepatocytes. This causes an increased clearance of LDL particles from the plasma and lowers steady state LDL-C levels. BAS drugs effect quite modest reductions in total and LDL-C, particularly in comparison to currently marketed doses of statins.

Pharmacology
Colesevelam is a hydrophilic, water-insoluble polymer that is not hydrolyzed by digestive enzymes and is not absorbed.

Efficacy
WelChol® reduces total-C, LDL-C, Apo B, and increases HDL-C when administered either alone or in combination with an HMG-CoA reductase inhibitor in patients with primary hypercholesterolemia. In a study in patients with LDL-C between 130 and 220 mg/dL (mean 158 mg/dL), WelChol® was given for 24 weeks in divided doses with the morning and evening meals. The mean LDL-C reductions were 15% and 18% at the 3.8 g and 4.5 g doses. The respective mean total-C reductions were 7% and 10%. The mean Apo B reductions were 12% in both treatment groups. WelChol® at both doses increased HDL-C by 3%. There were small increases in triglycerides (TG) at both WelChol® doses that were not statistically different from placebo.

Combination Therapy: Co-administration of Welchol and a statin (atorvastatin 10mg, lovastatin 10 mg, or simvastatin 10 and 20 mg) in 3 clinical studies demonstrated an additive reduction of LDL-C. The mean baseline LDL-C was 184 mg/dL in the atorvastatin study (range 156-236 mg/dL), 171 mg/dL in the lovastatin study (range 115-247 mg/dL), and 188 mg/dL in the simvastatin study (range 148-352 mg/dL). Welchol doses of 2.3 g to 3.8 g resulted in an additional 8% to 16% reduction in LDL-C above that seen with the statin alone. There are no data regarding Welchol added to moderate or high dose statin therapy in the label.

Safety
Because WelChol® is not absorbed, the risk of systemic toxicity is low. In the original NDA, the comparison of frequent (>5%) treatment emergent adverse events between placebo and colesevelam groups shows that colesevelam use was associated with higher incidences of the GI events of constipation (11% vs. 7%) and dyspepsia (8.3% vs. 3.5%). WelChol® is contraindicated in individuals with bowel obstruction, serum triglycerides > 500 mg/dL, or a history of hypertriglyceridemia-induced pancreatitis. Caution should be exercised when treating

patients with TG levels greater than 300 mg/dL, with susceptibility to vitamin K or fat-soluble vitamin deficiencies, or with dysphagia, swallowing disorders, severe gastrointestinal motility disorders, or major gastrointestinal tract surgery.

2.2 Tables of Currently Available Treatments for Proposed Indications

The following sections contain the current 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

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

2.4 Important Safety Issues With Consideration to Related Drugs

The following are important safety considerations with Welchol and bile acid sequestrants in general as well as concerns for the pediatric population:

- Welchol can increase triglycerides, particularly when used with insulin or sulfonylureas. Marked hypertriglyceridemia can cause acute pancreatitis. The effect of hypertriglyceridemia on the risk of coronary artery disease is uncertain.
- Bile acid sequestrants (BAS) may decrease absorption of vitamin K and other fat-soluble vitamins—monitored by PT/PTT and vitamin A and E levels in this submission
- Gastrointestinal adverse effects (e.g., constipation, dyspepsia)
- BAS have constipating effects and are not recommended in patients at risk of bowel obstruction (e.g., patients with gastroparesis, other gastrointestinal motility disorders or a history of major gastrointestinal surgery)
- Because of the tablet size, Welchol can cause dysphagia or esophageal obstruction. The pediatric formulation is a powder for oral suspension. The tablet was used in the pediatric studies in this submission.
- Welchol reduces gastrointestinal absorption of some drugs and drugs with a known interaction with colesevelam should be given at least 4 hours prior to Welchol.
- Effects on liver and muscle as monitored by serum transaminase and creatine kinase levels in this submission
- Effects on growth and sexual maturation as assessed by stadiometry and Tanner staging

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The approval letter for primary hypercholesterolemia from the FDA, dated May 2000, required that an assessment of the safety and efficacy of Welchol be conducted in pediatric subjects. DSPD submitted a proposed Pediatric Drug Development Plan to the FDA in March 2001. In December 2002, the FDA issued a Written Request to DSPD that outlined the pediatric information needed in order to develop Welchol in pediatric subjects in response to the Pediatric Drug Development Plan. In October 2003, DSPD withdrew, without prejudice, the pediatric study. In April 2004, DSPD submitted a new Proposed Pediatric Study Request to the FDA. FDA issued a new Written Request in August 2004 that outlined the study design, subject population, statistics, and timing of the submission. The Written Request was amended on 19 January 2006 (Amendment 1), 28 March 2006 (Amendment 2), and 2 April 2007 (Amendment 3).

- Amendment 1 changed the study design to include a placebo run-in/statin stabilization period, updated the population to include subjects 10 to 17 years of age who were on a stable dose of a statin or were treatment naïve to statin therapy, updated study endpoints to reflect changes to the study design, removed the weight stratification for doses, updated statistical information to reflect the changes to the study design, and added height velocity and sexual maturation assessments.
- Amendment 2 updated the timing of the height velocity and sexual maturation assessments.
- Amendment 3 allowed for a decrease in the number of subjects needed to complete the trial, from approximately 200 subjects to approximately 132 subjects, as well as extended the timeframe for the submission.

DSPD has also submitted NDA 22-362 for the Welchol Powder for Oral Suspension dosage form. The Powder for Oral Suspension dosage form was designed to meet the Written Request requirement that a dosage form suitable for pediatric subjects be available.

2.6 Other Relevant Background Information

Daiichi Sankyo claims 3 years of exclusivity for Welchol® Tablet and Powder for Oral Suspension to reduce elevated LDL-C in children 10 to 17 years of age with primary hyperlipidemia (Fredrickson Type IIa) as monotherapy or in combination with a statin.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The applicant states that adverse events, medical/surgical history, and concomitant medications were coded by a coding specialist and reviewed by a medical monitor prior to the study being unblinded. Adverse events and medical/surgical history were coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) (version 6.0).

Concomitant medications were coded to Anatomical Therapeutic Chemical (ATC) class and preferred term using the World Health Organization (WHO) Drug Dictionary (version 2.4).

The following provisions were included to enhance data integrity:

- A clinical research associate conducted periodic on-site visits to assure adherence to the protocol, review CRFs and patient records for accuracy and completeness of information, examine site records for documentation of drug receipt and administration, observe the progress of the trial, and review investigator files for required documents.
- The quality control review included a comparison of original CRFs, data clarification forms, and data change logs to the audit report from the clean data entry database. A sample of 10% of subjects was selected for a 100% review of CRF data.
- A central laboratory performed all study-related laboratory tests.

3.2 Compliance with Good Clinical Practices

The applicant states that the protocol and informed consent documents were submitted to and approved by the Institutional Review Board (IRB) or Ethics Committee (EC) for each site prior to initiation of the study. Copies of the letter of approval and IRB/EC membership roster were received by the applicant prior to any drug shipment.

The applicant states that the study was conducted in accordance with the Declaration of Helsinki and with all applicable laws and regulations of the locale and country where the study was conducted, and in compliance with Good Clinical Practice Guidelines.

The applicant states that the rationale of the study, procedural details, and investigational goals were explained to each subject, along with potential risks and benefits. Each subject was assured of his/her right to withdraw from the study at any time. Prior to the initiation of any study procedures, each subject signed and dated an approved informed consent form

3.3 Financial Disclosures

The investigators in all 41 sites certified that they did not enter into any financial arrangements with Daiichi Sankyo whereby the value of compensation to the investigators could be affected by the outcome of the studies. The investigators were required to disclose to Daiichi Sankyo whether they have a proprietary interest in the product or a significant equity in Daiichi Sankyo and they did not disclose any such interests. The investigators were not recipients of significant payments of other sorts.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No new information with this submission.

4.2 Preclinical Pharmacology/Toxicology

No new information with this submission.

4.3 Clinical Pharmacology

No new information with this submission. Welchol Powder for Oral Suspension, the subject of pending NDA 22-362, is the dose formulation recommended for use in the children. Please refer to NDA 22-362 for the clinical pharmacology review of the bioequivalency study.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

Study No. **(No. of Centers)**	**Protocol Title**	**Primary Objectives of the Study**	**Study Status (Completion Date)**	**Test Products Dose Regimen Route of Administration**	**Type of Patients, Number Randomized (Number Completed)**
WEL-410 (41 clinical sites in Australia, Austria, Canada, Hungary, Israel, New Zealand, Norway, Slovakia, S. Africa, Czech Republic, Netherlands, and the US)	R, DB,Placebo-Controlled Efficacy and Safety Study of Colesevelam HCl Administered to Pediatric Patients with Heterozygous Familial Hypercholesterolemia on a Stable Dose of Statins or Treatment Naïve to Lipid-Lowering Therapy (WEL-410)	The objectives of this study were to evaluate the lipid-lowering efficacy and safety of colesevelam HCl (Welchol™) therapy administered to heFH pediatric subjects 10 to 17 years of age who were on a stable dose of a pediatric-approved statin monotherapy (atorvastatin, lovastatin, simvastatin, or pravastatin), or who were treatment naïve to lipid-lowering therapy.	Completed (12/2007)	**Test Product:** Placebo Low-dose colesevelam HCl (1875 mg) High-dose colesevelam HCl (3750 mg) **Dose Regimen**: 6 tablets per day, either once, or as divided doses in the morning and evening, with meals **Route of Administration:** Oral	Male and female subjects 10 to 17 years of age on a NCEP Step I diet or equivalent diet, with a diagnosis of heFH who met LDL-C inclusion criteria (>130 mg/dL for statin-stabilized subjects and >160 mg/dL for naïve subjects) 194 (173)

5.2 Review Strategy

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

5.3 Discussion of Individual Studies

This sNDA is based on Study WEL-410. The detailed review is included in the main body of this document.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The applicant is requesting the follow changes to the indication for Welchol:

(b) (4)

[redacted]

6.1.1 Methods

This was an 8-week, multi-center, randomized, double-blind, placebo-controlled, parallel-group, pediatric study to evaluate the efficacy and safety of colesevelam HCl in diet-controlled heFH male and female subjects, 10 to 17 years of age, who were currently taking a stable dose of an FDA-approved statin or who were naïve to lipid-lowering therapy. This study consisted of 3 periods as follows:

Period I – Stabilization (approximately 4 weeks): Period I was a single-blind stabilization period. All subjects received single-blind placebo (6 placebo tablets daily). The objective was to evaluate the dosing compliance and tolerability to the tablets.

Period II – Double-Blind Treatment (Day 1 to Week 8): Period II was an 8-week, randomized, double-blind, parallel-group, placebo-controlled treatment period. Subjects were assigned randomly in a 1:1:1 ratio to high-dose colesevelam HCl (3750 mg), low-dose colesevelam HCl (1875 mg), or placebo. Subjects continued to take their currently prescribed statin (atorvastatin,

simvastatin, pravastatin, or lovastatin), or no statin if treatment naïve. Subjects were stratified by background statin therapy (atorvastatin, simvastatin, or other statin).

Period III – Open-Label Treatment (Week 8 to Week 26): Period III was an 18-week, open-label high-dose colesevelam HCl (3750 mg) treatment period to evaluate the safety profile of high-dose colesevelam HCl as either combination therapy or monotherapy. All subjects were treated with colesevelam HCl 3750 mg to the goal LDL-C of <110 mg/dL. Subjects taking only colesevelam HCl or placebo during Period II were eligible for statin therapy during Period III, as prescribed by the investigator, in addition to high-dose colesevelam HCl. Subjects not achieving the LDL-C goal were eligible to receive an escalating dose of statin, at the discretion of the investigator, to the maximum recommended dose.

All statin therapy was open label. The database was locked and unblinded on 11 February 2008.

An outline of the treatment sequence is detailed below.

Period I – Single Blind Week -4 to Day 1 (~4 weeks)	**Period II – Double Blind Day 1 to Week 8 (8 weeks)**	**Period III – Open Label Week 8 to Week 26 (18 weeks)**
Placebo + Statin	Placebo + Statin Colesevelam low dose (1875 mg) + Statin Colesevelam high dose (3750 mg) + Statin	Colesevelam high dose + Statin
Placebo	Placebo Colesevelam low dose (1875 mg) Colesevelam high dose (3750 mg)	Colesevelam high dose + Statin initiated as appropriate

Important inclusion criteria:

- Age 10 to 17 years, inclusive;
- LDL-C >130 mg/dL for subjects on statin therapy, or LDL-C >160 mg/dL for subjects naïve to hypolipidemic therapy and on a stable diet;
- Triglycerides (TG) <250 mg/dL (2.83 mmol/L) at Visit 1;
- At least Tanner stage II;
- Diagnosis of heFH, defined as a known mutation in a copy of the subject's LDL-receptor or apo B gene. In the absence of a genetic diagnosis the subject must have had the following LDL-C criteria to be classified as a heFH subject:
  A documented history of untreated LDL-C >160 mg/dL in combination with at least 1 of the following:
  • The history or presence of a documented tendinous or cutaneous xanthoma or premature (before the age of 45 years) corneal arcus in the subject or a first-degree relative;
  • The history or presence of a documented mutation in a copy of the individual's (relative or offspring) LDL-receptor or apo B gene in an adult first-degree relative of biological offspring;
  • The presence of documented untreated LDL-C >190 mg/dL in an adult first-degree relative or sibling <18 years old with LDL-C >160 mg/dL; or
  • A documented history of premature coronary artery disease or sudden death from natural causes prior to 55 years of age if male, or prior to 60 years of age if female in a first-degree relative.

Important exclusion criteria:

- Homozygous FH;
- History of dysphagia, swallowing disorders, or intestinal motility disorders;
- Hypertension due to renal disease; untreated thyroid disease; clinically important liver or renal disorder or vasculitis, poorly controlled type 1 or type 2 diabetes, defined as hemoglobin A1c (HbA1c) >9.0%, abnormal lab values (hmgb, ALT/AST, CPK, total BR)

The following medications were excluded, regardless of the indication of their use, because they may have interfered with efficacy or safety evaluation:

- All hypolipidemic medication and over-the-counter products affecting lipid measurements except currently prescribed statins;
- Amphetamines, weight loss medications, and amphetamine-derived agents;
- Anticoagulants;
- Corticosteroids and anticonvulsants; and
- Erythromycin, clarithromycin, cyclosporine, human immunodeficiency virus protease inhibitors, nefazodone, ketoconazole, and itraconazole.

Selection of Doses:
The doses used in this study were colesevelam HCl 3750 mg and 1875 mg. The high dose studied is the approved recommended dose. The low dose studied was chosen to demonstrate a dose-response relationship. The statin dose the subject was currently taking was not to exceed the recommended dose prescribed by the respective statin package insert.

6.1.2 Demographics

The randomized population included all subjects who were randomized and received at least 1 dose of randomized study medication. This population was used to summarize all demographic and baseline characteristics. Table 6.1.2.1 lists demographic and baseline characteristics for the randomized population. Of the 194 subjects, 123 (63.4%) subjects were male and 169 (87.1%) subjects were Caucasian. The mean age was 14.1 years. Three subjects in the study were 18 years of age at randomization. According to the applicant, enrollment of these subjects was not in violation of the protocol because they were all 17 years of age at the time they provided informed consent (age assessment time point). Mean weight was 60.3 kg, mean height was 162.5 cm, and mean BMI was 22.5 kg/m2. Forty-seven (24.2%) subjects were taking statins at screening and 147 (75.8%) subjects were statin-naïve at screening.

Evaluating subjects for statin use within the US regional sites only, 71.1% (32/45 subjects) of subjects were statin naïve and 28.9% (13/45) were non-naïve to statins. For the Non-US sites only 77.2% (115/149) of the subjects were statin naïve and 22.8% (34/149) were non-naïve to statin treatment. Overall, 75.8% (147/194) of study subjects were naïve to statin treatment and 24.2% (47/194) were non-naïve to statin treatment.

From the total study cohort perspective, for US sites 16.5% of the subjects were statin naïve and 6.7% non-naïve to statins. For the same total study cohort, for the Non-US sites 59.3% of the subjects were statin naïve and 17.5% non-naïve to statin treatment.

Table 6.1.2.1: Summary of Demographic and Baseline Characteristics –Randomized Population

Demographic Characteristics	Colesevelam HCl 3750 mg (N = 64)	Colesevelam HCl 1875 mg (N = 65)	Placebo (N = 65)	Total (N = 194)
Age (years) [1]				
n	64	65	65	194
Mean (SD)	13.9 (2.00)	14.1 (2.19)	14.3 (1.74)	14.1 (1.98)
p-value [2]		0.4672		
Age Group (n, %)				
10-11 years	8 (12.5)	9 (13.8)	4 (6.2)	21 (10.8)
12-13 years	18 (28.1)	19 (29.2)	21 (32.3)	58 (29.9)
14-15 years	21 (32.8)	14 (21.5)	21 (32.3)	56 (28.9)
16-17 years	17 (26.6)	23 (35.4)	19 (29.2)	59 (30.4)
p-value [2]		0.5543		
Gender (n, %)				
Male	40 (62.5)	39 (60.0)	44 (67.7)	123 (63.4)
Female	24 (37.5)	26 (40.0)	21 (32.3)	71 (36.6)
p-value [2]		0.6498		
Race (n, %)				
Caucasian	58 (90.6)	57 (87.7)	54 (83.1)	169 (87.1)
Black	2 (3.1)	2 (3.1)	2 (3.1)	6 (3.1)
Asian	2 (3.1)	3 (4.6)	3 (4.6)	8 (4.1)
Multiple	2 (3.1)	3 (4.6)	5 (7.7)	10 (5.2)
Other	0 (0.0)	0 (0.0)	1 (1.5)	1 (0.5)
p-value [2]		0.8755		
Statin status at screening (n, %)				
Statin non-naïve	15 (23.4)	15 (23.1)	17 (26.2)	47 (24.2)
Statin naïve	49 (76.6)	50 (76.9)	48 (73.8)	147 (75.8)
p-value		0.9048		
Weight (kg)				
n	64	65	65	194
Mean (SD)	59.0 (16.81)	61.5 (20.77)	60.3 (15.32)	60.3 (17.72)
p-value [2]		0.7383		
Height (cm)				
n	64	65	65	194
Mean (SD)	162.1 (11.94)	160.7 (10.90)	164.8 (10.35)	162.5 (11.16)
p-value [2]		0.0967		
Body mass index (kg/m^2)				
n	64	65	65	194
Mean (SD)	22.2 (4.75)	23.4 (6.14)	21.9 (4.30)	22.5 (5.14)
p-value [2]		0.2265		

1. Age was calculated using the date of informed consent.
2. P-values are presented for comparing baseline characteristics of 3 treatment groups.

HCl = hydrochloride; SD = standard deviation.
Source: Post-text Table 14.1.6

Source: Applicant's Table 10.3

The mean and median age in years for **males** in each of the three treatment groups is provided below:

	Placebo	*Col. 1875 mg*	*Col. 3750 mg*
Mean (yrs)	*14.0*	*13.6*	*13.6*
Median (yrs)	*14.0*	*13.0*	*13.5*

The mean and median age in years for **females** in each of the three treatment groups is provided below

	Placebo	*Col. 1875 mg*	*Col. 3750 mg*
Mean (yrs)	*15.1*	*14.9*	*14.4*
Median (yrs)	*15.0*	*15.0*	*15.0*

Table 6.1.2.2 lists the Tanner stage of subjects at screening by gender and for all subjects combined. At screening, none of the subjects were at Tanner stage I. From the subgroup of females, only 1 subject (colesevelam HCl 1875 mg) was at Tanner stage II; the remainder of female subjects was at Tanner stage III to V.

Table 6.1.2.2: Summary of Tanner Stage at Screening – Randomized Population

Subject Population Tanner Stage	**Colesevelam HCl 3750 mg (N = 64)**	**Colesevelam HCl 1875 mg (N = 65)**	**Placebo (N = 65)**
All subjects (n, %)			
Stage I	0 (0.0)	0 (0.0)	0 (0.0)
Stage II	15 (23.4)	15 (23.1)	9 (13.8)
Stage III	16 (25.0)	16 (24.6)	20 (30.8)
Stage IV	20 (31.3)	19 (29.2)	23 (35.4)
Stage V	13 (20.3)	15 (23.1)	13 (20.0)
p-value [1]		0.8016	
Males (n, %)			
Stage I	0 (0.0)	0 (0.0)	0 (0.0)
Stage II	15 (23.4)	14 (21.5)	9 (13.8)
Stage III	8 (12.5)	9 (13.8)	14 (21.5)
Stage IV	8 (12.5)	10 (15.4)	14 (21.5)
Stage V	9 (14.1)	6 (9.2)	7 (10.8)
p-value [1]		0.4774	
Females (n, %)			
Stage I	0 (0.0)	0 (0.0)	0 (0.0)
Stage II	0 (0.0)	1 (1.5)	0 (0.0)
Stage III	8 (12.5)	7 (10.8)	6 (9.2)
Stage IV	12 (18.8)	9 (13.8)	9 (13.8)
Stage V	4 (6.3)	9 (13.8)	6 (9.2)
p-value [1]		0.6557	

1. P-values are presented for comparing baseline characteristics of 3 treatment groups.
HCl = hydrochloride.
Source: Post-text Table 14.1.9

Source: Applicant's Table 10.4

The baseline mean lipid and lipoprotein values for each treatment group in the randomized population were similar. Mean LDL-C was 201, 199, and 197 mg/dl for the colesevelam 3750 mg, colesevelam 1875 mg, and placebo group, respectively. However, across all treatment groups, the subgroup of subjects who were on a statin at screening had lower mean baseline LDL-C, TC, non-HDL-C, and apo B values than the statin-naïve subgroup. Mean LDL-C was 213, 212, and 206 mg/dl for the statin-naïve colesevelam 3750 mg, colesevelam 1875 mg, and placebo group, respectively. Mean LDL-C was 164 (n=15), 158 (n=15), and 169 (n=17) mg/dl for the statin-non-naïve colesevelam 3750 mg, colesevelam 1875 mg, and placebo group, respectively.

Concomitant Medications
A total of 122 (62.9%) subjects took concomitant medication during Period II. The most commonly used concomitant medications in Period II included HMG-CoA reductase inhibitors (statins) (24.7%), anilides (12.9%), and propionic acid derivatives (9.3%). Sixteen (25.0%) subjects in the colesevelam HCl 3750 mg group, 14 (21.5%) subjects in the colesevelam HCl 1875 mg group, and 18 (27.7%) subjects in the placebo group took a statin.

Table 6.1.2.3 presents the numbers and percentages of subjects in the safety population who took statins during Period II. During Period II, the use of statins was similar across treatment groups. The most commonly used statin was atorvastatin (15.5%).

Table 6.1.2.3: Number (%) of Subjects Who Took Statins During Period II – Safety Population for Period II

ATC CLASSIFICATION Preferred Term	Treatment During Period II			Total (N = 194) n (%)
	Colesevelam HCl 3750 mg (N = 64) n (%)	Colesevelam HCl 1875 mg (N = 65) n (%)	Placebo (N = 65) n (%)	
HMG CoA reductase inhibitors	16 (25.0)	14 (21.5)	18 (27.7)	48 (24.7)
Atorvastatin	10 (15.6)	9 (13.8)	11 (16.9)	30 (15.5)
Lovastatin	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.5)
Pravastatin	0 (0.0)	1 (1.5)	1 (1.5)	2 (1.0)
Simvastatin	6 (9.4)	3 (4.6)	6 (9.2)	15 (7.7)

ATC = Anatomical Therapeutic Chemical; HCl = hydrochloride; HMG CoA = 3-hydroxy-3-methylglutaryl coenzyme A.
Source: Post-text Table 14.1.13

Source: Applicant's Table 10.8

The statin used and dose for the subjects who took statins during Period II for each of the 3 treatment arms was as follows:
Placebo:
Atorvastatin: 40 mg: 2 subjects; 20 mg: 4 subjects; 10 mg: 5 subjects
Simvastatin: 40mg: 2 subjects; 20 mg: 2 subjects; 10 mg: 2 subjects
Pravastatin: 40 mg: 1 subject
Colesevelam 1875 mg:
Atorvastatin: 40 mg: 3 subjects; 20 mg: 2 subjects; 10 mg: 4 subjects

Simvastatin: 40mg: 1 subject; 20 mg: 0 subject; 10 mg: 2 subjects
Pravastatin: 20 mg: 1 subject
Lovastatin: 20 mg: 1 subject

Colesevelam 3750 mg:

Atorvastatin: 40 mg: 0 subjects; 20 mg: 4 subjects; 10 mg: 3 subjects; 5 mg: 1 subject
Simvastatin: 40mg: 1 subject; 20 mg: 4 subjects; 10 mg: 1 subject

A total of 138 (75%) subjects took concomitant medication during Period III. The most commonly used concomitant medications in Period III included statins (38%), anilides (18%), and propionic acid derivatives (12%).

Table 6.1.2.4 presents the numbers and percentages of subjects in the safety population who took statins during Period III. Overall, 70 (38.0%) subjects took a statin in addition to treatment with colesevelam HCl 3750 mg during Period III. The most commonly used statin was atorvastatin (18.5%).

Table 6.1.2.4: Number (%) of Subjects Who Took Statins During Period III – Safety Population for Period III*

ATC CLASSIFICATION Preferred Term	Treatment During Period II			Period III
	Colesevelam HCl 3750 mg (N = 62) n (%)	Colesevelam HCl 1875 mg (N = 59) n (%)	Placebo (N = 63) n (%)	Colesevelam HCl 3750 mg (N = 184) n (%)
HMG CoA reductase inhibitors	25 (40.3)	19 (32.2)	26 (41.3)	70 (38.0)
Atorvastatin	13 (21.0)	10 (16.9)	11 (17.5)	34 (18.5)
Lovastatin	0 (0.0)	2 (3.4)	1 (1.6)	3 (1.6)
Pravastatin	3 (4.8)	3 (5.1)	2 (3.2)	8 (4.3)
Rosuvastatin	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.5)
Simvastatin	10 (16.1)	4 (6.8)	11 (17.5)	25 (13.6)

ATC = Anatomical Therapeutic Chemical; HCl = hydrochloride; HMG CoA = 3-hydroxy-3-methylglutaryl coenzyme A.
Source: Post-text Table 14.1.14

Source: Applicant's Table 10.10

*The applicant included statin users in Period III as long as the statin start date is after first dose date of Period III medication. This table includes three subjects (004-06, 008-03, and 012-02) who started statins in Period III after their last dose of colesevelam. These 3 subjects were included in the applicant's Table 10.10 as statin users but were listed as naïve to lipid-lowering medication/no change in Table 10.11 (below) since their statin status did not change during treatment with colesevelam.

Table 6.1.2.5 presents a summary of the change in subject statin use between Period II and Period III. Of the 184 subjects in the safety population for Period III, 116 (63.0%) subjects who were statin-naïve during Period II had no change in their statin status and 23 (12.5%) subjects who were statin-naïve during Period II added a statin to their regimen during Period III. Of the 184 subjects in the safety population for Period III, 40 (21.7%) subjects who were taking statins during Period II did not change their statin dose during Period III, 4 (2.2%) subjects who were taking statins during Period II increased their statin dose during Period III, and 1 (0.5%) subject who was taking statins during Period II decreased their statin dose during Period III.

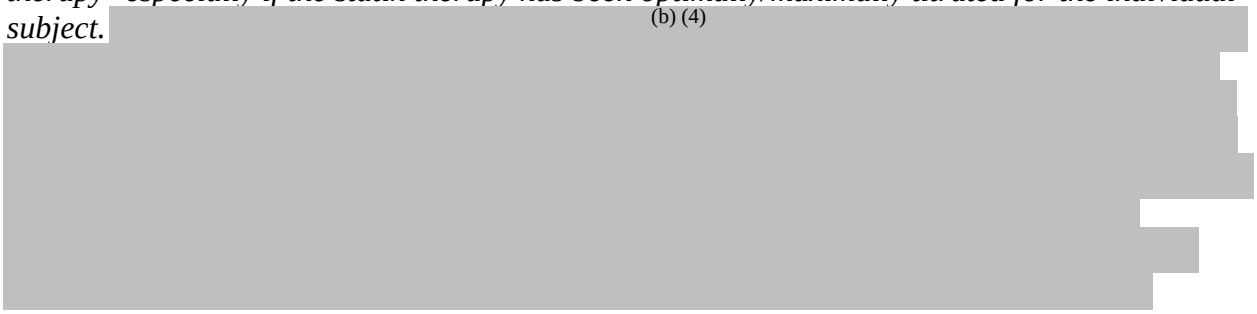
Table 6.1.2.5: Change in Statin Dose Status from Period II to Period III – Safety Population for Period III*

STATIN STATUS AT SCREENING Type of Change	Treatment During Period II			Period III
	Colesevelam HCl 3750 mg (N = 62) n (%)	Colesevelam HCl 1875 mg (N = 59) n (%)	Placebo (N = 63) n (%)	Colesevelam HCl 3750 mg (N = 184) n (%)
Subjects naïve to lipid-lowering medication				
No change	39 (62.9)	39 (66.1)	38 (60.3)	116 (63.0)
Statin therapy added	9 (14.5)	6 (10.2)	8 (12.7)	23 (12.5)
Subjects non-naïve to lipid-lowering medication				
No change	12 (19.4)	12 (20.3)	16 (25.4)	40 (21.7)
Statin dose increased	2 (3.2)	1 (1.7)	1 (1.6)	4 (2.2)
Statin dose decreased	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.5)

Subjects were assigned randomly to 1 of the 3 treatment groups at the beginning of Period II. At Period III, all subjects were given colesevelam HCl 3750 mg with or without a statin.
HCl = hydrochloride.
Source: Post-text Table 14.1.15

Source: Applicant's Table 10.11
*The applicant's Table 10.11 includes one subject who was not included in Table 10.10. This subject, 005-04, discontinued their statin prior to the start of Period III. In Table 10.11 this subject was included in the category "subjects non-naive to lipid-lowering medication/statin dose decreased".

Reviewer comment: Similar to pediatric studies with other lipid-lowering agents, there are fewer subjects in the 10-11 age group and the majority of subjects are Caucasian. There are very few subjects at Tanner II stage, notably only one female (colesevelam 1875 mg group) was at Tanner stage II at randomization. Of note, females were required to be at least 1 year post-menarchal for inclusion in the study and, on average, are ~1 year older than the males. The treatment groups appear comparable with respect to demographic and baseline characteristics. This reviewer is surprised that in this population of HeFH children, 76% of them were statin-naïve. This is relevant because it is easier for Welchol to show a statistically significant difference between Welchol and placebo but much more difficult when subjects are on baseline statin therapy--especially if the statin therapy has been optimally/maximally titrated for the individual subject. (b) (4)



6.1.3 Patient Disposition

Table 6.1.3.1 summarizes subject disposition for Period II. In total, 194 subjects were assigned randomly to treatment: 64 subjects to colesevelam HCl 3750 mg, 65 subjects to colesevelam HCl

1875 mg, and 65 subjects to placebo. Four subjects discontinued during the randomized treatment period due to an adverse event: 1 (1.6%) subject in the colesevelam HCl 3750 mg group and 3 (4.6%) subjects in the colesevelam HCl 1875 mg group. In total, 186 subjects completed Period II: 62 (96.9%) subjects in the colesevelam HCl 3750 mg group, 60 (92.3%) subjects in the colesevelam HCl 1875 mg group, and 64 (98.5%) subjects in the placebo group.

Table 6.1.3.1: Subject Disposition – Period II – Randomized Population

Disposition	Colesevelam HCl 3750 mg (N = 64) n (%)	Colesevelam HCl 1875 mg (N = 65) n (%)	Placebo (N = 65) n (%)	Total (N = 194) n (%)
Randomized	64 (100.0)	65 (100.0)	65 (100.0)	194 (100.0)
Completed Period II	62 (96.9)	60 (92.3)	64 (98.5)	186 (95.9)
Discontinued during Period II	2 (3.1)	5 (7.7)	1 (1.5)	8 (4.1)
Adverse event	1 (1.6)	3 (4.6)	0 (0.0)	4 (2.1)
Withdrawal of consent	1 (1.6)	1 (1.5)	1 (1.5)	3 (1.5)
Other [1]	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.5)
Safety population [2]	64 (100.0)	65 (100.0)	65 (100.0)	194 (100.0)
Intent-to-treat population [3]	63 (98.4)	63 (96.9)	65 (100.0)	191 (98.5)
Per-protocol population [4]	54 (84.4)	51 (78.5)	56 (86.2)	161 (83.0)

1. Other = subject was non-compliant.
2. The safety population included all randomized subjects who took at least 1 dose of randomized study medication.
3. The intent-to-treat population included all randomized subjects with a valid study baseline lipid measurement who had taken at least 1 dose of study medication and had at least 1 post-baseline lipid measurement in Period III.
4. The per-protocol population included all randomized subjects who took double-blind study medication and did not have major protocol violations.

HCl = hydrochloride.
Sources: Post-text Tables 14.1.3 and 14.1.4

Source: Applicant's Table 10.1

Table 6.1.3.2 summarizes subject disposition for Period III. In total, 173 (89.2%) subjects completed Period III: 60 (93.8%) subjects whose Period II treatment was colesevelam HCl 3750 mg, 54 (83.1%) subjects whose Period II treatment was colesevelam HCl 1875 mg, and 59 (90.8%) subjects whose Period II treatment was placebo. Five subjects discontinued during Period III due to an adverse event: 1 (1.6%) subject whose Period II treatment was colesevelam HCl 3750 mg, 3 (4.6%) subjects whose Period II treatment was colesevelam HCl 1875 mg, and 1 (1.5%) subject whose Period II treatment was placebo.

Table 6.1.3.2: Subject Disposition – Period III – Randomized Population

Disposition	Treatment During Period II			Period III
	Colesevelam HCl 3750 mg (N = 64) n (%)	Colesevelam HCl 1875 mg (N = 65) n (%)	Placebo (N = 65) n (%)	Colesevelam HCl 3750 mg (N = 194) n (%)
Completed Period II	62 (96.9)	60 (92.3)	64 (98.5)	186 (95.9)
Discontinued after completing Period II but before entering Period III	0 (0.0)	1 (1.5)	1 (1.5)	2 (1.0)
Withdrawal of consent	0 (0.0)	0 (0.0)	1 (1.5)	1 (0.5)
Lost to follow-up	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.5)
Completed Period III	60 (93.8)	54 (83.1)	59 (90.8)	173 (89.2)
Discontinued during Period III	2 (3.1)	5 (7.7)	4 (6.2)	11 (5.7)
Adverse event	1 (1.6)	3 (4.6)	1 (1.5)	5 (2.6)
Withdrawal of consent	1 (1.6)	1 (1.5)	2 (3.1)	4 (2.1)
Lost to follow-up	0 (0.0)	0 (0.0)	1 (1.5)	1 (0.5)
Other [1]	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.5)
Safety population [2]	62 (96.9)	59 (90.8)	63 (96.9)	184 (94.8)
Intent-to-treat population [3]	60 (93.8)	56 (86.2)	62 (95.4)	178 (91.8)

1. Other = subject required restricted medication.
2. The safety population at Period III included all subjects who entered Period III and took at least 1 dose of study medication in Period III.
3. The intent-to-treat (ITT) population in Period III includes subjects from the ITT population from Period II who had taken at least 1 dose of Period III study medication and had at least 1 valid lipid measurement in Period III.

HCl = hydrochloride.
Sources: Post-text Tables 14.1.3 and 14.1.4

Source: Applicant's Table 10.2

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy parameter was the percent change in LDL-C from study baseline (Visit 3/Day 1) to the end of the double-blind treatment period (Period II) (Visit 5/Week 8). If a subject discontinued from the study prior to Week 8, the last observed value during the randomized double-blind treatment period was carried forward (LOCF).

Statistical Methods:
The primary null hypotheses were tested sequentially in the following order: 1) no difference between the high-dose colesevelam HCl and placebo for percent change in LDL-C from study baseline to Week 8 endpoint with the last observation carried forward (LOCF) and 2) no difference between the low-dose colesevelam HCl and placebo for percent change in LDL-C from study baseline to Week 8 endpoint with LOCF. The hypotheses were tested at a 2-sided significance level of 5%. Efficacy analyses were performed on the intent-to-treat (ITT) populations, defined as all randomized subjects with a valid baseline lipid measurement who had taken at least 1 dose of study medication and had at least 1 valid post-baseline lipid measurement for Period II. For Period III, the ITT population was defined as all subjects from the ITT

population who had taken at least 1 dose of Period III study medication and had at least 1 valid lipid measurement in Period III.

An Analysis of Covariance (ANCOVA) model, with treatment group as a factor and LDL-C value at study baseline as a covariate, was used for the primary analysis. Due to the small expected number of subjects per center, center was not included in any of the applicant's models. If the parametric ANCOVA model was inappropriate, a non-parametric ANCOVA model with treatment groups as a factor and LDL-C value at study baseline as a covariate was used for the primary efficacy analyses.

Percent changes in lipid parameters (TC, HDL-C, non-HDL-C, apo A-I, apo B, and TG) were summarized from study baseline to Week 8, from the start of Period III (Week 8) to Week 26, and from study baseline to Week 26. Treatment comparisons were made between the high-dose colesevelam HCl group and the placebo group, and between the low-dose colesevelam HCl group and the placebo group using an ANCOVA model.

Analyses Performed After Unblinding:
The following analyses were not included in the data analysis plan or protocol:

- adding assessment of height velocity
- adding non-HDL-C to the evaluated lipid parameters
- changing the BMI subgroup parameter from 30 kg/m2 to 25 kg/m2
- adding a dosing schedule subgroup
- adding a Period III statin status subgroup
- adding a table for compliance by age group
- adding a table for baseline lipid and apolipoproteins by statin status.

Sample Size Determination by Applicant:
Assuming placebo and high-dose colesevelam HCl results in LDL-C percent changes of 0% and -10%, respectively, from study baseline (Day 1) to the end of the double-blind treatment period (Week 8), with a common standard deviation of 12%, and assuming an equal (1:1) allocation of subjects to placebo and high-dose colesevelam HCl groups during Period II, a sample size of 40 completed subjects in each of these treatment groups provided a 95% power at a 2-sided significance level of 5%. To account for an early drop-out rate of 10%, a sample size of 44 randomized subjects in each of the placebo and high-dose colesevelam HCl groups were needed to demonstrate approximately 95% power that the high-dose colesevelam HCl group was superior to the placebo group with respect to percent change in LDL-C from study baseline (Day 1) to the end of the double-blind treatment period (Week 8).

A sample size of 44 randomized subjects (approximately 40 completed subjects) in the low-dose colesevelam HCl group provided at least 73% power at a 2-sided significance level of 5% for demonstrating the superiority of the low-dose colesevelam HCl group to the placebo group with respect to percent change in LDL-C from study baseline (Day 1) to the end of the double-blind treatment period (Week 8). A total of at least 132 subjects were to be randomized. The applicant attempted to randomize approximately 200 subjects so that approximately 100 subjects would complete Period III.

Study Population for Efficacy:
The ITT population for Period II included 191 (98.5%) randomized subjects with a valid baseline lipid measurement who took at least 1 dose of study medication and had at least 1 valid post-baseline lipid measurement: 63 (98.4%) subjects in the colesevelam HCl 3750 mg group, 63 (96.9%) subjects in the colesevelam HCl 1875 mg group, and 65 (100.0%) subjects in the placebo group. The ITT population for Period III included 178 (91.8%) subjects from the ITT population from Period II who took at least 1 dose of Period III study medication and had at least 1 valid lipid measurement in Period III.

Efficacy Results:
Table 6.1.4.1 presents the results for percent changes in LDL-C from study baseline (Day 1) to Week 8 with LOCF for the Period II ITT population which includes subjects on background statin therapy as well as those not on statin therapy. The mean percent change in LDL-C from study baseline to Week 8 with LOCF was -10.6% for the colesevelam HCl 3750 mg group, -3.7% for the colesevelam HCl 1875 mg group, and 2.9% for the placebo group. The LS mean percent change in LDL-C from study baseline to Week 8 with LOCF was -10.0% for the colesevelam HCl 3750 mg group, -3.8% for the colesevelam HCl 1875 mg group, and 2.5% for the placebo group. The difference in LS mean percent change between the colesevelam HCl 3750 mg group and the placebo group was -12.5%, ($p < 0.0001$). The difference in LS mean percent change between the colesevelam HCl 1875 mg group and the placebo group was -6.3%, ($p=0.0307$).

Reviewer Comment: Traditionally, the Division has required a minimum of 15% reduction from baseline in LDL-Cholesterol, in the absence of unfavorable alterations in other lipid parameters, for a drug to be considered for approval. As colesevelam is a non-absorbable agent with a reasonable safety profile, a more modest effect has been historically accepted.

Table 6.1.4.1: Mean Percent Changes in Low-Density Lipoprotein Cholesterol (mg/dL) From Study Baseline (Day 1) to Week 8 With LOCF – Intent-to-Treat Population for Period II

Treatment Group	n	Day 1 Baseline Mean (SD)	Week 8 With LOCF Mean (SD)	Percent Change From Baseline	
				Mean (SD)	LS Mean (SE)
Colesevelam HCl 3750 mg	63	202.3 (50.07)	178.2 (45.47)	-10.6 (19.36)	-10.0 (2.08)
Colesevelam HCl 1875 mg	63	198.5 (43.95)	187.3 (37.00)	-3.7 (18.36)	-3.8 (2.08)
Placebo	65	196.7 (43.56)	198.7 (36.00)	2.9 (16.46)	2.5 (2.04)

Treatment Comparison	Treatment Difference		
	LS Mean (SE)	95% CI	p-value
Colesevelam HCl 3750 mg vs. Placebo	-12.5 (2.92)	(-18.3 , -6.8)	<0.0001
Colesevelam HCl 1875 mg vs. Placebo	-6.3 (2.91)	(-12.1 , -0.6)	0.0307

Study baseline was defined as the last value measured before or on Day 1 prior to the first dose of randomized study medication.
Only subjects with values at both study baseline and endpoint are included in this table.
LS Mean, SE, 95% CI, and p-value are from an Analysis of Covariance model with treatment as a fixed effect and study baseline as a covariate.
Treatment difference = colesevelam HCl – placebo.
CI = confidence interval; HCl = hydrochloride; LOCF = last observation carried forward; LS = least squares;
SD = standard deviation; SE = standard error.
Sources: Post-text Tables 14.2.1 and 14.2.9

Source: Applicant Table 11.1

6.1.5 Analysis of Secondary Endpoints(s)

The secondary efficacy parameters included the following:

- Percent changes in total cholesterol (TC), HDL-C, non-high-density lipoprotein cholesterol (non-HDL-C), TG, apolipoprotein A-I (apo A-I), and apo B from study baseline to the end of double-blind treatment;
- Percent change in LDL-C from the start of Period III (Visit 5/Week 8) to the end of open-label treatment (Visit 7/Week 26);
- Percent changes in TC, HDL-C, non-HDL-C, TG, apo A-I, and apo B from the start of Period III to the end of open-label treatment;
- Percent change in LDL-C from study baseline (Visit 3/Day 1) to the end of open-label treatment (Visit 7/Week 26); and
- Percent changes in TC, HDL-C, non-HDL-C, TG, apo A-I, and apo B from study baseline to the end of open-label treatment.

6.1.5.1 Percent changes in total cholesterol (TC), HDL-C, non-high-density lipoprotein cholesterol (non-HDL-C), TG, apolipoprotein A-I (apo A-I), and apo B from study baseline to the end of double-blind treatment

Period II (Day 1 to Week 8)
Table 6.1.5.1.1 presents the results for change in lipid parameters from study baseline (Day 1) to Week 8 with LOCF and the treatment differences for the colesevelam HCl groups versus the placebo group for the ITT population for Period II.

TC

The mean percent change in TC from study baseline to Week 8 with LOCF was -5.4% for the colesevelam HCl 3750 mg group, -1.1% for the colesevelam HCl 1875 mg group, and 2.9% for the placebo group. The LS mean percent change in TC from study baseline to Week 8 with LOCF was -5.1% for the colesevelam HCl 3750 mg group, -0.9% for the colesevelam HCl 1875 mg group, and 2.3% for the placebo group. The difference in LS mean percent change between the colesevelam HCl 3750 mg group and the placebo group was -7.4%; this treatment difference was small but was statistically significant (p=0.0011). The difference in LS mean percent change between the colesevelam HCl 1875 mg group and the placebo group was -3.2%; this treatment difference was not statistically significant (p=0.1514).

TG

The median percent change in TG from study baseline to Week 8 with LOCF was 12.5% for the colesevelam HCl 3750 mg group, 16.9% for the colesevelam HCl 1875 mg group, and 12.5% for the placebo group. There were no statistically significant treatment differences for either colesevelam HCl dose compared to placebo.

HDL

The mean percent change in HDL-C from study baseline to Week 8 with LOCF was 8.5% for the colesevelam HCl 3750 mg group, 3.9% for the colesevelam HCl 1875 mg group, and 2.5% for the placebo group. The LS mean percent change in HDL-C from study baseline to Week 8 with LOCF was 8.3% for the colesevelam HCl 3750 mg group, 4.5% for the colesevelam HCl 1875 mg group, and 2.2% for the placebo group. The difference in LS mean percent change between the colesevelam HCl 3750 mg group and the placebo group was 6.1%; this treatment difference was statistically significant (p=0.0081). The difference in LS mean percent change between the colesevelam HCl 1875 mg group and the placebo group was 2.4%; this treatment difference was not statistically significant (p=0.3055).

Non-HDL

The mean percent change in non-HDL-C from study baseline to Week 8 with LOCF was -8.4% for the colesevelam HCl 3750 mg group, -2.1% for the colesevelam HCl 1875 mg group, and 3.4% for the placebo group. The LS mean percent change in non-HDL-C from study baseline to Week 8 with LOCF was -7.9% for the colesevelam HCl 3750 mg group, -2.1% for the 1875 mg group, and 3.0% for the placebo group. The difference in LS mean percent change between the colesevelam HCl 3750 mg group and the placebo group was -10.9%; this treatment difference was statistically significant (p=0.0001). The difference in LS mean percent change between the colesevelam HCl 1875 mg group and the placebo group was -5.1%; this treatment difference was not statistically significant (p=0.0635).

Apolipoprotein A-I

The mean percent change in apo A-I from study baseline to Week 8 with LOCF was 11.2% for the colesevelam HCl 3750 mg group, 7.0% for the colesevelam HCl 1875 mg group, and 4.4% for the placebo group. The LS mean percent change in apo A-I from study baseline to Week 8 with LOCF was 10.8% for the colesevelam HCl 3750 mg group, 7.9% for the colesevelam HCl 1875 mg group, and 3.9% for the placebo group. The difference in LS mean percent change between the colesevelam HCl 3750 mg group and the placebo group was 6.9%;

this treatment difference was statistically significant (p=0.0055). The difference in LS mean percent change between the colesevelam HCl 1875 mg group and the placebo group was 4.0%; this treatment difference was not statistically significant (p=0.1061).

Apolipoprotein B
The mean percent change in apo B from study baseline to Week 8 with LOCF was -7.0% for the colesevelam HCl 3750 mg group, -0.7% for the colesevelam HCl 1875 mg group, and 2.3% for the placebo group. The LS mean percent change in apo B from study baseline to Week 8 with LOCF was -6.2% for the colesevelam HCl 3750 mg group, -1.2% for the colesevelam HCl 1875 mg group, and 2.1% for the placebo group. The difference in LS mean percent change between the colesevelam HCl 3750 mg group and the placebo group was -8.3%; this treatment difference was statistically significant (p=0.0009). The difference in LS mean percent change between the colesevelam HCl 1875 mg group and the placebo group was -3.4%; this treatment difference was not statistically significant (p=0.1743).

In summary, treatment with colesevelam HCL 3750 mg for 8 weeks significantly reduced LDL-C, TC, non-HDL-C, and apo B and significantly increased HDL-C and apo A-I compared to placebo. A moderate increase in TG was observed in the colesevelam HCl 3750 mg group and 1875 mg group. This increase in TG was 5.1% for the colesevelam 3750 mg group vs placebo and 6.4% for the colesevelam 1875 mg group vs placebo; these treatment increases were not statistically significantly.

Table 6.1.5.1.1. Percent Change in Lipid and Apolipoprotein Parameters From Study Baseline (Day 1) to Week 8 With LOCF – Intent-to-Treat Population for Period II

Lipid Parameter	Statistic	Colesevelam HCl 3750 mg	Colesevelam HCl 1875 mg	Placebo
LDL-C	n	63	63	65
	Mean (SD)	-10.6 (19.36)	-3.7 (18.36)	2.9 (16.46)
	p-value	<0.0001	0.1122	0.1587
	Treatment Difference vs. Placebo			
	LS mean (SE)	-12.5 (2.92)‡	-6.3 (2.91)*	--
TC	n	63	63	65
	Mean (SD)	-5.4 (15.80)	-1.1 (14.22)	2.9 (13.29)
	p-value	0.0085	0.5260	0.0883
	Treatment Difference vs. Placebo			
	LS mean (SE)	-7.4 (2.23)‡	-3.2 (2.23)	--
TG [1]	n	63	63	65
	Median (IQR)	12.5 (52.9)	16.9 (53.7)	12.5 (53.8)
	p-value	0.0008	<0.0001	0.0076
	Treatment Difference vs. Placebo			
	LS mean (SE)	5.1 (76.52)	6.4 (70.65)	--
HDL-C	n	63	63	65
	Mean (SD)	8.5 (14.72)	3.9 (12.45)	2.5 (12.52)
	p-value	<0.0001	0.0155	0.1073
	Treatment Difference vs. Placebo			
	LS mean (SE)	6.1 (2.28)†	2.4 (2.30)	--
Non-HDL-C	n	63	63	65
	Mean (SD)	-8.4 (18.28)	-2.1 (17.32)	3.4 (16.01)
	p-value	0.0006	0.3482	0.0933
	Treatment Difference vs. Placebo			
	LS mean (SE)	-10.9 (2.75)‡	-5.1 (2.75)	--
Apo A-I	n	61	62	63
	Mean (SD)	11.2 (16.79)	7.0 (13.96)	4.4 (14.62)
	p-value	<0.0001	0.0002	0.0209
	Treatment Difference vs. Placebo			
	LS mean (SE)	6.9 (2.45)†	4.0 (2.45)	--
Apo B	n	61	62	63
	Mean (SD)	-7.0 (14.45)	-0.7 (16.52)	2.3 (14.78)
	p-value	0.0003	0.7433	0.2157
	Treatment Difference vs. Placebo			
	LS mean (SE)	-8.3 (2.48)‡	-3.4 (2.46)	--

Only subjects with values at both study baseline and endpoint are included in this table.
LS mean, SE, and p-value are from an Analysis of Covariance model with treatment as fixed effect and study baseline as a covariate.
* = statistically significant p<0.05.
† = statistically significant p<0.01.
‡ = statistically significant p<0.001.
1. TG is not normally distributed. The median values are reported rather than the mean values. The IQR is reported rather than the SD.
Apo A-I = apolipoprotein A-I; Apo B = apolipoprotein B; HCl = hydrochloride;
HDL-C = high-density lipoprotein cholesterol; IQR = interquartile range;
LDL-C = low-density lipoprotein cholesterol; LS = least squares;
non-HDL-C = non-high-density lipoprotein cholesterol; SD = standard deviation;
SE = standard error; TC = total cholesterol; TG = triglycerides.

6.1.5.2 Percent change in LDL-C from the start of Period III (Visit 5/Week 8) to the end of open-label treatment (Visit 7/Week 26)

Table 6.1.5.2.1 shows the results for percent changes in lipid parameters from the start of Period III to Week 26 with LOCF for the Period III ITT population. The start of Period III mean values reflect the lipid value after 8 weeks of Period II treatment.

For all subjects treated during Period III, the mean percent change in LDL-C from the start of Period III (Week 8) to Week 26 with LOCF was -9.3%. As expected, the largest mean percent change in LDL-C in Period III occurred in the group of subjects who received placebo (-14.5%) followed by the group of subjects who received colesevelam HCl 1875 mg (-11.6%) during Period II. The group of subjects who were treated with colesevelam HCl 3750 mg during Period II and remained on the same dose during Period III had a mean change of -1.9%.

Between Period II to Period III, 11 subjects whose Period II treatment was colesevelam HCl 3750 mg added a statin or increased their statin dose, 7 subjects whose Period II treatment was colesevelam HCl 1875 mg added a statin or increased their statin dose, and 9 subjects whose Period II treatment was placebo added a statin or increased their statin dose.

Table 6.1.5.2.1: Mean Percent Changes in Lipid Parameters (mg/dL) From the Start of Period III (Week 8) to Week 26 With LOCF – Intent-to-Treat Population for Period III

Lipid Parameter Treatment Group	n	Week 8 Baseline Mean (SD)	Week 26 With LOCF Mean (SD)	Percent Change Mean (SD)
LDL-C				
Colesevelam HCl 3750 mg in Period II	60	175.9 (44.74)	168.6 (44.43)	-1.9 (21.11)
Colesevelam HCl 1875 mg in Period II	56	188.1 (37.89)	165.3 (45.78)	-11.6 (19.76)
Placebo in Period II	62	199.1 (36.35)	169.2 (45.45)	-14.5 (18.49)
Colesevelam HCl 3750 mg in Period III	178	187.8 (40.76)	167.8 (44.99)	-9.3 (20.43)
TC				
Colesevelam HCl 3750 mg in Period II	60	246.6 (44.77)	240.5 (47.73)	-1.5 (15.40)
Colesevelam HCl 1875 mg in Period II	56	260.8 (37.77)	241.0 (46.06)	-7.0 (15.99)
Placebo in Period II	62	265.7 (38.81)	237.6 (48.36)	-10.2 (15.05)
Colesevelam HCl 3750 mg in Period III	178	257.7 (41.20)	239.6 (47.19)	-6.3 (15.80)
TG [1]				
Colesevelam HCl 3750 mg in Period II	60	94.2 (62.8)	100.9 (51.3)	7.2 (45.9)
Colesevelam HCl 1875 mg in Period II	56	88.9 (50.0)	88.1 (73.5)	6.6 (54.3)
Placebo in Period II	62	99.1 (50.4)	83.6 (50.4)	-6.5 (47.2)
Colesevelam HCl 3750 mg in Period III	178	93.8 (54.0)	90.7 (57.5)	1.8 (53.0)
HDL-C				
Colesevelam HCl 3750 mg in Period II	60	50.0 (10.56)	50.1 (12.18)	0.9 (16.47)
Colesevelam HCl 1875 mg in Period II	56	51.3 (13.68)	52.7 (14.35)	4.3 (20.12)
Placebo in Period II	62	46.0 (8.72)	47.4 (10.28)	3.6 (15.37)
Colesevelam HCl 3750 mg in Period III	178	49.0 (11.25)	50.0 (12.43)	2.9 (17.31)
Non-HDL-C				
Colesevelam HCl 3750 mg in Period II	60	196.6 (46.06)	190.4 (48.91)	-1.7 (19.14)
Colesevelam HCl 1875 mg in Period II	56	209.6 (37.92)	188.3 (48.23)	-9.8 (18.79)
Placebo in Period II	61	220.0 (39.55)	190.6 (47.38)	-12.8 (17.63)
Colesevelam HCl 3750 mg in Period III	177	208.8 (42.28)	189.8 (47.91)	-8.1 (19.02)

Only subjects with values at both Period III and endpoint are included in this table.
Week 8 baseline was defined as the last value measured during Period II and before the first dose of open-label study medication during Period III.
Week 26 (LOCF) was defined as the Week 26 measurement. If the Week 26 measurement was unavailable, the last on-treatment observation prior to Week 26 was used.
1. Triglycerides are not normally distributed. The median values are reported rather than the mean value. The interquartile range is reported rather than the standard deviation.

HCl = hydrochloride; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LOCF = last observation carried forward; non-HDL-C = non-high-density lipoprotein cholesterol; SD = standard deviation; TC = total cholesterol; TG = triglycerides.
Sources: Post-text Tables 14.2.12, 14.2.13, 14.2.14, 14.2.15, and 14.2.16

Source: Applicant's Table 11.8

6.1.5.3 Percent changes in TC, HDL-C, non-HDL-C, TG, apo A-I, and apo B from the start of Period III to the end of open-label treatment (refer to Table 6.1.5.2.1.)

TC

For all subjects treated during Period III, there was a mean percent change in TC from the start of Period III (Week 8) to Week 26 with LOCF of -6.3%. Mean percent change in TC from the start of Period III to Week 26 with LOCF was -1.5% for those subjects whose Period II treatment

was colesevelam HCl 3750 mg, -7.0% for those subjects whose Period II treatment was colesevelam HCl 1875 mg, and -10.2% for those subjects on placebo.

TG
For all subjects treated during Period III, the median percent change in TG from the start of Period III (Week 8) to Week 26 with LOCF was 1.8%. Median percent change in TG from the start of Period III to Week 26 with LOCF was 7.2% for those subjects whose Period II treatment was colesevelam HCl 3750 mg, 6.6% for those subjects whose Period II treatment was colesevelam HCl 1875 mg, and -6.5% for those subjects whose Period II treatment was placebo.

HDL-C
For all subjects treated during Period III, the mean percent change in HDL-C from the start of Period III (Week 8) to Week 26 with LOCF was 2.9%. Mean percent change in HDL-C from the start of Period III (Week 8) to Week 26 with LOCF was 0.9% for those subjects whose Period II treatment was colesevelam HCl 3750 mg, 4.3% for those subjects whose Period II treatment was colesevelam HCl 1875 mg, and 3.6% for those subjects whose Period II treatment was placebo.

Non-HDL-C
For all subjects treated during Period III, the mean percent change in non-HDL-C from the start of Period III (Week 8) to Week 26 with LOCF was -8.1%. Mean percent change in non-HDL-C from the start of Period III to Week 26 with LOCF was -1.7% for those subjects whose Period II treatment was colesevelam HCl 3750 mg, -9.8% for those subjects whose Period II treatment was colesevelam HCl 1875 mg, and -12.8% for those subjects whose Period II treatment was placebo.

Apolipoprotein A-I
For all subjects treated during Period III, the mean percent change in apo A-I from the start of Period III (Week 8) to Week 26 with LOCF was -1.6%. Mean percent change in apo A-I from the start of Period III (Week 8) to Week 26 with LOCF was -4.2% for those subjects whose Period II treatment was colesevelam HCl 3750 mg, -0.8% for those subjects whose Period II treatment was colesevelam HCl 1875 mg, and 0.3% for those subjects whose Period II treatment was placebo. See Table 11.9.

Apolipoprotein B
For all subjects treated during Period III, the mean percent change in apo B from the start of Period III (Week 8) to Week 26 with LOCF was -8.0%. Mean percent change in apo B from the start of Period III (Week 8) to Week 26 with LOCF was -3.9% for those subjects whose Period II treatment was colesevelam HCl 3750 mg, -8.6% for those subjects whose Period II treatment was colesevelam HCl 1875 mg, and -11.8% for those subjects whose Period II treatment was placebo.

6.1.5.4 Percent change in LDL-C from study baseline (Visit 3/Day 1) to the end of open-label treatment (Visit 7/Week 26)

For all subjects in the Period III ITT population, the mean percent change in LDL-C from study baseline (Day 1) to Week 26 with LOCF was -14.0%. Mean percent change in LDL-C from

study baseline to Week 26 with LOCF was -13.5% for those subjects whose Period II treatment was colesevelam HCl 3750 mg, -16.8% for those subjects whose Period II treatment was colesevelam HCl 1875 mg, and -11.9% for those subjects whose Period II treatment was placebo.

6.1.5.5 Percent changes in TC, HDL-C, non-HDL-C, TG, apo A-I, and apo B from study baseline to the end of open-label treatment.

TC
For all subjects in the Period III ITT population, the mean percent change in TC from study baseline (Day 1) to Week 26 with LOCF was -8.0%. Mean percent change in TC from study baseline to Week 26 with LOCF was -7.5% for those subjects whose Period II treatment was colesevelam HCl 3750 mg, -9.1% for those subjects whose Period II treatment was colesevelam HCl 1875 mg, and -7.5% for those subjects whose Period II treatment was placebo.

TG
For all subjects in the Period III ITT population, the median percent change in TG from study baseline (Day 1) to Week 26 with LOCF was 11.5%. Median percent change in TG from study baseline to Week 26 with LOCF was 14.2% for those subjects whose Period II treatment was colesevelam HCl 3750 mg, 19.5% for those subjects whose Period II treatment was colesevelam HCl 1875 mg, and -5.3% for those subjects whose Period II treatment was placebo.

HDL-C
For all subjects in the Period III ITT population, the mean percent change in HDL-C from study baseline (Day 1) to Week 26 with LOCF was 8.1%. Mean percent change in HDL-C from study baseline to Week 26 with LOCF was 9.3% for those subjects whose Period II treatment was colesevelam HCl 3750 mg, 8.5% for those subjects whose Period II treatment was colesevelam HCl 1875 mg, and 6.6% for those subjects whose Period II treatment was placebo.

Non-HDL-C
For all subjects in the Period III ITT population, the mean percent change in non-HDL-C from study baseline (Day 1) to Week 26 with LOCF was -11.3%. Mean percent change in non-HDL-C from study baseline to Week 26 with LOCF was -11.0% for those subjects whose Period II treatment was colesevelam HCl 3750 mg, -13.2% for those subjects whose Period II treatment was colesevelam HCl 1875 mg, and -10.0% for those subjects whose Period II treatment was placebo.

apo A-I
For all subjects in the Period III ITT population, the mean percent change in apo A-I from study baseline (Day 1) to Week 26 with LOCF was 5.6%. Mean percent change in apo A-I from study baseline to Week 26 with LOCF was 7.2% for those subjects whose Period II treatment was colesevelam HCl 3750 mg, 4.9% for those subjects whose Period II treatment was colesevelam HCl 1875 mg, and 4.7% for those subjects whose Period II treatment was placebo.

apo B

For all subjects in the Period III ITT population, the mean percent change in apo B from study baseline (Day 1) to Week 26 with LOCF was -11.3%. Mean percent change in apo B from study baseline to Week 26 with LOCF was -11.2% for those subjects whose Period II treatment was colesevelam HCl 3750 mg, -11.3% for those subjects whose Period II treatment was colesevelam HCl 1875 mg, and -11.4% for those subjects whose Period II treatment was placebo.

Table 6.1.5.5.1 presents the results for percent changes in lipid parameters from study baseline (Day 1) to Week 26 with LOCF for the Period III ITT population.

Table 6.1.5.5.1: Mean Percent Changes in Lipid Parameters (mg/dL) From Study Baseline (Day 1) to Week 26 With LOCF – Entire Study – Intent-to-Treat Population for Period III

Lipid Parameter Treatment Group	n	Day 1 Baseline Mean (SD)	Week 26 With LOCF Mean (SD)	Percent Change Mean (SD)
LDL-C				
Colesevelam HCl 3750 mg in Period II	60	199.6 (47.93)	168.6 (44.43)	-13.5 (21.58)
Colesevelam HCl 1875 mg in Period II	56	200.1 (41.01)	165.3 (45.78)	-16.8 (19.85)
Placebo in Period II	62	195.9 (43.73)	169.2 (45.45)	-11.9 (22.39)
Colesevelam HCl 3750 mg in Period III	178	198.4 (44.17)	167.8 (44.99)	-14.0 (21.32)
TC				
Colesevelam HCl 3750 mg in Period II	60	264.3 (49.62)	240.5 (47.73)	-7.5 (17.55)
Colesevelam HCl 1875 mg in Period II	56	267.5 (41.82)	241.0 (46.06)	-9.1 (16.91)
Placebo in Period II	62	259.8 (46.89)	237.6 (48.36)	-7.5 (17.21)
Colesevelam HCl 3750 mg in Period III	178	263.8 (46.17)	239.6 (47.19)	-8.0 (17.15)
TG [1]				
Colesevelam HCl 3750 mg in Period II	60	85.0 (54.9)	100.9 (51.3)	14.2 (64.5)
Colesevelam HCl 1875 mg in Period II	56	84.5 (41.6)	88.1 (73.5)	19.5 (58.0)
Placebo in Period II	62	92.9 (39.8)	83.6 (50.4)	-5.3 (59.1)
Colesevelam HCl 3750 mg in Period III	178	86.7 (46.0)	90.7 (57.5)	11.5 (61.8)
HDL-C				
Colesevelam HCl 3750 mg in Period II	60	46.2 (9.68)	50.1 (12.18)	9.3 (19.37)
Colesevelam HCl 1875 mg in Period II	56	49.0 (12.02)	52.7 (14.35)	8.5 (20.33)
Placebo in Period II	62	44.8 (9.37)	47.4 (10.28)	6.6 (13.64)
Colesevelam HCl 3750 mg in Period III	178	46.6 (10.46)	50.0 (12.43)	8.1 (17.86)
Non-HDL-C				
Colesevelam HCl 3750 mg in Period II	60	218.1 (49.76)	190.4 (48.91)	-11.0 (20.80)
Colesevelam HCl 1875 mg in Period II	56	218.6 (41.07)	188.3 (48.23)	-13.2 (19.90)
Placebo in Period II	61	215.7 (46.85)	190.6 (47.38)	-10.0 (21.04)
Colesevelam HCl 3750 mg in Period III	177	217.4 (45.90)	189.8 (47.91)	-11.3 (20.53)

Only subjects with values at both study baseline and endpoint are included in this table.
Study baseline was defined as the last value measured before or on Day 1 prior to the first dose of randomized study medication.
Week 26 (LOCF) was defined as the Week 26 measurement. If the Week 26 measurement was unavailable, the last on-treatment observation prior to Week 26 was used.
1. Triglycerides are not normally distributed. The median values are reported rather than the mean value. The interquartile range is reported rather than the standard deviation.

HCl = hydrochloride; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LOCF = last observation carried forward; non-HDL-C = non-high-density lipoprotein cholesterol; SD = standard deviation; TC = total cholesterol; TG = triglycerides.
Sources: Post-text Tables 14.2.19, 14.2.20, 14.2.21, 14.2.22, and 14.2.23

Source: Applicant's Table 11.10

6.1.6 Other Endpoints

Subjects Achieving Goal (LDL-C <110 mg/dL) for Period II

Seven (3.7%) subjects achieved the LDL-C goal of <110 mg/dL during Period II: 5 (7.9%) subjects in the colesevelam HCl 3750 mg group, 2 (3.2%) subjects in the colesevelam HCl 1875 mg group, and 0 (0.0%) subjects in the placebo group. Of the 7 subjects who achieved the LDL-C goal, 2 subjects were statin-naïve and 5 subjects were taking statins at screening.

As per protocol, none of the 7 subjects, either naïve or not naïve to lipid lowering medication began or changed their dose of statin in Period II. The statin treatment of the 5 non-naïve subjects taking concomitant statin was as follows:

025-02	Pravastatin 20 mg/day [maximum recommended dose is 20 mg (age 8-13) and 40 mg (age 14-18]
028-01	Atorvastatin 20 mg/day (maximum recommended dose is 20 mg)
005-01	Atorvastatin 10mg/day
011-04	Atorvastatin 5mg/day
018-09	Simvastatin 20 mg/day (maximum recommended dose is 40 mg)

Subjects Achieving Goal (LDL-C <110 mg/dL) for the Entire Study

At Week 26, a total of 14 (7.9%) subjects achieved the LDL-C goal of <110 mg/dL: 4 (6.7%) subjects whose Period II treatment was colesevelam HCl 3750 mg, 7 (12.5%) subjects whose Period II treatment was colesevelam HCl 1875 mg, and 3 (4.8%) subjects whose Period II treatment was placebo. Of the 14 subjects who achieved the LDL-C goal, 7 subjects were statin-naïve and 7 subjects were taking statins at screening. However, only 3 of the 14 subjects who achieved their LDL-C goal at Week 26 were not on a statin during Period III and were only taking colesevelam as monotherapy.

As per protocol, none of these 14 subjects changed their statin dose during Period II. Of the 7 subjects who were statin-naïve, 4 began a statin in Period III and 1 changed the dose of the statin in Period III (listed below).

Statin-naive subjects who began a statin in Period III

014-02	Atorvastatin 10 mg/day changed to atorvastatin 20 mg/day
020-08	Simvastatin 10mg/day
014-18	Atorvastatin 10/day
020-09	Simvastatin 10mg/day

Of the 7 subjects who were taking statins at screening, one changed their dose in period III (listed below):

Non-naive subjects who changed statin dose in Period III

25-01	Simvastatin 20mg/day changed to simvastatin 40mg/day

The statin used and dose information for the other 9 subjects that achieved the LDL-C goal of < 110 mg/dL in Period III are as follows:

014-03	Atorvastatin 10 mg
025-02	Pravastatin 20 mg
018-10	Simvastatin 40 mg

047-12	Atorvastatin 40 mg
005-01	Atorvastatin 10 mg
011-04	Atorvastatin 5 mg
026-01	No statin
040-01	No statin
09-02	No statin

From the double-blind period to the open-label period, subjects were eligible to start statin therapy or receive escalating statin therapy to the maximum recommended dose approved in each particular statin label. Despite the protocol design allowing for the addition of a statin, most subjects did not add a statin to their colesevelam HCl 3750 mg regimen or change their statin status (increase or decrease the dose). Only 23 subjects who were naïve to statin therapy and 5 subjects who were non-naïve to statin therapy added a statin to their colesevelam HCl 3750 mg regimen or changed statin dose. As a result, after 26 weeks of treatment, only 14 (7.9%) subjects achieved the LDL-C goal of <110 mg/dL. Despite the protocol design allowing for the addition of a statin, few investigators optimized the statin therapy by escalating doses of statins or starting statins in pediatric subjects in this study.

6.1.7 Subpopulations

Analyses were performed on the following subgroups: gender (male or female), age (≤13 years or >13 years), race (Caucasian or non-Caucasian), BMI (<25 kg/m2 or ≥25 kg/m2), statin status at screening (naïve or non-naïve), and Tanner stage at baseline (II or III to V), and dosing schedule (divided dose [3 tablets at noon and 3 tablets in the evening] or single dose [6 tablets in the evening]).

Gender

Table 6.1.7.1 presents the results for percent changes in LDL-C from study baseline (Day 1) to Week 8 with LOCF for the Period II ITT population by gender subgroup (males and females). During Period II, the mean percent changes in LDL-C achieved by male and female subgroups treated with colesevelam HCl 3750 mg were of similar magnitude (-10.1% and -11.3%, respectively); these within-treatment group reductions in LDL-C were statistically significant for both subgroups. Mean percent increases in LDL-C occurred in the placebo-treated subjects with females having a larger increase than males (7% vs. 1%, respectively).

Table 6.1.7.1: Mean Percent Changes in Low-Density Lipoprotein Cholesterol (mg/dL) From Study Baseline (Day 1) to Week 8 With LOCF – Gender Subgroups – Intent-to-Treat Population for Period II

Subgroup Treatment Group	n	Day 1 Baseline Mean (SD)	Week 8 With LOCF Mean (SD)	Percent Change Mean (SD)	p-value
Male					
Colesevelam HCl 3750 mg	39	206.5 (54.56)	181.9 (47.89)	-10.1 (21.27)	0.0052
Colesevelam HCl 1875 mg	39	200.2 (38.42)	189.3 (29.78)	-3.1 (19.49)	0.3220
Placebo	44	197.0 (43.27)	195.4 (34.24)	1.0 (15.75)	0.6828
Female					
Colesevelam HCl 3750 mg	24	195.6 (42.00)	172.1 (41.49)	-11.3 (16.19)	0.0024
Colesevelam HCl 1875 mg	24	195.7 (52.50)	184.1 (46.99)	-4.7 (16.74)	0.1822
Placebo	21	196.0 (45.24)	205.7 (39.41)	7.0 (17.56)	0.0841

Study baseline was defined as the last value measured before or on Day 1 prior to the first dose of randomized study medication.
Only subjects with values at both study baseline and endpoint are included in this table.
P-values are from a 1-sample t-test of percent change within group.
HCl = hydrochloride; LOCF = last observation carried forward; SD = standard deviation.
Source: Post-text Table 14.2.27

Source: Applicant's Table 11.12

Age

Table 6.1.7.2 presents the results for percent changes in LDL-C from study baseline (Day 1) to Week 8 with LOCF for the Period II ITT population by age subgroup (≤13 years of age and >13 years of age). For subjects treated with placebo, the mean percent change in LDL-C was -0.6% for the subgroup ≤13 years of age and 5.1% for the subgroup >13 years of age. During Period II, treatment with colesevelam HCl 3750 mg resulted in similar changes in LDL-C for the subgroups ≤13 years of age and >13 years of age -11.4% and -10.0%, respectively); these within-treatment group reductions in LDL-C were statistically significant for both subgroups.

Table 6.1.7.2: Mean Percent Changes in Low-Density Lipoprotein Cholesterol (mg/dL) From Study Baseline (Day 1) to Week 8 With LOCF – Age Subgroups – Intent-to-Treat Population for Period II

Subgroup Treatment Group	n	Day 1 Baseline Mean (SD)	Week 8 With LOCF Mean (SD)	Percent Change Mean (SD)	p-value
≤13 Years of Age					
Colesevelam HCl 3750 mg	26	202.8 (46.21)	178.5 (50.97)	-11.4 (20.75)	0.0096
Colesevelam HCl 1875 mg	28	208.0 (40.81)	191.4 (32.07)	-6.6 (14.01)	0.0185
Placebo	25	202.8 (44.86)	200.3 (38.94)	-0.6 (8.86)	0.7570
>13 Years of Age					
Colesevelam HCl 3750 mg	37	202.0 (53.24)	178.0 (41.90)	-10.0 (18.60)	0.0025
Colesevelam HCl 1875 mg	35	190.9 (45.45)	184.1 (40.69)	-1.4 (21.13)	0.6973
Placebo	40	192.8 (42.85)	197.8 (34.52)	5.1 (19.60)	0.1093

Study baseline was defined as the last value measured before or on Day 1 prior to the first dose of randomized study medication.
Only subjects with values at both study baseline and endpoint are included in this table.
P-values are from a 1-sample t-test of percent change within group.
HCl = hydrochloride; LOCF = last observation carried forward; SD = standard deviation.
Source: Post-text Table 14.2.28

Source: Applicant's Table 11.13

Race

Table 6.1.7.3 presents the results for percent changes in LDL-C from study baseline (Day 1) to Week 8 with LOCF for the Period II ITT population by race subgroup (Caucasian and non-Caucasian).

Reviewer comment: The vast majority of subjects were Caucasian, and this group achieved a statistically significant reduction in LDL. The small number of subjects in the non-Caucasian subgroup did not achieve a statistically significant reduction in LDL on colesevelam; however, the small number of subjects makes it difficult to draw any conclusions from this lack of efficacy at the 3750 mg dose of colesevelam.

Table 6.1.7.3: Mean Percent Changes in Low-Density Lipoprotein Cholesterol (mg/dL) From Study Baseline (Day 1) to Week 8 With LOCF – Race Subgroups – Intent-to-Treat Population for Period II

Subgroup Treatment Group	n	Day 1 Baseline Mean (SD)	Week 8 With LOCF Mean (SD)	Percent Change Mean (SD)	p-value
Caucasian					
Colesevelam HCl 3750 mg	57	199.9 (48.55)	174.4 (44.26)	-11.5 (19.30)	<0.0001
Colesevelam HCl 1875 mg	56	198.0 (43.16)	188.5 (37.03)	-2.8 (18.71)	0.2619
Placebo	54	193.7 (45.25)	196.2 (37.40)	3.4 (17.71)	0.1633
Non-Caucasian					
Colesevelam HCl 3750 mg	6	225.0 (63.27)	214.4 (44.17)	-1.1 (18.98)	0.8878
Colesevelam HCl 1875 mg	7	202.3 (53.58)	177.7 (38.17)	-10.9 (14.41)	0.0929
Placebo	11	211.4 (31.75)	211.1 (26.08)	0.5 (8.08)	0.8463

Study baseline was defined as the last value measured before or on Day 1 prior to the first dose of randomized study medication.
Only subjects with values at both study baseline and endpoint are included in this table.
P-values are from a 1-sample t-test of percent change within group.
HCl = hydrochloride; LOCF = last observation carried forward; SD = standard deviation.
Source: Post-text Table 14.2.29

Source: Applicant's Table 11.14

Body Mass Index

During Period II, treatment with colesevelam HCl 3750 mg resulted in similar changes in LDL-C for the subgroups <25 kg/m2 and ≥25 kg/m2 (-10.4% and -10.9%, respectively); these within-treatment group reductions in LDL-C were statistically significant for both subgroups. Treatment with colesevelam HCl 1875 mg resulted in the following changes in LDL-C for the subgroups <25 kg/m2 and ≥25 kg/m2 (-4.7% and -1.6%, respectively), while treatment with placebo resulted in a 3.4% increase in mean percent change in LDL-C for the subgroup <25 kg/m2 and a 0.4% increase for the subgroup ≥25 kg/m2.

Tanner Stage at Study Baseline

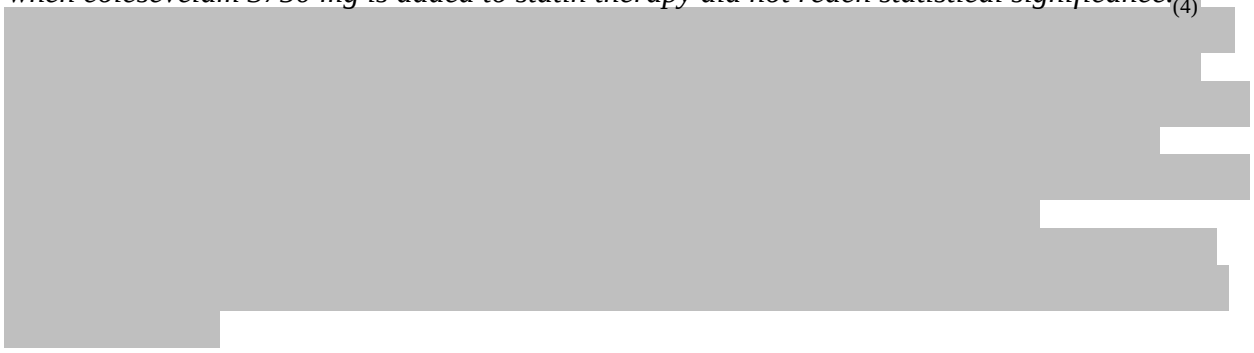
During Period II, the mean percent change in LDL-C achieved by subjects treated with colesevelam HCl 3750 mg in the Tanner stage II subgroup (n=15) was larger than the change in LDL-C achieved by subjects treated with colesevelam HCl 3750 mg in the Tanner stage III to V

subgroup (n=48), (-13.9% and -9.5%, respectively). The small number of subjects in the Tanner stage II subgroup makes it difficult to draw any meaningful comparisons between subgroups.

Statin Status-Period II

Table 6.1.7.4 presents the results for percent changes in LDL-C from study baseline (Day 1) to Week 8 with LOCF for the Period II ITT population by statin status subgroup (statin-naïve and statin non-naïve). For both statin-naïve and statin non-naïve subgroups, the largest mean percent reductions in LDL-C were observed in subjects treated with colesevelam HCl 3750 mg. During Period II, mean percent reductions in LDL-C occurred in the colesevelam HCl 1875 mg and placebo-treated subjects in the statin-naïve subgroup. Surprisingly, during Period II, mean percent increases in LDL-C occurred in the colesevelam HCl 1875 mg and placebo-treated subjects in the statin non-naïve subgroup. The statistical reviewer, Cynthia Liu, found that this finding was mainly due to the large variation in the % change data in the small number of statin non-naïve subjects. Across the three study groups, the standard deviations of the % changes for the statin non-naïve subjects were all much larger than those for the statin-naïve subjects. The statistical reviewer evaluated the median % changes in LDL-C from Day 1 to Week 8. They were -13.3%, -3.0%, and +2.8% for the high-dose, low-dose, and placebo groups, respectively, for the statin non-naïve subjects, and -13.6%, -8.2%, and +0.2% for the statin-naïve subjects.

Reviewer comment: Although the smaller number of subjects on background statin therapy compared to statin-naive limits interpretation, the very modest amount of 5.8% LDL-C lowering when colesevelam 3750 mg is added to statin therapy did not reach statistical significance. (b) (4)



This limited additional LDL-lowering efficacy when colesevelam is added to statin raises the issue of whether colesevelam 3750mg should primarily be used in statin-intolerant subjects or in subjects who are on a maximally- or optimally-dosed statin and have not reached their LDL-C goal or need to address other lipid parameter abnormalities such as HDL-C.

Table 6.1.7.4: Mean Percent Changes in Low-Density Lipoprotein Cholesterol (mg/dL) From Study Baseline (Day 1) to Week 8 With LOCF– Statin Status Subgroups – Intent-to-Treat Population for Period II

Subgroup Treatment Group	n	Day 1 Baseline Mean (SD)	Week 8 With LOCF Mean (SD)	Percent Change Mean (SD)	p-value
Statin-naïve					
Colesevelam HCl 3750 mg	49	212.8 (47.77)	185.9 (42.12)	-11.9 (12.83)	<0.0001
Colesevelam HCl 1875 mg	48	211.0 (39.73)	194.1 (35.60)	-7.1 (13.33)	0.0006
Placebo	48	206.4 (43.61)	203.0 (37.18)	-0.6 (10.97)	0.6880
Statin Non-naïve					
Colesevelam HCl 3750 mg	14	165.8 (41.05)	151.2 (48.00)	-5.8 (33.91)	0.5307
Colesevelam HCl 1875 mg	15	158.3 (31.46)	165.6 (33.82)	7.0 (27.08)	0.3305
Placebo	17	169.3 (30.43)	186.6 (30.23)	12.9 (24.21)	0.0425

Study baseline was defined as the last value measured before or on Day 1 prior to the first dose of randomized study medication.
Only subjects with values at both study baseline and endpoint are included in this table.
P-values are from a 1-sample t-test of percent change within group.
HCl = hydrochloride; LOCF = last observation carried forward; SD = standard deviation.
Source: Post-text Table 14.2.32

Source: Applicant's Table 11.17

The statin used and dose for the subjects who are non-naïve at screening for each of the 3 treatment arms was as follows:

Placebo:

Atorvastatin: 40 mg: 2 subjects; 20 mg: 3 subjects; 10 mg: 5 subjects
Simvastatin: 40mg: 2 subjects; 20 mg: 2 subjects; 10 mg: 2 subjects
Pravastatin: 40 mg: 1 subject

Colesevelam 1875 mg:

Atorvastatin: 40 mg: 3 subjects; 20 mg: 2 subjects; 10 mg: 4 subjects
Simvastatin: 40mg: 1 subject; 20 mg: 1 subject; 10 mg: 2 subjects
Pravastatin: 20 mg: 1 subject
Lovastatin: 20 mg: 1 subject

Colesevelam 3750 mg:

Atorvastatin: 40 mg: 0 subjects; 20 mg: 4 subjects; 10 mg: 3 subjects; 5 mg: 1 subject
Simvastatin: 40mg: 1 subject; 20 mg: 4 subjects; 10 mg: 1 subject

Across the 3 study arms in Period III, few of these patients had their statin dose titrated to a higher dose: 2 subjects on simvastatin 20 mg were increased to 40 mg and 3 subjects on 10 mg atorvastatin were increased to 20 mg.

Table 6.1.7.5 presents the results for LS mean percent changes in LDL-C, TC, TG, HDL-C, and non-HDL-C from study baseline (Day 1) to Week 8 with LOCF for the Period II ITT population by statin use subgroup (statin-naïve and statin non-naïve).

Table 6.1.7.5: Mean Percent Changes in Lipid Parameters (mg/dL) From Study Baseline (Day 1) to Week 8 With LOCF – Statin Status Subgroups – Intent-to-Treat Population for Period II

Lipid Parameter Treatment Group	n	Day 1 Baseline Mean (SE)	Week 8 With LOCF Mean (SE)	Percent Change LS Mean (SE)
Statin-naïve				
LDL-C				
Colesevelam HCl 3750 mg	49	212.8 (6.82)	185.9 (6.02)	-11.6 (1.67)
Colesevelam HCl 1875 mg	48	211.0 (5.73)	194.1 (5.14)	-7.0 (1.69)
Placebo	48	206.4 (6.29)	203.0 (5.37)	-1.0 (1.69)
TC				
Colesevelam HCl 3750 mg	49	277.0 (6.88)	256.4 (6.04)	-6.6 (1.33)
Colesevelam HCl 1875 mg	48	278.1 (5.98)	264.3 (5.32)	-4.0 (1.34)
Placebo	48	271.3 (6.88)	269.4 (5.76)	-0.3 (1.34)
TG [1]				
Colesevelam HCl 3750 mg	49	91.2 (55.75)	104.4 (76.99)	15.3 (37.15)
Colesevelam HCl 1875 mg	48	81.4 (48.67)	86.7 (43.81)	15.7 (35.50)
Placebo	48	92.9 (43.36)	99.1 (45.13)	9.3 (37.75)
HDL-C				
Colesevelam HCl 3750 mg	49	45.1 (1.44)	48.6 (1.60)	8.1 (1.85)
Colesevelam HCl 1875 mg	48	48.4 (1.73)	49.6 (1.95)	3.5 (1.88)
Placebo	48	45.4 (1.30)	45.6 (1.25)	1.1 (1.87)
Non-HDL-C				
Colesevelam HCl 3750 mg	49	231.9 (6.97)	207.9 (6.29)	-9.5 (1.56)
Colesevelam HCl 1875 mg	48	229.7 (5.92)	214.7 (5.46)	-5.7 (1.58)
Placebo	48	225.9 (6.83)	223.7 (5.88)	-0.3 (1.58)
Statin Non-naïve				
LDL-C				
Colesevelam HCl 3750 mg	14	165.8 (10.97)	151.2 (12.83)	-5.4 (6.69)
Colesevelam HCl 1875 mg	15	158.3 (8.12)	165.6 (8.73)	4.5 (6.50)
Placebo	17	169.3 (7.38)	186.6 (7.33)	14.8 (6.09)
TC				
Colesevelam HCl 3750 mg	14	230.3 (12.68)	221.8 (12.45)	-0.5 (4.85)
Colesevelam HCl 1875 mg	15	227.9 (9.13)	244.8 (9.72)	8.2 (4.69)
Placebo	17	231.5 (6.99)	252.9 (7.72)	11.2 (4.40)
TG [1]				
Colesevelam HCl 3750 mg	14	69.5 (29.20)	93.8 (49.56)	26.7 (55.28)
Colesevelam HCl 1875 mg	15	85.0 (59.29)	93.8 (100.9)	28.1 (36.60)
Placebo	17	85.0 (46.02)	91.2 (50.44)	18.2 (29.60)
HDL-C				
Colesevelam HCl 3750 mg	14	47.4 (2.36)	51.2 (2.73)	9.0 (3.49)
Colesevelam HCl 1875 mg	15	48.7 (3.13)	52.2 (3.60)	7.9 (3.39)
Placebo	17	44.7 (2.67)	46.5 (2.24)	5.0 (3.19)
Non-HDL-C				
Colesevelam HCl 3750 mg	14	182.9 (12.34)	170.5 (12.96)	-3.5 (6.12)
Colesevelam HCl 1875 mg	15	179.1 (7.80)	192.6 (8.28)	8.2 (5.93)
Placebo	17	186.8 (7.41)	206.4 (7.47)	14.5 (5.57)

Only subjects with values at both study baseline and endpoint are included in this table.
Study baseline was defined as the last value measured before or on Day 1 prior to the first dose of randomized study medication.
Week 8 (LOCF) was defined as the Week 8 measurement. If the Week 8 measurement was unavailable, the last on-treatment observation prior to Week 26 was used.
1. Triglycerides are not normally distributed. The median values are reported rather than the mean value. The interquartile range is reported rather than the standard error.

HCl = hydrochloride; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol;
LOCF = last observation carried forward; LS = least squares; non-HDL-C = non-high-density lipoprotein cholesterol;
SE = standard error; TC = total cholesterol; TG = triglycerides.
Source: Post-text Tables 14.2.33

Source: Applicant's Table 11.18

Table 6.1.7.6 presents the results for mean percent changes in apolipoproteins from study baseline to Week 8 with LOCF for the Period II ITT population by statin use subgroup (statin-naïve and statin non-naïve). The addition of colesevelam 3750 mg did decrease the Apo B/Apo A-I ratio in both the statin and statin-naïve group:

Statin-naïve group: Placebo Apo B/Apo A-I: baseline=1.19; Week 8=1.14
Colesevelam 3750 Apo B/Apo A-I: baseline=1.22; Week 8=1.04
Statin group: Placebo Apo B/Apo A-I: baseline=1.05; Week 8=1.08
Colesevelam 3750 Apo B/Apo A-I: baseline=1.05; Week 8=0.84

Table 6.1.7.6: Mean Percent Changes in Apolipoproteins (mg/dL) From Study Baseline (Day 1) to Week 8 With LOCF – Statin Status Subgroups – Intent-to-Treat Population for Period II

Lipid Parameter Treatment Group	n	Day 1 Baseline Mean (SE)	Week 8 With LOCF Mean (SE)	Percent Change LS Mean (SE)
Statin-naïve				
Apo A-I				
Colesevelam HCl 3750 mg	48	137.8 (3.58)	150.4 (3.63)	10.1 (2.00)
Colesevelam HCl 1875 mg	47	140.2 (3.91)	146.5 (3.79)	6.1 (2.02)
Placebo	48	137.8 (3.19)	141.4 (3.10)	3.6 (2.00)
Apo B				
Colesevelam HCl 3750 mg	48	168.8 (4.28)	156.0 (4.14)	-6.4 (1.62)
Colesevelam HCl 1875 mg	47	162.1 (3.98)	155.4 (3.74)	-3.7 (1.63)
Placebo	48	163.5 (4.94)	161.5 (4.11)	-0.3 (1.61)
Statin Non-naïve				
Apo A-I				
Colesevelam HCl 3750 mg	13	133.9 (6.55)	150.1 (5.61)	13.1 (3.61)
Colesevelam HCl 1875 mg	15	146.1 (5.61)	162.3 (7.91)	13.4 (3.41)
Placebo	15	133.2 (7.06)	139.6 (5.92)	4.8 (3.37)
Apo B				
Colesevelam HCl 3750 mg	13	140.2 (10.13)	126.8 (7.81)	-6.6 (5.30)
Colesevelam HCl 1875 mg	15	138.4 (5.02)	146.2 (6.23)	6.8 (4.94)
Placebo	15	140.3 (6.47)	151.4 (6.34)	10.3 (4.94)

Only subjects with values at both study baseline and endpoint are included in this table.
Study baseline was defined as the last value measured before or on Day 1 prior to the first dose of randomized study medication.
Week 8 (LOCF) was defined as the Week 8 measurement. If the Week 8 measurement was unavailable, the last on-treatment observation prior to Week 26 was used.
apo A-I = apolipoprotein A-I; apo B = apolipoprotein B; HCl = hydrochloride; LOCF = last observation carried forward; LS = least squares; SE = standard error.
Source: Post-text Tables 14.2.33

Source: Applicant's Table 11.19

Reviewer comment: In the statin-naïve treatment group, colesevelam 3750 mg therapy provides 11.6% reduction in LDL-C ($p<0.0001$), 8.1% increase in HDL-C, and a 15.3% increase in TG. The LDL lowering and HDL rising is modest as is the TG increase. The lipid parameter changes

in the background statin therapy group is not as beneficial. In the background-statin treatment group, colesevelam 3750 mg therapy provides a 5.4% reduction in LDL-C (p=0.5) coupled with a 26.7% increase in TG. The HDL-C increase is consistent with a 9.0% increase in HDL-C. Thus the LDL lowering is minimal and not statistically significant and there is a greater TG increase. Although the smaller number of subjects on background statin therapy compared to statin-naive limits interpretation, the lipid parameter changes warrant some concern. This raises the question of whether colesevelam 3750mg should primarily be used in statin-intolerant subjects or in subjects on optimally-dosed statin therapy and not at goal; at least until there is data in children that shows that the addition of colesevelam to a lower dose or less than maximally titrated statin provides some reasonable lipid-altering efficacy to offset the safety/tolerability concern and TG rising that accompany the addition of colesevelam.

Of note, in the clinical studies section of the current Welchol label, co-administration of Welchol and a statin (atorvastatin 10mg, lovastatin 10 mg, or simvastatin 10 and 20 mg) in 3 clinical studies demonstrated an additive reduction of LDL-C of 8% to 16% above that seen with the statin alone. However, there are no data regarding Welchol added to moderate or high dose statin therapy in the label.

Statin Status-Period III

Table 6.1.7.6 presents the results for percent changes in LDL-C from the start of Period III (Week 8) to Week 26 with LOCF for the Period III ITT population by statin status subgroup (statin-naïve, statin-naïve + statin-stable, and changed statin dose + added statin). During Period III, the mean percent change in LDL-C was -6.6% for the statin-naïve subgroup, -6.0% for the statin-naïve + statin-stable subgroup, and -27.9% for the changed statin dose + added statin subgroup. The largest mean percent reductions in LDL-C were observed in the subgroup of subjects who changed statin dose or added a statin to the colesevelam HCl 3750 mg regimen during Period III—these reductions ranged from a 41% LDL-C reduction in the group who received placebo in Period II and statin+Welchol 3750mg in Period III to a 20% LDL-C reduction in the group who received colesevelam 3750 mg in Period II and statin+colesevelam 3750mg in Period III.

Reviewer comment: Clearly, to achieve the greatest LDL reduction involves use of a statin that has been titrated to optimize efficacy. The colesevelam efficacy is quite modest when used alone or added to a statin.

For all Period III statin status subgroups, the largest mean percent reductions in LDL-C during Period III were observed in subjects whose Period II treatment was placebo. For both the statin-naïve subgroup and statin-naïve + statin-stable subgroup, subjects whose Period II treatment was colesevelam HCl 3750 mg had small percent changes in LDL-C during Period III (-1.4% and 1.6%, respectively).

Table 6.1.7.7: Mean Percent Changes in Low-Density Lipoprotein Cholesterol (mg/dL) From the Start of Period III (Week 8) to Week 26 With LOCF – Period III Statin Status Subgroups – Intent-to-Treat Population for Period III

Subgroup Treatment Group	n	Week 8 Baseline Mean (SD)	Week 26 With LOCF Mean (SD)	Percent Change Mean (SD)
Statin-naïve				
Colesevelam HCl 3750 mg in Period II	38	178.5 (40.67)	174.4 (42.66)	-1.4 (14.43)
Colesevelam HCl 1875 mg in Period II	36	198.0 (35.48)	181.9 (39.58)	-7.5 (15.98)
Placebo in Period II	38	200.6 (38.88)	178.2 (45.75)	-11.0 (15.55)
Colesevelam HCl 3750 mg in Period III	112	192.3 (39.39)	178.1 (42.52)	-6.6 (15.71)
Statin-naïve + statin-stable				
Colesevelam HCl 3750 mg in Period II	50	171.3 (43.84)	170.8 (45.01)	1.6 (20.46)
Colesevelam HCl 1875 mg in Period II	48	188.6 (38.90)	169.3 (44.61)	-9.5 (18.19)
Placebo in Period II	53	196.6 (36.71)	176.2 (42.63)	-10.1 (15.23)
Colesevelam HCl 3750 mg in Period III	151	185.7 (41.02)	172.2 (43.86)	-6.0 (18.71)
Changed statin dose + added statin [1]				
Colesevelam HCl 3750 mg in Period II	10	198.7 (44.32)	158.0 (41.97)	-19.7 (14.83)
Colesevelam HCl 1875 mg in Period II	8	185.1 (33.28)	140.8 (48.04)	-23.7 (25.49)
Placebo in Period II	9	214.3 (31.81)	128.1 (41.33)	-40.8 (13.81)
Colesevelam HCl 3750 mg in Period III	27	199.9 (37.80)	142.9 (43.84)	-27.9 (19.96)

1. One subject (005-04) in the colesevelam HCl 1875 mg group in Period II had their statin dose decreased in Period III. All other subjects increased the dose of statin they were taking or added a statin to their colesevelam HCl 3750 mg regimen in Period III.

Week 8 baseline was defined as the last value measured before or on Week 8 prior to the first dose of Period III study medication.
Only subjects with values at both Week 8 baseline and endpoint are included in this table.
P-values are from a 1-sample t-test of percent change within group.
HCl = hydrochloride; LOCF = last observation carried forward; SD = standard deviation.
Sources: Post-text Tables 14.2.36 and 14.2.43

Source: Applicant's Table 11.23

Dosing Schedule

For both dosing schedule subgroups(divided dose [3 tablets at noon/3 tablets in the evening] and single dose [6 tablets in the evening]), similar LDL-C mean percent changes were observed across the treatments: 11.9% LDL lowering for colesevelam 3750 mg as a divided dose ($p<0.0001$) and 9.3% LDL lowering when given as a single dose ($p=0.038$). The treatment difference in mean percent change in LDL-C between the colesevelam HCl 3750 mg group and the placebo group was similar for the dosing schedule subgroups.

Table 6.1.7.8: Mean Percent Changes in Low-Density Lipoprotein Cholesterol (mg/dL) From Study Baseline Day 1) to Week 8 with LOCF-Dosing Schedule Subgroups – Intent-to-Treat Population for Period II

Subgroup Treatment Group	n	Day 1 Baseline Mean (SD)	Week 8 With LOCF Mean (SD)	Percent Change Mean (SD)	p-value
Divided Dose					
Colesevelam HCl 3750 mg	30	208.4 (40.54)	182.9 (38.94)	-11.9 (10.93)	<0.0001
Colesevelam HCl 1875 mg	39	195.6 (33.72)	186.1 (30.15)	-3.5 (15.87)	0.1738
Placebo	38	198.1 (46.43)	198.2 (41.43)	1.7 (17.08)	0.5323
Single Dose					
Colesevelam HCl 3750 mg	33	196.8 (57.46)	173.9 (50.91)	-9.3 (24.80)	0.0384
Colesevelam HCl 1875 mg	24	203.1 (57.38)	189.3 (46.71)	-4.1 (22.20)	0.3793
Placebo	27	194.7 (39.95)	199.6 (27.33)	4.6 (15.73)	0.1446

Study baseline was defined as the last value measured before or on Day 1 prior to the first dose of randomized study medication.
Only subjects with values at both study baseline and endpoint are included in this table.
P-values are from a 1-sample t-test of percent change within group.
HCl = hydrochloride; LOCF = last observation carried forward; SD = standard deviation.
Source: Post-text Table 14.2.34

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

During the double-blind period, treatment with colesevelam HCl at both the 3750 mg and 1875 mg doses resulted in statistically significant reductions in LDL-C compared to placebo. The mean LDL-C at baseline was 202.3 mg/dL for the colesevelam HCl 3750 mg group, 198.5 mg/dL for the colesevelam HCl 1875 mg group, and 196.7 mg/dL in the placebo group. Colesevelam HCl 3750 mg treatment reduced LDL-C by 12.5% ($p < 0.0001$) and colesevelam HCl 1875 mg treatment reduced LDL-C by 6.3% ($p=0.0307$). There appears to be an incremental benefit with the higher dose of colesevelam HCl. The high dose studied (3750 mg) is the approved recommended dose. The low dose studied (1875 mg) was chosen to demonstrate a dose-response relationship but is not the recommended marketed dose.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Refer to Table 6.1.7.6 for details. For subjects who were statin-naïve or statin-naïve + statin stable and received colesevelam HCl 3750 mg for both the double-blind and open-label periods of the study, LDL-C levels were relatively stable during the open-label period. For the statin-naïve subjects, LDL-C was reduced by 1.4% during the open-label period. For the statin-naïve + statin stable subjects, LDL-C was increased by 1.6% during the open-label period. The results of these two stable subgroups demonstrate the maintenance of therapeutic effect of colesevelam 3750 mg over 26 weeks of treatment in pediatric subjects.

6.1.10 Additional Efficacy Issues/Analyses

According to the statistical reviewer, Cynthia Liu, in general, there were no serious statistical issues and the statistical analyses the sponsor performed met the statistical requirements listed in the Written Request. Please refer to Cynthia Liu's review for additional efficacy analyses.

7 Review of Safety

Safety Summary

7.1 Methods

Safety evaluations were based on the safety population, defined as all randomized subjects (194 subjects) who took at least 1 dose of randomized study medication: 64 (100.0%) subjects in the colesevelam HCl 3750 mg group, 65 (100.0%) subjects in the colesevelam HCl 1875 mg group, and 65 (100.0%) subjects in the placebo group. The safety population for Period III included 184 (94.8%) subjects who took at least 1 dose of study medication during Period III.

Safety assessments included treatment-emergent adverse events (TEAEs), vital signs, physical examination results, serum pregnancy testing, Tanner staging, and clinical laboratory measurements (hematology, blood chemistry, urinalysis, hormones, lipid-soluble vitamins, hsCRP, prothrombin time, and partial thrombin-plastin time).

During the study, the immunoassay platform for the measurement of dehydroepiandrosterone sulfate, estradiol, follicle-stimulating hormone (FSH), and testosterone changed from the ELECSYS system to the CENTAUR system. The normal ranges differed between the 2 systems. To account for such changes, summary tables were produced for the following 1) n (%) of subjects in each treatment group with laboratory parameters measured by ELECSYS and CENTAUR systems at each scheduled visit and at early termination; 2) mean values at study baseline, Week 8 and Week 26, and the changes from study baseline to Week 8 and Week 26 endpoints, measured by ELECSYS and CENTAUR, respectively; and 3) shift tables of dehydroepiandrosterone sulfate, estradiol, FSH, testosterone, and other relevant parameters from study baseline to Week 8 and Week 26 endpoints.

7.1.1 Clinical Studies Used to Evaluate Safety

This sNDA is based on Study WEL-410.

7.1.2 Adequacy of Data

WelChol is a currently marketed drug in the US. Thus, an adequate number of adult subjects with pertinent risk factors have been exposed to the drug in clinical studies as well as in the

postmarketing environment. In this pediatric study, duration of exposure and drug dosage was limited, but adequate, to assess most safety issues.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

Not applicable.

7.2 Adequacy of Safety Assessments

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

Compliance with Study Drug
Mean percent compliance with study medication during Period II was similar for the treatment groups. Overall mean percent compliance with study medication was 87.3% for the colesevelam HCl 3750 mg group, 85.3% for the colesevelam HCl 1875 mg group, and 85.5% for the placebo group. Mean percent compliance with study medication in subjects >13 years of age was 90.4% for the colesevelam HCl 3750 mg group, 86.5% for the colesevelam HCl 1875 mg group, and 83.8% for the placebo group. Mean percent compliance with study medication in subjects ≤13 years of age was 82.9% for the colesevelam HCl 3750 mg group, 83.7% for the colesevelam HCl 1875 mg group, and 88.1% for the placebo group.

Extent of Exposure
For the safety population, mean exposure to study medication during Period II was similar for the treatment groups: 55.4 days for the colesevelam HCl 3750 mg group, 56.1 days for the colesevelam HCl 1875 mg group, and 56.4 days for the placebo group. Median exposure values were similar to the mean exposure values.

For the safety population, mean exposure to study medication during Period III was similar for the Period II treatment groups: 123.8 days for subjects whose Period II treatment was colesevelam HCl 3750 mg, 116.7 days for subjects whose Period II treatment was colesevelam HCl 1875 mg, and 122.3 days for subjects whose Period II treatment was placebo. Median exposure values were similar to the mean exposure values.

For the safety population, mean exposure to study medication during the 26-week study was similar for the treatment groups: 179.4 days for subjects whose Period II treatment was colesevelam HCl 3750 mg, 173.8 days for subjects whose Period II treatment was colesevelam HCl 1875 mg, and 179.1 days for subjects whose Period II treatment was placebo. Median exposure values were similar to the mean exposure values. During the study, 41 subjects were exposed to study medication >26 weeks.

7.2.2 Explorations for Dose Response

The doses used in this study were colesevelam HCl 3750 mg and 1875 mg. The high dose studied is the approved recommended dose. The low dose studied was chosen to demonstrate a dose-response relationship but is not the recommended marketed dose.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

Safety assessments included adverse events, clinical laboratory measurements, vital signs, and physical examinations, in addition to the chemistry, hematology, urinalysis, special chemistry analytes, hormones, vitamins, hsCRP, and clotting factors:

- complete medical history at Visit 1 (Week -4)
- full physical examination was performed at Visit 1 (Week -4) and Visit 7 (Week 26), or upon early withdrawal
- vital signs, including blood pressure and heart rate, were obtained at all scheduled and unscheduled visits
- height was measured at Visit 1 (Week -4) and Visit 7 (Week 26), or upon early withdrawal.
- weight was obtained at Visit 1 (Week -4), Visit 3 (Day 1), Visit 5 (Week 8), and Visit 7 (Week 26), or upon early withdrawal.
- Assessment for adverse events as well as prior and concomitant medications occurred at Visit 2 (Week -2) through Visit 7 (Week 26), or upon early withdrawal.
- Laboratory safety parameters (serum chemistry, hematology, and urinalysis) were measured at Visit 1 (Week -4), Visit 3 (Day 1), Visit 5 (Week 8), Visit 6 (Week 17), and Visit 7 (Week 26), or upon early withdrawal.
- A serum pregnancy test was performed in women of childbearing potential at Visit 1 (Week -4), Visit 3 (Day 1), Visit 5 (Week 8), Visit 6 (Week 17), and Visit 7 (Week 26), or upon early withdrawal.
- Tanner staging was performed at Visit 1 (Week -4) and Visit 7 (Week 26), or upon early withdrawal.
- Various hormones including estradiol (female subjects only), testosterone (male subjects only), luteinizing hormone, follicle-stimulating hormone (FSH), cortisol, thyroid-stimulating hormone (TSH), dehydroepiandrosterone sulfate (DHEAS), fat-soluble including vitamins A and E, and clotting factors including prothrombin and partial thromboplastin times, high-sensitivity C-reactive protein (hsCRP) were evaluated at Visit 3 (Day 1), Visit 5 (Week 8), Visit 7 (Week 26), or upon early withdrawal.

Table 7.2.4.1: Schedule of Assessments

	Screening[a]	Period I[b]	Treatment Double-Blind Period II			Treatment Open-Label Period III		Early Withdrawal[c]	Unscheduled or Follow-up Visit[d]
Visit number:	**1**	**2**	**3**	**4**	**5**	**6**	**7**		**8**
Week number:	**-4**	**-2**	**Day 1**	**4**	**8**	**17**	**26**		**28**
Signed informed consent	X								
Medical history	X								
Physical examination	X						X	X	
Vital signs[e]	X	X	X	X	X	X	X	X	X
Height	X						X	X	
Weight	X		X		X		X	X	
Lipids[f]	X		X		X	X	X	X	X
TSH, hormones			X		X		X	X	
Blood and urine for safety laboratory evaluations	X		X		X	X	X	X	X[g]
Serum pregnancy test[i]	X		X		X	X	X	X	X[h]
PT, PPT, Vitamin A and E			X		X		X	X	
hsCRP			X		X		X	X	
Prior/concomitant medications	X	X	X	X	X	X	X	X	X
Tanner staging	X						X	X	
Adverse events		X	X	X	X	X	X	X	X
Study medication dispensing	X	X	X		X	X			
Compliance control		X	X	X	X	X	X	X	
Study medication collection		X	X	X	X	X	X	X	

a: Subjects passing inclusion/exclusion requirements proceeded with a 4-week stabilization of current statin therapy with placebo. Newly diagnosed heFH subjects naïve to lipid-lowering therapy must have had at least a 4-week diet adjustment prior to Visit 1.
b: The purpose of this visit was to ensure compliance with placebo and statin therapy. Reinforcement of compliance may have been necessary. Compliance during Period I needed to be ≥75% at Visit 3 assessment for randomization.
c: Early withdrawal visits for all subjects withdrawing from study medication before completing 26 weeks of treatment.
d: Unscheduled visits were completed as needed for adverse event evaluation. Follow-up visits occurred 2 weeks after Week 26 of open-label Period III.
e: Vital signs included Blood pressure and sitting heart rate after 5 minutes.
f: Partial plasma lipid profile included LDL-C, HDL-C, non-HDL-C, TG, and TC at Visits 1 and 6. Complete lipid profile (LDL-C, HDL-C, non-HDL-C, TG, TC, apo A-I, and apo B) at Visits 3, 5, and 7. Partial lipid profile optional at Visit 8.
g,h: Safety laboratory and serum pregnancy was optional at Visit 8.
i: Performed in women of childbearing potential.
apo A-I = apolipoprotein A-I; apo B = apolipoprotein B; HDL-C = high-density lipoprotein cholesterol; heFH = heterozygous familial hypercholesterolemia; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; non-HDL-C = non-high-density lipoprotein cholesterol; PT = prothrombin time; PPT = partial thromboplastin time; TC = total cholesterol; TG = triglycerides; TSH = thyroid-stimulating hormone.
Source: Study Protocol

Source: Applicant's Table 9.2

Table 7.2.4.2:

CLINICAL LABORATORY ANALYTES FROM CENTRAL LABORATORY
Fasted Evaluation

Hematology (Visits 1, 3, 5, 6, 7, 8 (optional))	
Hemoglobin	WBC
Hematocrit	WBC differential
RBC	Neutrophils
MCV	Bands
MCH	Lymphocytes
MCHC	Monocytes
RBC Morphology	Eosinophils
Basophils	Platelets
Blood Chemistry (Visits 1, 3, 5, 6, 7, 8 (optional))	
Total bilirubin	Phosphorus
Alkaline Phosphatase	Total Protein
ALT (SGPT)	Albumin
AST (SGOT)	Sodium
GGT	Potassium
BUN	Bicarbonate
Creatinine	Chloride
Glucose	CPK
Uric Acid	Calcium
Lipid Profile (Visits 1, 3, 5, 6, 7)	
Cholesterol (Total LDL-C, HDL-C) (calculated LDL-C)	
Triglycerides	
Apo A-1, Apo B (Visits 3, 5, 7)	
hsCRP (Visits 3, 5, 7)	
Serum Pregnancy (Visits 1, 3, 5, 6, 7, 8 (optional))	
Safety Urinalysis (Visits 1, 3, 5, 6, 7, 8 (optional)) by Central Lab Dipstick	
Microscopy if abnormal minimally RBC, WBC, casts, bacteria	
Hormones, Vitamins and Clotting Factors (Visits 3. 5, 7) –All patients	
Serum Vitamin A	Serum Vitamin E
Partial Thromboplastin Time	Prothrombin Time
Testosterone (males only)	Estradiol (females only)
LH	DHEAS
FSH	Cortisol
TSH	

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable.

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

Bile acid sequestrants have never been approved by the FDA for use in children but were the only class of drugs recommended by NCEP for pharmacological lipid-lowering therapy because of their long track record of safety over three decades[1,2]. As a class, these agents can cause significant tolerability issues as well as providing only a modest LDL-C reduction of < 15%. Liacouras et al.[3] found that 82.5% of children discontinued BAS after an average of 21.9 months, secondary to gritty taste and gastrointestinal complaints. In randomized clinical trials, cholestyramine did not affect height velocity.[4] Levels of fat-soluble vitamins were maintained, except the BAS group had significantly lower 25- hydroxyvitamin D than the placebo group. Low folate and high homocysteine levels have been reported on BAS.[5]

7.3 Major Safety Results

7.3.1 Deaths

No subjects died during the study (Period II or Period III).

7.3.2 Nonfatal Serious Adverse Events

Period II: One subject (033-10) had SAEs of contusion (motorcycle accident) and renal hypoplasia (discovered during abdominal U/S for trauma) during Period II.

Period III: Four subjects had SAEs during Period III (GERD, deliberate poisoning, idiopathic thrombocytopenia, nasopharyngeal cancer). One subject (018-14) discontinued from the study due to an SAE of nasopharyngeal cancer. This reviewer has reviewed all of the case narratives and believes it is unlikely that these AEs are related to Welchol administration. Two of the subject narratives are summarized below:

Subject 031-02 (b) (6) gastroesophageal reflux: an 18-year-old Caucasian female, began the placebo run-in period and was randomized to placebo. The subject completed the randomized treatment period and began taking colesevelam HCl 3750 mg during the open-label period on Study Day 58. On Study Day 176, the subject experienced chest pain described as radiating upper gastric discomfort and was admitted to the hospital for evaluation and treatment. Cardiac work-up was negative and the subject was subsequently diagnosed with gastroesophageal reflux. Treatment of the event included Mylanta, lidocaine, and omeprazole. The study medication was interrupted on Study Day 177 and reintroduced on Study Day 178. The subject was discharged from the hospital on Study Day 177 and the outcome was recorded as recovered.

Subject 039-02 (b) (6) idiopathic thrombocytopenia purpura: a 16-year-old Caucasian female, was randomized to placebo, completed the randomized treatment period and began taking colesevelam HCl 3750 mg during the open-label period on Study Day 57. On Study Day 174 the subject presented to the hospital with a 2 week history of sporadic petechia on the legs and a two-month history of thrombocytopenia. Laboratory testing on admission revealed a platelet count of 23 x 10(9)/L (reference range 130-440 x 10(9)/L). On Study Day 175, laboratory testing revealed a platelet count of 34 x 10(9)/L. On Study Day 180, central laboratory testing showed a

platelet count of 35 x 10(9)/L (reference range 135-400 x 10(9)/L). The subject's condition remained stable and the purpura resorbed spontaneously. No treatment was given for the event. The study medication was interrupted on Study Day 173, and was not restarted. The subject was discharged from the hospital on Study Day 181, and the outcome was recorded as ongoing. The subject completed the study per protocol on Study Day 197, (b) (6) with a platelet count of 38 x 10(9)/L. On 18-Jan-2008, local laboratory testing revealed a platelet count of 49 x 10(9)/L, and on 28-Jan-2008 a platelet count of 29 x 10(9)/L. On (b) (6), bone marrow aspiration results correlated with the diagnoses of idiopathic thrombocytopenic purpura. The subject's medical history includes hypercholesterolemia. Concomitant medications include estradiol and Ascorutin (according to Czech Republic product website contains rutoside trihydrate 20 mg, ascorbic acid 100 mg; indication: symptomatic treatment of increased capillary fragility and permeability of various etiology, mainly in hypovitaminosis and vitamin C deficiency, in anaphylactoid purpura and other forms of vascular purpura, in lower limb venous insufficiency, in treatment of lower limb local swellings of post-traumatic and lymph origin, in hemorrhoids. It is also used to treat local bleeding symptoms in diabetic retinopathy, in polycythaemia, in ulcerous proctocolitis and other diseases in which positive effect of the preparation may be anticipated).

7.3.3 Dropouts and/or Discontinuations

Period II
Table 7.3.3.1 lists the four subjects who discontinued from the study during Period II.

Table 7.3.3.1: Listing of Subjects Who Discontinued From the Study Due to an Adverse Event During Period II – Safety Population for Period II

Period II Treatment Subject No.	Adverse Event Preferred Term	Relationship	SAE
Colesevelam HCl 1875 mg			
012-04	Fatigue	possible	no
020-07	Nausea	probable	no
045-07 [1]	Hypothyroidism	unrelated	no
Colesevelam HCl 3750 mg			
033-15	Diarrhea NOS	possible	no

1. Subject 045-07 had an adverse event that started during Period I and therefore was not treatment emergent.
HCl = hydrochloride; NOS = not otherwise specified; SAE = serious adverse event.
Source: Post-text Table 14.3.2.2

Source: Applicant's Table 12.13

Of these 4 subjects, 3 subjects had adverse events that were considered by the investigators and this reviewer to be possibly or probably related to study medication. The symptoms for the subject who discontinued in Period II due to hypothyroidism actually began during Period I when placebo alone was administered. The narratives of these 3 subjects are summarized below:

- **Fatigue**: Subject 012-04 (b) (6) a 16-year-old Caucasian male, began the placebo run-in period on 14-Mar-2006 and was randomized to colesevelam HCl 1875 mg on 11-Apr-2006. On that same date, the subject developed fatigue. No treatment was given for the event. The last dose of study medication was taken on Study Day 25, 05-May-2006. The event resolved on Study Day 35, 15-

May-2006. The subject was discontinued from the study due to the event on Study Day 38, 18-May-2006. The subject's medical history includes hypercholesterolemia and concentration problems. Concomitant medication includes methylphenidate.

- **Nausea**: Subject 020-07 (b) (6) a 14-year-old Caucasian female, began the placebo run-in period on 17-Aug-2006 and was randomized to colesevelam HCl 1875 mg on 14-Sep-2006. On that same date, the subject developed nausea. No treatment was given for the event. The last dose of study medication was taken and the event resolved on Study Day 16, 29-Sep-2006. The subject was discontinued from the study due to the event on Study Day 33, 16-Oct-2006. The subject's medical history includes hypercholesterolemia, vestibulitis, and episodic headaches. No concomitant medications were taken at the time of the event.
- **Diarrhea:** Subject 033-15 (b) (6) a 12-year-old Caucasian male, began the placebo run-in period on 02-Apr-2007 and was randomized to colesevelam HCl 3750 mg on 02-May-2007. On Study Day 22, 23-May-2007, the subject developed diarrhea. No treatment was given for the event. The last dose of study medication was taken on Study Day 36, 06-Jun-2007, and the event was considered resolved on Study Day 38, 08-Jun-2007. The subject was discontinued from the study due to the event on Study Day 55, 25-Jun-2007. The subject's medical history includes hypercholesterolemia, lactose intolerance, and bronchial asthma. Concomitant medications include cetirizine, budesonide, and albuterol.

Period III

Table 7.3.3.2 lists the 5 subjects who discontinued from the study during Period III. For 3 of the 5 subjects, the adverse events that led to discontinuation were considered by the investigator to be related to study medication (nausea, flatulence, and decreased appetite). This reviewer agrees that the subjects with AEs of flatulence and decreased appetite may be due to the drug and the subjects with migraine and nasopharyngeal cancer are unrelated to study drug. The subject with nausea seems doubtful to be related as the symptoms started while on placebo in the run-in period and continued until Study Day 158 when treatment was stopped and symptoms resolved on Day 161. The subject was on colesevelam 3750 mg only from Study Day 56 to 158.

Table 7.3.3.2: Listing of Subjects Who Discontinued From the Study Due to an Adverse Reaction During Period III – Safety Population for Period II

Period II Treatment Subject No.	Adverse Event Preferred Term	Relationship	SAE
Placebo			
011-05	Nausea	possible	no
Colesevelam HCl 1875 mg			
018-04	Flatulence	definite	no
018-14	Nasopharyngeal cancer NOS	unrelated	yes
020-01 [1]	Appetite decreased NOS	possible	no
Colesevelam HCl 3750 mg			
008-04	Migraine NOS	unlikely	no

1. Subject 020-01 had a TEAE that started during Period II but the subject did not discontinue until Period III.
HCl = hydrochloride; NOS = not otherwise specified; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Source: Post-text Table 14.3.2.2

Source: Applicant's Table 12.14

7.3.4 Significant Adverse Events

During Period II of the study, 83 (42.8%) subjects experienced adverse reactions. The percentages of subjects who experienced adverse reactions as well as the severity of the adverse reactions during Period II were similar across the treatment groups. All the adverse reactions were mild-moderate in severity.

Table 7.3.4.1: Adverse Reactions – Safety Population for Period II

	Colesevelam HCl 3750 mg (N = 64) n (%)	Colesevelam HCl 1875 mg (N = 65) n (%)	Placebo (N = 65) n (%)	Total (N = 194) n (%)
Subjects with TEAEs				
Any TEAEs	26 (40.6)	31 (47.7)	26 (40.0)	83 (42.8)
Any drug-related TEAEs	4 (6.3)	7 (10.8)	7 (10.8)	18 (9.3)
Maximum severity of TEAEs				
Mild	15 (23.4)	17 (26.2)	15 (23.1)	47 (24.2)
Moderate	11 (17.2)	14 (21.5)	11 (16.9)	36 (18.6)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Treatment-emergent adverse events (TEAEs) were defined as adverse events that occurred on or after the first dose date of study medication.
Source: Applicant's Table 12.1

Adverse reactions in Table 7.3.4.2 are provided by Period II treatment and cumulatively by the Period III treatment (colesevelam HCl 3750 mg). During Period III of the study, 93 (50.5%) subjects experienced an adverse reaction. The distribution of subjects with adverse reactions mild in severity by Period II treatment was similar across the treatment groups. More subjects in the colesevelam group experienced an adverse reaction that was moderate in severity.

Table 7.3.4.2: Adverse Reactions – Safety Population for Period III

	Treatment During Period II			Period III
	Colesevelam HCl 3750 mg (N = 62) n (%)	Colesevelam HCl 1875 mg (N = 59) n (%)	Placebo (N = 63) n (%)	Colesevelam HCl 3750 mg (N = 184) n (%)
Subjects with TEAEs				
Any TEAEs	33 (53.2)	28 (47.5)	32 (50.8)	93 (50.5)
Any drug-related TEAEs	4 (6.5)	3 (5.1)	4 (6.3)	11 (6.0)
Maximum severity of TEAEs				
Mild	18 (29.0)	13 (22.0)	21 (33.3)	52 (28.3)
Moderate	15 (24.2)	14 (23.7)	8 (12.7)	37 (20.1)
Severe	0 (0.0)	1 (1.7)	3 (4.8)	4 (2.2)

Treatment-emergent adverse events (TEAEs) were defined as adverse events that occurred on or after the first dose date of study medication for Period III.
Source: Applicant's Table 12.2

7.3.5 Submission Specific Primary Safety Concerns

Gastrointestinal disorders

Twenty (10.3%) subjects experienced gastrointestinal adverse events: 4 (6.3%) subjects in the colesevelam HCl 3750 mg group, 9 (13.8%) subjects in the colesevelam HCl 1875 mg group, and 7 (10.8%) subjects in the placebo group. Thirteen subjects reported gastrointestinal adverse events that were mild in severity and 7 subjects reported gastrointestinal adverse events that were moderate in severity.

Adverse reactions that were reported more frequently in the colesevelam groups as compared to the placebo group include: vomiting, nausea, abdominal pain, anal fissure, constipation, and flatulence. Overall, the number of adverse reactions was small and evenly distributed across treatment groups.

Two subjects had gastrointestinal TEAEs that led to discontinuation during Period II. Subject 020-07, in the colesevelam HCl 1875 mg group, had an adverse event of nausea that led to discontinuation. Subject 033-15, in the colesevelam HCl 3750 mg group, had an adverse event of diarrhea that led to discontinuation.

Table 7.3.5.1: Summary of Treatment-Emergent Adverse Events in the System Organ Class of Gastrointestinal Disorders by Preferred Term – Safety Population for Period II

	Treatment During Period II			
Preferred Term	**Colesevelam HCl 3750 mg (N = 64) n (%)**	**Colesevelam HCl 1875 mg (N = 65) n (%)**	**Placebo (N = 65) n (%)**	**Total (N = 194) n (%)**
Treatment-emergent adverse events				
Vomiting NOS	1 (1.6)	2 (3.1)	1 (1.5)	4 (2.1)
Diarrhea NOS	1 (1.6)	0 (0.0)	2 (3.1)	3 (1.5)
Dyspepsia	1 (1.6)	1 (1.5)	1 (1.5)	3 (1.5)
Nausea	0 (0.0)	2 (3.1)	1 (1.5)	3 (1.5)
Abdominal pain NOS	1 (1.6)	1 (1.5)	0 (0.0)	2 (1.0)
Abdominal pain upper	0 (0.0)	1 (1.5)	1 (1.5)	2 (1.0)
Anal fissure	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.5)
Constipation	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.5)
Flatulence	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.5)
Gastritis NOS	0 (0.0)	0 (0.0)	1 (1.5)	1 (0.5)
Toothache	0 (0.0)	0 (0.0)	1 (1.5)	1 (0.5)

Treatment-emergent adverse events (TEAEs) were defined as adverse events that occurred on or after the first dose date of randomized study medication. Although a subject may have had 2 or more treatment-emergent adverse events, the subject was counted only once within a category. The same subject may have appeared in different categories.
Source: Applicant's Table 12.9

Period III

Twenty-four (13.0%) subjects experienced gastrointestinal adverse events. The gastrointestinal adverse events were mild in severity for 16 subjects, moderate in severity for 7 subjects, and severe for 1 subject. The most frequently reported gastrointestinal treatment-emergent AEs were

nausea (3.8%) and abdominal pain (3.3%). Subject 031-02, whose Period II treatment was placebo, had an SAE of Gastroesophageal reflux disease in Period III. As discussed in Section 7.3.2, this reviewer believes it is unlikely that this was related to colesevelam. Two subjects had gastrointestinal adverse events that led to discontinuation during Period III. Subject 011-05, whose Period II treatment was placebo, had an adverse event of nausea that led to discontinuation during Period III. Subject 018-04, whose Period II treatment was colesevelam HCl 1875 mg, had an adverse event of flatulence. As discussed in Section 7.3.3, this reviewer believes that only the case of flatulence was likely related to colesevelam.

Table 7.3.5.2: Summary of Treatment-Emergent Adverse Events in the System Organ Class of Gastrointestinal Disorders by Preferred Term – Safety Population for Period III

	Treatment During Period II			Period III
Preferred Term	Colesevelam HCl 3750 mg (N = 62) n (%)	Colesevelam HCl 1875 mg (N = 59) n (%)	Placebo (N = 63) n (%)	Colesevelam HCl 3750 mg (N = 184) n (%)
Treatment-emergent adverse events				
Nausea	3 (4.8)	2 (3.4)	2 (3.2)	7 (3.8)
Abdominal pain NOS	3 (4.8)	2 (3.4)	1 (1.6)	6 (3.3)
Diarrhea NOS	0 (0.0)	0 (0.0)	2 (3.2)	2 (1.1)
Dyspepsia	2 (3.2)	0 (0.0)	0 (0.0)	2 (1.1)
Flatulence	1 (1.6)	1 (1.7)	0 (0.0)	2 (1.1)
Toothache	1 (1.6)	1 (1.7)	0 (0.0)	2 (1.1)
Vomiting NOS	1 (1.6)	0 (0.0)	1 (1.6)	2 (1.1)
Abdominal pain lower	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.5)
Abdominal pain upper	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.5)
Constipation	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.5)
Gastritis NOS	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.5)
Gastrointestinal disorder NOS	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.5)
Gastroesophageal reflux disease	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.5)

Source: Applicant's Table 12.10

Serum transaminases and creatine phosphokinase

Three subjects had increases in CPK that were adverse events:

- Subject 010-03 in the colesevelam HCl 1875 mg group (no concomitant statin therapy) had an adverse event of increased CPK (364 IU/L and 491 IU/L [normal range 30 IU/L to 180 IU/L]). The adverse event was considered by the investigator to be mild in severity and possibly related to study medication.
- Subject 014-04 in the colesevelam HCl 3750 mg group (concomitant atorvastatin therapy in Period II [10 mg] and Period III [20 mg]) had the adverse event of increased CPK (844 IU/L [normal range 30 IU/L to 180 IU/L]). The adverse event was considered by the investigator to be moderate in severity and unrelated to study medication.
- Subject 027-07 in the colesevelam HCl 1875 mg group (no concomitant statin therapy) had the adverse events of increased CPK (4175 IU/L [normal range 30 IU/L to 180 IU/L]), increased ALT (77 IU/L [normal range 5 IU/L to 25 IU/L]), and increased AST

(179 IU/L [normal range 8 IU/L to 30 IU/L]). The adverse events were considered by the investigator to be mild in severity unrelated to study medication.

For these subjects, CPK levels returned to normal and the subjects continued in the study. See Section 7.4.2 for additional information.

Swallowing/Choking
During the study, no adverse events of choking or difficulty swallowing study medication (dysphagia, choking sensation, esophageal obstruction, or foreign body trauma) were reported.

Hypothyroidism
Period I
During Period I, Subject 045-07, who was later randomized to colesevelam HCl 1875 mg, had an adverse event of hypothyroidism (TSH of 792.5 mIU/L [normal range 0.300 mIU/L to 5.000 mIU/L]). Corresponding free thyroxine assessments were not performed for this subject. The adverse event of hypothyroidism started during Period I, but the subject did not discontinue from the study until Period II, making it unlikely that the adverse event of hypothyroidism was related to colesevelam.

Period II
During Period II, Subject 008-04, in the colesevelam HCl 3750 mg group, had an adverse event of hypothyroidism. The adverse event of hypothyroidism was considered by the investigator to be moderated in severity and unrelated to study medication. This subject had an adverse event of increased blood TSH (TSH 14.0 mIU/L [normal range 0.300 mIU/L to 5.000 mIU/L] and corresponding free thyroxine 11.6 pmol/L [normal range 9.0 pmol/L to 28.4 pmol/L) at the same time as the adverse event of hypothyroidism. See Section 7.4.2 for additional information.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Period II
Table 7.4.1.1 summarizes AEs by SOC. The colesevelam group has more AEs than placebo in the following SOCs: Gastrointestinal disorders; Respiratory, thoracic, and mediastinal disorders; General disorders and administration site conditions; and Skin and subcutaneous tissue disorders.

Table 7.4.1.1: Summary of Treatment-Emergent Adverse Events by System Organ Class – Safety Population for Period II

SYSTEM ORGAN CLASS	Colesevelam HCl 3750 mg (N = 64) n (%)	Colesevelam HCl 1875 mg (N = 65) n (%)	Placebo (N = 65) n (%)
Infections and infestations	12 (18.8)	12 (18.5)	13 (20.0)
Gastrointestinal disorders	4 (6.3)	9 (13.8)	7 (10.8)
Respiratory, thoracic, and mediastinal disorders	3 (4.7)	8 (12.3)	1 (1.5)
Nervous system disorders	2 (3.1)	4 (6.2)	5 (7.7)
General disorders and administration site conditions	4 (6.3)	3 (4.6)	1 (1.5)
Investigations	2 (3.1)	2 (3.1)	3 (4.6)
Musculoskeletal and connective tissue disorders	1 (1.6)	2 (3.1)	4 (6.2)
Injury, poisoning, and procedural complications	1 (1.6)	2 (3.1)	2 (3.1)
Metabolism and nutrition disorders	0 (0.0)	1 (1.5)	2 (3.1)
Skin and subcutaneous tissue disorders	0 (0.0)	3 (4.6)	0 (0.0)
Blood and lymphatic system disorders	1 (1.6)	0 (0.0)	1 (1.5)
Reproductive system and breast disorders	2 (3.1)	0 (0.0)	0 (0.0)
Congenital, familial, and genetic disorders	0 (0.0)	1 (1.5)	0 (0.0)
Endocrine disorders	1 (1.6)	0 (0.0)	0 (0.0)
Eye disorders	0 (0.0)	1 (1.5)	0 (0.0)
Renal and urinary disorders	0 (0.0)	0 (0.0)	1 (1.5)
Vascular disorders	0 (0.0)	0 (0.0)	1 (1.5)

Treatment-emergent adverse events (TEAEs) were defined as adverse events that occurred on or after the first dose date of randomized study medication.
Although a subject may have had 2 or more TEAEs, the subject was counted only once within a category. The same subject may have appeared in different categories.
HCl = hydrochloride.
Source: Post-text Table 14.3.1.4

Source: Applicant's Table 12.3

Table 7.4.1.2 summarizes the most common (experienced by ≥3% of subjects in any treatment group) TEAEs during Period II of the study by system organ class and preferred term. The colesevelam group has more AEs than placebo for the following Preferred Terms: Nasopharyngitis, Influenza, Vomiting, Nausea, Rhinitis, Pharyngolaryngeal pain, Fatigue, Blood creatine phosphokinase increased, and Myalgia

Table 7.4.1.2: Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (≥3% in Any Treatment Group) – Safety Population for Period II

SYSTEM ORGAN CLASS Preferred Term	Colesevelam HCl 3750 mg (N = 64) n (%)	Colesevelam HCl 1875 mg (N = 65) n (%)	Placebo (N = 65) n (%)
Infections and infestations			
Nasopharyngitis	4 (6.3)	4 (6.2)	3 (4.6)
Upper respiratory tract infection NOS	1 (1.6)	1 (1.5)	3 (4.6)
Ear infection NOS	0 (0.0)	1 (1.5)	3 (4.6)
Gastrointestinal viral NOS	0 (0.0)	0 (0.0)	2 (3.1)
Influenza	2 (3.1)	0 (0.0)	0 (0.0)
Gastrointestinal disorders			
Vomiting NOS	1 (1.6)	2 (3.1)	1 (1.5)
Diarrhea NOS	1 (1.6)	0 (0.0)	2 (3.1)
Nausea	0 (0.0)	2 (3.1)	1 (1.5)
Respiratory, thoracic, and mediastinal disorders			
Rhinitis NOS	0 (0.0)	3 (4.6)	0 (0.0)
Pharyngolaryngeal pain	0 (0.0)	2 (3.1)	0 (0.0)
Nervous system disorders			
Headache	2 (3.1)	3 (4.6)	2 (3.1)
Dizziness	0 (0.0)	0 (0.0)	2 (3.1)
General disorders and administration site conditions			
Fatigue	2 (3.1)	3 (4.6)	1 (1.5)
Investigations			
Blood creatine phosphokinase increased	1 (1.6)	2 (3.1)	0 (0.0)
Musculoskeletal and connective tissue disorders			
Myalgia	0 (0.0)	2 (3.1)	0 (0.0)

Treatment-emergent adverse events (TEAEs) were defined as adverse events that occurred on or after the first dose date of randomized study medication.
Although a subject may have had 2 or more TEAEs, the subject was counted only once within a category. The same subject may have appeared in different categories.
HCl = hydrochloride; NOS = not otherwise specified.
Source: Post-text Table 14.3.1.4

Source: Applicant's Table 12.4

Drug-Related Adverse Reactions in Period II

Drug-related adverse reactions were defined as adverse reactions that the investigator considered definitely, probably, or possibly related to study medication. For all treatment groups, the most common system organ class of drug-related AEs was gastrointestinal disorders: 4 (6.3%) subjects in the colesevelam HCl 3750 mg group, 5 (7.7%) subjects in the colesevelam HCl 1875 mg group, and 3 (4.6%) subjects in the placebo group. One (1.6%) subject in the colesevelam HCl 3750 mg group and 2 (3.1%) subjects in the placebo group had diarrhea; this was the most frequently reported drug-related AE. One (1.5%) subject in the colesevelam HCl 1875 mg group had drug-related constipation during Period II.

Period III

Table 7.4.1.3 summarizes AEs by SOC. Adverse reactions are provided by Period II treatment and cumulatively by the Period III treatment (colesevelam HCl 3750 mg). Overall, the most common system organ classes of adverse reactions were infections and infestations (22.3%), gastrointestinal disorders (13.0%), and nervous system disorders (9.2%).

Table 7.4.1.3: Summary of Treatment-Emergent Adverse Events by System Organ Class – Safety Population for Period III

	Treatment During Period II			Period III
SYSTEM ORGAN CLASS	Colesevelam HCl 3750 mg (N = 62) n (%)	Colesevelam HCl 1875 mg (N = 59) n (%)	Placebo (N = 63) n (%)	Colesevelam HCl 3750 mg (N = 184) n (%)
Infections and infestations	9 (14.5)	14 (23.7)	18 (28.6)	41 (22.3)
Gastrointestinal disorders	11 (17.7)	5 (8.5)	8 (12.7)	24 (13.0)
Nervous system disorders	8 (12.9)	5 (8.5)	4 (6.3)	17 (9.2)
Respiratory, thoracic, and mediastinal disorders	8 (12.9)	5 (8.5)	2 (3.2)	15 (8.2)
Musculoskeletal and connective tissue disorders	5 (8.1)	1 (1.7)	5 (7.9)	11 (6.0)
Injury, poisoning, and procedural complications	4 (6.5)	2 (3.4)	3 (4.8)	9 (4.9)
Psychiatric disorders	2 (3.2)	2 (3.4)	4 (6.3)	8 (4.3)
Skin and subcutaneous tissue disorders	3 (4.8)	0 (0.0)	4 (6.3)	7 (3.8)
General disorders and administration site conditions	1 (1.6)	2 (3.4)	1 (1.6)	4 (2.2)
Reproductive system and breast disorders	2 (3.2)	2 (3.4)	0 (0.0)	4 (2.2)
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)	1 (1.6)	1 (1.7)	0 (0.0)	2 (1.1)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.5)
Investigations	1 (1.6)	0 (0.0)	0 (0.0)	1 (0.5)
Metabolism and nutrition disorders	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.5)

Treatment-emergent adverse events (TEAEs) were defined as adverse events that occurred on or after the first dose date of study medication for Period III.
Although a subject may have had 2 or more TEAEs, the subject was counted only once within a category. The same subject may have appeared in different categories.
HCl = hydrochloride.
Source: Post-text Table 14.3.1.17

Source: Applicant's Table 12.5

Table 7.4.1.4 summarizes the most common (experienced by ≥3% of subjects in any treatment group) adverse reactions during Period III of the study by system organ class and preferred term. Adverse reactions are provided by Period II treatment and cumulatively by the Period III treatment (colesevelam HCl 3750 mg). The most frequently reported adverse reactions during Period III were headache (7.6%), nasopharyngitis (5.4%), and upper respiratory tract infection (4.9%).

Table 7.4.1.4: Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (≥3% in Any Treatment Group) – Safety Population for Period III

SYSTEM ORGAN CLASS Preferred Term	Treatment During Period II			Period III
	Colesevelam HCl 3750 mg (N = 62) n (%)	Colesevelam HCl 1875 mg (N = 59) n (%)	Placebo (N = 63) n (%)	Colesevelam HCl 3750 mg (N = 184) n (%)
Infections and infestations				
Nasopharyngitis	3 (4.8)	4 (6.8)	3 (4.8)	10 (5.4)
Upper respiratory tract infection NOS	3 (4.8)	3 (5.1)	3 (4.8)	9 (4.9)
Influenza	1 (1.6)	3 (5.1)	3 (4.8)	7 (3.8)
Gastrointestinal NOS	2 (3.2)	1 (1.7)	1 (1.6)	4 (2.2)
Ear infection NOS	0 (0.0)	2 (3.4)	1 (1.6)	3 (1.6)
Pharyngitis	0 (0.0)	1 (1.7)	2 (3.2)	3 (1.6)
Gastrointestinal disorders				
Nausea	3 (4.8)	2 (3.4)	2 (3.2)	7 (3.8)
Abdominal pain NOS	3 (4.8)	2 (3.4)	1 (1.6)	6 (3.3)
Diarrhea NOS	0 (0.0)	0 (0.0)	2 (3.2)	2 (1.1)
Dyspepsia	2 (3.2)	0 (0.0)	0 (0.0)	2 (1.1)
Nervous system disorders				
Headache	6 (9.7)	4 (6.8)	4 (6.3)	14 (7.6)
Respiratory, thoracic, and mediastinal disorders				
Pharyngolaryngeal pain	4 (6.5)	2 (3.4)	0 (0.0)	6 (3.3)
Rhinitis NOS	0 (0.0)	2 (3.4)	1 (1.6)	3 (1.6)
Musculoskeletal and connective tissue disorders				
Pain in extremity	1 (1.6)	0 (0.0)	3 (4.8)	4 (2.2)
Injury, poisoning, and procedural complications				
Joint sprain	0 (0.0)	0 (0.0)	2 (3.2)	2 (1.1)
Psychiatric disorders				
Anxiety	0 (0.0)	0 (0.0)	2 (3.2)	2 (1.1)
Skin and subcutaneous disorders				
Acne NOS	2 (3.2)	0 (0.0)	1 (1.6)	3 (1.6)
Reproductive system and breast disorders				
Dysmenorrhea	2 (3.2)	1 (1.7)	0 (0.0)	3 (1.6)

Treatment-emergent adverse events (TEAEs) were defined as adverse events that occurred on or after the first dose date of study medication for Period III.
Although a subject may have had 2 or more TEAEs, the subject was counted only once within a category. The same subject may have appeared in different categories.
HCl = hydrochloride; NOS = not otherwise specified.
Source: Post-text Table 14.3.1.17

Source: Applicant's Table 12.6

7.4.2 Laboratory Findings

No subjects had an SAE related to a laboratory abnormality or discontinued from the study due to a laboratory abnormality.

Mean Laboratory Changes

Chemistry

The table below shows the mean changes in ALT, AST and CPK. Creatine phosphokinase was elevated in the colesevelam HCl 1875 mg group at study baseline and Week 8 endpoint (152.3 IU/L and 106.9 IU/L, respectively). The variability of CPK during Period II was due in part to the maximum value of 4175 IU/L reported by 1 subject (027-07) in the colesevelam HCl 1875 mg treatment group (no concomitant statin therapy). All other CPK values were within the normal range (30 IU/L to 180 IU/L) for this subject.

Three subjects (all in the colesevelam group) had increases in CPK that were considered adverse events:

- Subject 010-03 in the colesevelam 1875 mg group (no concomitant statin therapy) had an adverse event of increased CPK (491 IU/L at Week 8 and 364 IU/L at a Week 8 unscheduled visit [normal range 30 IU/L to 180 IU/L]). The baseline (Day 1) CPK level was 57 IU/L. The elevated CPK level returned to within the normal range at the next available evaluation (Week 17). The adverse event was considered by the investigator to be mild in severity and possibly related to study medication.
- Subject 014-04 in the colesevelam 3750 mg group (concomitant atorvastatin therapy in Period II [10 mg] and Period III [20 mg]) had an adverse event of increased CPK (844 IU/L at Day 1 [normal range 30 IU/L to 180 IU/L]). The elevated CPK level returned to within the normal range at the next available evaluation (Week 8). The adverse event was considered by the investigator to be moderate in severity and unrelated to study medication.
- Subject 027-07 in the colesevelam 1875 mg group (no concomitant statin therapy) had the adverse events of increased CPK (4175 IU/L at Day 1 [normal range 30 IU/L to 180 IU/L]), increased alanine aminotransferase (ALT) (77 IU/L at Day 1 [normal range 5 IU/L to 25 IU/L]), and increased aspartate aminotransferase (AST) (179 IU/L at Day 1 [normal range 8 IU/L to 30 IU/L]). The elevated CPK, ALT, and AST levels returned to within the normal range at the next available evaluation (Week 4). The adverse events were considered by the investigator to be mild in severity and unrelated to study medication.

For all 3 of these subjects, CPK levels returned to within the normal range and the subjects continued in the study. No investigator comments were made attributing any of the CPK elevations to exercise. As these adverse events were not serious AEs or AEs leading to discontinuation from the study, the sponsor does not have any additional information from the investigator for the cause of the laboratory abnormalities.

Table 7.4.2.1: Mean Changes in ALT, AST and CPK Parameters From Study Baseline (Day 1) to Week 8 Endpoint – Safety Population for Period II

Parameter	Colesevelam HCl 3750 mg (N = 64)	Colesevelam HCl 1875 mg (N = 65)	Placebo (N = 65)
Alanine aminotransferase (IU/L)			
N	63	63	64
Study baseline mean (SD)	12.2 (4.10)	13.3 (9.47)	13.4 (7.23)
Week 8 endpoint mean (SD)	13.6 (6.53)	13.6 (8.19)	11.6 (5.54)
Mean change from study baseline (SD)	1.4 (6.10)	0.3 (8.22)	-1.8 (4.76)
Aspartate aminotransferase (IU/L)			
N	63	63	65
Study baseline mean (SD)	16.7 (4.74)	18.8 (21.25)	16.4 (4.93)
Week 8 endpoint mean (SD)	16.8 (3.88)	17.2 (8.19)	15.2 (4.35)
Mean change from study baseline (SD)	0.1 (5.21)	-1.6 (20.42)	-1.2 (3.76)
Creatine phosphokinase (IU/L)			
N	63	63	65
Study baseline mean (SD)	90.4 (106.72)	152.3 (530.97)	82.2 (48.50)
Week 8 endpoint mean (SD)	82.9 (60.90)	106.9 (162.29)	79.3 (52.28)
Mean change from study baseline (SD)	-7.5 (117.98)	-45.3 (537.97)	-2.8 (46.58)

Study baseline was defined as the last value measured before or on Day 1 prior to the first dose of randomized study medication.
If subjects did not have a Week 8 measurement, the last on-treatment observation prior to Week 8 was used.
HCl = hydrochloride; SD = standard deviation.
Source: Post-text Table 14.3.4.1

Source: Applicant's Table 12.15

Shift tables for AST/ALT did not show any clinically meaningful changes. Shift tables for CPK from Baseline to Week 8 and Baseline to Week 26 are shown below. The percentage of subjects with a low or normal CPK that increases to high over the course of the study is small and not meaningfully different among the different treatment groups.

TABLE 14.3.4.14
SHIFT TABLE OF CHEMISTRY LABORATORY PARAMETERS FROM BASELINE TO WEEK 8 (LOCF)
SAFETY POPULATION FOR PERIOD II

PARAMETER (UNIT) / TREATMENT / BASELINE VALUE [1]	CATEGORIZED LAB VALUE AT WEEK 8/ENDPOINT: LOW N (%)	NORMAL N (%)	HIGH N (%)	TOTAL N (%)
CREATINE PHOSPHOKINASE (IU/L)				
PLACEBO (N=65)				
LOW	0 (0.0)	0 (0.0)	0 (0.0)	0 (0
NORMAL	0 (0.0)	60 (92.3)	2 (3.1)	62 (95
HIGH	0 (0.0)	2 (3.1)	1 (1.5)	3 (4
TOTAL	0 (0.0)	62 (95.4)	3 (4.6)	65 (100
COLESEVELAM 1875 mg (N=63)				
LOW	0 (0.0)	0 (0.0)	0 (0.0)	0 (0
NORMAL	0 (0.0)	57 (90.5)	4 (6.3)	61 (96
HIGH	0 (0.0)	1 (1.6)	1 (1.6)	2 (3
TOTAL	0 (0.0)	58 (92.1)	5 (7.9)	63 (100
COLESEVELAM 3750 mg (N=63)				
LOW	1 (1.6)	0 (0.0)	0 (0.0)	1 (1
NORMAL	0 (0.0)	55 (87.3)	2 (3.2)	57 (90
HIGH	0 (0.0)	4 (6.3)	1 (1.6)	5 (7
TOTAL	1 (1.6)	59 (93.7)	3 (4.8)	63 (100

[1] STUDY BASELINE IS DEFINED AS THE LAST VALUE THAT IS MEASURED BEFORE OR ON DAY 1 (VISIT 3) PRIOR TO THE FIRST DOSE OF RANDOMI
STUDY MEDICATION.

TABLE 14.3.4.15
SHIFT TABLE OF CHEMISTRY LABORATORY PARAMETERS FROM BASELINE TO WEEK 26 (LOCF)
SAFETY POPULATION FOR PERIOD III

PARAMETER (UNIT) / TREATMENT / BASELINE VALUE [1]	CATEGORIZED LAB VALUE AT WEEK 26/ENDPOINT: LOW N (%)	NORMAL N (%)	HIGH N (%)	TOTAL N (%)
CREATINE PHOSPHOKINASE (IU/L)				
PLACEBO (N=63)				
LOW	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
NORMAL	1 (1.6)	55 (87.3)	4 (6.3)	60 (95.2)
HIGH	0 (0.0)	2 (3.2)	1 (1.6)	3 (4.8)
TOTAL	1 (1.6)	57 (90.5)	5 (7.9)	63 (100.0)
COLESEVELAM 1875 mg (N=58)				
LOW	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
NORMAL	1 (1.7)	54 (93.1)	2 (3.4)	57 (98.3)
HIGH	0 (0.0)	0 (0.0)	1 (1.7)	1 (1.7)
TOTAL	1 (1.7)	54 (93.1)	3 (5.2)	58 (100.0)
COLESEVELAM 3750 mg (N=61)				
LOW	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
NORMAL	0 (0.0)	52 (85.2)	4 (6.6)	56 (91.8)
HIGH	0 (0.0)	3 (4.9)	2 (3.3)	5 (8.2)
TOTAL	0 (0.0)	55 (90.2)	6 (9.8)	61 (100.0)

[1] STUDY BASELINE IS DEFINED AS THE LAST VALUE THAT IS MEASURED BEFORE OR ON DAY 1 (VISIT 3) PRIOR TO THE FIRST DOSE OF RANDOMIZED
STUDY MEDICATION.

For the total bilirubin parameter, there were slightly more subjects on colesevelam who had a shift from normal to high value for bilirubin from Baseline to Week 8 but this did not continue to increase in the Baseline to Week 26 shift table (see tables below).

TABLE 14.3.4.14
SHIFT TABLE OF CHEMISTRY LABORATORY PARAMETERS FROM BASELINE TO WEEK 8 (LOCF)
SAFETY POPULATION FOR PERIOD II

PARAMETER (UNIT) / TREATMENT / BASELINE VALUE [1]	CATEGORIZED LAB VALUE AT WEEK 8/ENDPOINT: LOW N (%)	NORMAL N (%)	HIGH N (%)	TOTAL N (%)
TOTAL BILIRUBIN (micromol/L)				
PLACEBO (N=65)				
LOW	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.
NORMAL	0 (0.0)	64 (98.5)	1 (1.5)	65 (100.
HIGH	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.
TOTAL	0 (0.0)	64 (98.5)	1 (1.5)	65 (100.
COLESEVELAM 1875 mg (N=63)				
LOW	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.
NORMAL	0 (0.0)	54 (85.7)	3 (4.8)	57 (90.
HIGH	0 (0.0)	2 (3.2)	4 (6.3)	6 (9.
TOTAL	0 (0.0)	56 (88.9)	7 (11.1)	63 (100.
COLESEVELAM 3750 mg (N=63)				
LOW	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.
NORMAL	0 (0.0)	52 (82.5)	5 (7.9)	57 (90.
HIGH	0 (0.0)	2 (3.2)	4 (6.3)	6 (9.
TOTAL	0 (0.0)	54 (85.7)	9 (14.3)	63 (100.

[1] STUDY BASELINE IS DEFINED AS THE LAST VALUE THAT IS MEASURED BEFORE OR ON DAY 1 (VISIT 3) PRIOR TO THE FIRST DOSE OF RANDOMI
STUDY MEDICATION.

TABLE 14.3.4.15
SHIFT TABLE OF CHEMISTRY LABORATORY PARAMETERS FROM BASELINE TO WEEK 26 (LOCF)
SAFETY POPULATION FOR PERIOD III

PARAMETER (UNIT) / TREATMENT / BASELINE VALUE [1]	CATEGORIZED LAB VALUE AT WEEK 26/ENDPOINT: LOW N (%)	NORMAL N (%)	HIGH N (%)	TOTAL N (%)
TOTAL BILIRUBIN (micromol/L)				
PLACEBO (N=63)				
LOW	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0
NORMAL	0 (0.0)	61 (96.8)	2 (3.2)	63 (100.0
HIGH	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0
TOTAL	0 (0.0)	61 (96.8)	2 (3.2)	63 (100.0
COLESEVELAM 1875 mg (N=58)				
LOW	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0
NORMAL	0 (0.0)	51 (87.9)	2 (3.4)	53 (91.4
HIGH	0 (0.0)	1 (1.7)	4 (6.9)	5 (8.6
TOTAL	0 (0.0)	52 (89.7)	6 (10.3)	58 (100.0
COLESEVELAM 3750 mg (N=61)				
LOW	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0
NORMAL	0 (0.0)	52 (85.2)	3 (4.9)	55 (90.2
HIGH	0 (0.0)	5 (8.2)	1 (1.6)	6 (9.8
TOTAL	0 (0.0)	57 (93.4)	4 (6.6)	61 (100.0

[1] STUDY BASELINE IS DEFINED AS THE LAST VALUE THAT IS MEASURED BEFORE OR ON DAY 1 (VISIT 3) PRIOR TO THE FIRST DOSE OF RANDOMIZ
STUDY MEDICATION.

Shift tables for glucose from Baseline to Week 8 and Baseline to Week 26 are shown below. One subject by Week 8 shifted from normal to low glucose on colesevelam 3750 mg and a total of 2 subjects (3.3%) shifted from normal to low glucose from baseline to Week 26.

TABLE 14.3.4.14
SHIFT TABLE OF CHEMISTRY LABORATORY PARAMETERS FROM BASELINE TO WEEK 8 (LOCF)
SAFETY POPULATION FOR PERIOD II

PARAMETER (UNIT) / TREATMENT / BASELINE VALUE [1]	CATEGORIZED LAB VALUE AT WEEK 8/ENDPOINT: LOW N (%)	NORMAL N (%)	HIGH N (%)	TOTAL N (%)
GLUCOSE (mmol/L)				
PLACEBO (N=65)				
LOW	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.5)
NORMAL	0 (0.0)	62 (95.4)	2 (3.1)	64 (98.5)
HIGH	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TOTAL	0 (0.0)	63 (96.9)	2 (3.1)	65 (100.0)
COLESEVELAM 1875 mg (N=63)				
LOW	0 (0.0)	1 (1.6)	0 (0.0)	1 (1.6)
NORMAL	0 (0.0)	60 (95.2)	1 (1.6)	61 (96.8)
HIGH	0 (0.0)	0 (0.0)	1 (1.6)	1 (1.6)
TOTAL	0 (0.0)	61 (96.8)	2 (3.2)	63 (100.0)
COLESEVELAM 3750 mg (N=63)				
LOW	0 (0.0)	1 (1.6)	0 (0.0)	1 (1.6)
NORMAL	1 (1.6)	61 (96.8)	0 (0.0)	62 (98.4)
HIGH	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TOTAL	1 (1.6)	62 (98.4)	0 (0.0)	63 (100.0)

[1] STUDY BASELINE IS DEFINED AS THE LAST VALUE THAT IS MEASURED BEFORE OR ON DAY 1 (VISIT 3) PRIOR TO THE FIRST DOSE OF RANDOMIZED STUDY MEDICATION.

TABLE 14.3.4.15
SHIFT TABLE OF CHEMISTRY LABORATORY PARAMETERS FROM BASELINE TO WEEK 26 (LOCF)
SAFETY POPULATION FOR PERIOD III

PARAMETER (UNIT) / TREATMENT / BASELINE VALUE [1]	CATEGORIZED LAB VALUE AT WEEK 26/ENDPOINT: LOW N (%)	NORMAL N (%)	HIGH N (%)	TOTAL N (%)
GLUCOSE (mmol/L)				
PLACEBO (N=63)				
LOW	0 (0.0)	1 (1.6)	0 (0.0)	1 (1.6)
NORMAL	0 (0.0)	62 (98.4)	0 (0.0)	62 (98.4)
HIGH	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TOTAL	0 (0.0)	63 (100.0)	0 (0.0)	63 (100.0)
COLESEVELAM 1875 mg (N=58)				
LOW	0 (0.0)	1 (1.7)	0 (0.0)	1 (1.7)
NORMAL	0 (0.0)	55 (94.8)	1 (1.7)	56 (96.6)
HIGH	0 (0.0)	0 (0.0)	1 (1.7)	1 (1.7)
TOTAL	0 (0.0)	56 (96.6)	2 (3.4)	58 (100.0)
COLESEVELAM 3750 mg (N=61)				
LOW	0 (0.0)	1 (1.6)	0 (0.0)	1 (1.6)
NORMAL	2 (3.3)	58 (95.1)	0 (0.0)	60 (98.4)
HIGH	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TOTAL	2 (3.3)	59 (96.7)	0 (0.0)	61 (100.0)

[1] STUDY BASELINE IS DEFINED AS THE LAST VALUE THAT IS MEASURED BEFORE OR ON DAY 1 (VISIT 3) PRIOR TO THE FIRST DOSE OF RANDOMIZED STUDY MEDICATION.

The other chemistry parameters did not have any clinically meaningful mean changes from Day 1 to Week 8 or 26 for any treatment group.

Hematology

The table below shows the mean changes in hematology parameters (hemoglobin, white blood cells, and platelet count). No clinically meaningful changes in hematology parameters from study baseline (Day 1) to Week 8 were noted. Subject 039-02, in the placebo group, experienced an SAE of idiopathic thrombocytopenic purpura, which may have contributed to the elevated baseline platelet count in the placebo group.

Table 7.4.2.2: Mean Changes in Key Hematology Parameters From Study Baseline (Day 1) to Week 8 Endpoint – Safety Population for Period II

Parameter	Colesevelam HCl 3750 mg (N = 64)	Colesevelam HCl 1875 mg (N = 65)	Placebo (N = 65)
Hemoglobin (g/L)			
N	58	62	61
Study baseline mean (SD)	140.9 (10.88)	139.7 (12.19)	139.9 (12.52)
Week 8 endpoint mean (SD)	141.3 (11.88)	141.3 (12.15)	140.3 (13.40)
Mean change from study baseline (SD)	0.4 (6.10)	1.6 (6.16)	0.5 (6.16)
White blood cells ($\times 10^9$/L)			
N	58	62	61
Study baseline mean (SD)	6.0 (1.60)	6.0 (1.49)	6.0 (1.76)
Week 8 endpoint mean (SD)	6.0 (1.36)	6.4 (1.89)	5.9 (1.49)
Mean change from study baseline (SD)	0.0 (1.35)	0.3 (1.43)	-0.1 (1.58)
Platelet count			
N	58	62	61
Study baseline mean (SD)	268.9 (65.13)	269.5 (50.36)	283.7 (60.26)
Week 8 endpoint mean (SD)	270.2 (62.13)	270.5 (44.94)	278.7 (60.61)
Mean change from study baseline (SD)	1.4 (27.77)	1.0 (33.49)	-5.0 (36.84)

Study baseline was defined as the last value measured before or on Day 1 prior to the first dose of randomized study medication.
If subjects did not have a Week 8 measurement, the last on-treatment observation prior to Week 8 was used.
HCl = hydrochloride; SD = standard deviation.
Source: Post-text Table 14.3.4.3

Source: Applicant's Table 12.16

The other hematology parameters did not have any clinically meaningful mean changes or shift changes from Day 1 to Week 8 or 26 for any treatment group.

Urinalysis
There were no clinically meaningful changes in the urinalysis parameters from Day 1 to Week 8 or Week 26.

Hormones, vitamins, and clotting factors
The table below presents the mean changes in hormones, vitamins, and clotting factors from study baseline (Day 1) to Week 8 endpoint. No clinically meaningful changes in hormones, vitamins, and clotting factors from study baseline (Day 1) to Week 8 were noted.

Table 7.4.2.3: Mean Changes in Hormones, Vitamins, and Clotting Factors From Study Baseline (Day 1) to Week 8 Endpoint – Safety Population for Period II

Parameter	Colesevelam HCl 3750 mg (N = 64)	Colesevelam HCl 1875 mg (N = 65)	Placebo (N = 65)
PTT (seconds)			
N	53	52	59
Study baseline mean (SD)	24.5 (2.73)	23.7 (2.11)	24.5 (2.31)
Week 8 endpoint mean (SD)	24.2 (2.98)	24.2 (3.17)	24.6 (2.34)
Mean change from study baseline (SD)	-0.3 (3.23)	0.5 (2.37)	0.1 (2.35)
Prothrombin time (seconds)			
N	53	52	59
Study baseline mean (SD)	11.8 (1.00)	11.8 (0.80)	12.1 (0.95)
Week 8 endpoint mean (SD)	11.8 (0.97)	12.0 (1.00)	12.1 (0.97)
Mean change from study baseline (SD)	0.0 (0.92)	0.2 (0.77)	0.0 (1.15)
Retinol (mcg/dL)			
N	61	62	62
Study baseline mean (SD)	45.6 (12.70)	46.9 (15.76)	46.9 (18.69)
Week 8 endpoint mean (SD)	48.6 (12.75)	46.5 (11.60)	44.7 (11.93)
Mean change from study baseline (SD)	3.0 (7.82)	-0.4 (14.45)	-2.2 (18.48)
Gamma tocopherol (mg/dL)			
N	61	62	62
Study baseline mean (SD)	0.15 (0.115)	0.14 (0.096)	0.15 (0.106)
Week 8 endpoint mean (SD)	0.15 (0.081)	0.16 (0.111)	0.15 (0.078)
Mean change from study baseline (SD)	0.01 (0.101)	0.02 (0.056)	-0.00 (0.063)
DHEAS (mcmol/L)			
N	57	57	59
Study baseline mean (SD)	5.0 (3.25)	4.7 (2.72)	5.3 (3.12)
Week 8 endpoint mean (SD)	4.6 (2.78)	4.7 (2.61)	5.6 (3.22)
Mean change from study baseline (SD)	-0.4 (1.14)	-0.1 (0.68)	0.3 (1.01)

Study baseline was defined as the last value measured before or on Day 1 prior to the first dose of randomized study medication.
If subjects did not have a Week 8 measurement, the last on-treatment observation prior to Week 8 was used.
DHEAS = dehydroepiandrosterone sulfate; HCl = hydrochloride; PTT = Partial thromboplastin time; SD = standard deviation.
Source: Post-text Table 14.3.4.7

Source: Applicant's Table 12.17

From Day 1 to Week 26 endpoint, there were small mean changes in PTT, PT, retinol, gamma tocopherol and DHEAS that are not likely to be clinically significant.

Hypothyroidism

During Period I, Subject 045-07, who was later randomized to colesevelam HCl 1875 mg, had an adverse event of hypothyroidism (thyroid-stimulating hormone [TSH] of 792.5 mIU/L at Day 1 [normal range 0.300 mIU/L to 5.000 mIU/L]). No other TSH evaluations were performed. Corresponding free thyroxine assessments were not performed for this subject. The adverse event of hypothyroidism started during Period I, but the subject did not discontinue from the study until Period II. This event of hypothyroidism is unrelated to colesevelam.

During Period II, Subject 008-04, in the colesevelam HCl 3750 mg group, had an adverse event of hypothyroidism. This subject had an adverse event of increased blood TSH (TSH 10.8 mIU/L at Day 1 and 14.0 mIU/L at Week 4 [normal range 0.300 mIU/L to 5.000 mIU/L] and corresponding free thyroxine 11.6 pmol/L at Week 4 [normal range 9.0 pmol/L to 28.4 pmol/L)

at the same time as the adverse event of hypothyroidism. This adverse event of increased blood TSH was unrelated to colesevelam as it began prior to drug administration.

There were also changes in estradiol, FSH, TSH, and testosterone from Day 1 to Week 8 and Week 26 that were small and did not appear to demonstrate a dose-related pattern of change. Shift tables for PTT, PT, DHEAS, estradiol, FSH, TSH, testosterone, gamma tocopherol, and retinol from Baseline to Week 8 and Baseline to Week 26 were reviewed and did not show any clinically meaningful changes. In a few cases there were minor shifts from normal involving ≤ 10% (n≤ 6) subjects. There was significant variability in the estradiol measurements throughout the study; however, there were no measurements outside the normal range.

Table 7.4.2.4: Mean Changes in Estradiol, Follicle-stimulating Hormone, Thyroid-stimulating Hormone, and Testosterone by the ELECSYS Method From Study Baseline (Day 1) to Week 8 Endpoint – Safety Population for Period II

Parameter	Colesevelam HCl 3750 mg (N = 64)	Colesevelam HCl 1875 mg (N = 65)	Placebo (N = 65)
Estradiol (pmol/L)			
N	15	12	13
Study baseline mean (SD)	213.3 (170.73)	175.5 (112.53)	254.8 (248.51)
Week 8 endpoint (SD)	264.8 (203.44)	230.7 (198.55)	231.5 (165.72)
Mean change from study baseline (SD)	51.5 (250.18)	55.2 (237.97)	-23.3 (149.13)
FSH (mIU/mL)			
N	35	34	34
Study baseline mean (SD)	4.3 (2.27)	4.0 (1.95)	4.0 (2.24)
Week 8 endpoint (SD)	3.8 (2.21)	4.2 (2.08)	4.2 (2.11)
Mean change from study baseline (SD)	-0.5 (1.54)	0.2 (1.15)	0.1 (1.68)
TSH (mIU/mL)			
N	36	35	35
Study baseline mean (SD)	2.6 (1.75)	2.4 (0.94)	2.8 (1.31)
Week 8 endpoint (SD)	2.9 (2.42)	2.7 (1.54)	2.7 (1.49)
Mean change from study baseline (SD)	0.3 (1.18)	0.3 (1.34)	-0.1 (1.18)
Testosterone (nmol/L)			
N	17	19	19
Study baseline mean (SD)	10.0 (8.36)	11.6 (10.26)	10.9 (7.05)
Week 8 endpoint (SD)	10.9 (8.45)	11.0 (10.27)	11.3 (6.83)
Mean change from study baseline (SD)	1.0 (3.05)	-0.7 (4.16)	0.4 (1.98)

Study baseline was defined as the last value measured before or on Day 1 prior to the first dose of randomized study medication.
If subjects did not have a Week 8 measurement, the last on-treatment observation prior to Week 8 was used.
FSH = follicle-stimulating hormone; HCl = hydrochloride; SD = standard deviation; TSH = thyroid-stimulating hormone.
Source: Post-text Table 14.3.4.10

Table 7.4.2.5: Mean Changes in Estradiol, Follicle-stimulating Hormone, Thyroid-stimulating Hormone, and Testosterone by the CENTAUR Method From Study Baseline (Day 1) to Week 8 Endpoint – Safety Population for Period II

Parameter	Colesevelam HCl 3750 mg (N = 64)	Colesevelam HCl 1875 mg (N = 65)	Placebo (N = 65)
Estradiol (pmol/L)			
N	7	6	6
Study baseline mean (SD)	189.9 (183.72)	150.8 (95.01)	390.2 (372.54)
Week 8 endpoint mean (SD)	334.7 (229.92)	198.8 (133.98)	197.0 (119.40)
Mean change from study baseline (SD)	144.9 (163.58)	48.0 (133.80)	-193.2 (302.12)
FSH (IU/mL)			
N	19	18	20
Study baseline mean (SD)	3.8 (2.12)	3.1 (2.02)	4.3 (2.26)
Week 8 endpoint mean (SD)	4.3 (2.45)	11.2 (31.26)	3.7 (1.70)
Mean change from study baseline (SD)	0.5 (1.77)	8.1 (31.43)	-0.5 (2.26)
TSH (mIU/mL)			
N	22	21	21
Study baseline mean (SD)	2.3 (0.64)	2.2 (0.83)	2.7 (1.56)
Week 8 endpoint mean (SD)	2.5 (1.14)	2.9 (1.54)	2.9 (1.18)
Mean change from study baseline (SD)	0.2 (1.06)	0.7 (1.15)	0.1 (1.26)
Testosterone (nmol/L)			
N	13	11	14
Study baseline mean (SD)	15.1 (10.08)	10.5 (9.14)	13.7 (6.94)
Week 8 endpoint mean (SD)	13.9 (8.77)	9.9 (6.34)	13.9 (7.16)
Mean change from study baseline (SD)	-1.2 (5.21)	-0.6 (4.76)	0.2 (3.72)

Study baseline was defined as the last value measured before or on Day 1 prior to the first dose of randomized study medication. If subjects did not have a Week 8 measurement, the last on-treatment observation prior to Week 8 was used.
FSH = follicle-stimulating hormone; HCl = hydrochloride; SD = standard deviation; TSH = thyroid-stimulating hormone.
Source: Post-text Table 14.3.4.12

7.4.3 Vital Signs

Mean changes in blood pressure, heart rate, and body weight from study baseline (Day 1) to Week 8 and Week 26 endpoint were similar for the treatment groups. Mean and median changes in body height from study baseline (Day 1) to Week 26 endpoint were similar for the treatment groups.

7.4.4 Electrocardiograms (ECGs)

Not applicable for this study.

7.4.5 Special Safety Studies

Not applicable for this study.

7.4.6 Immunogenicity

Not applicable for this study.

7.5 Other Safety Explorations

7.5.1 Drug-Demographic Interactions

Adverse Events by Demographic Subgroup:

Gender
For the subgroup of male subjects, 50 of 123 (40.7%) subjects experienced an adverse reaction: 15 (37.5%) in the colesevelam HCl 3750 mg group, 17 (43.6%) in the colesevelam HCl 1875 mg group, and 18 (40.9%) in the placebo group. The most common system organ classes of adverse reactions were infections and infestations (16.3%), gastrointestinal disorders (8.1%), and respiratory, thoracic, and mediastinal disorders (7.3%). Of note, 3 males in the colesevelam 1875 mg group and 1 male in the colesevelam 3750 mg group reported fatigue as an AE, compared to zero placebo subjects. While the numbers are small (1 to 2 subjects in each category), all the AST, ALT, GGT, and CPK elevations occurred in males on colesevelam as compared to placebo.

For the subgroup of female subjects, 33 of 71 (46.5%) subjects experienced an adverse reaction: 11 (45.8%) in the colesevelam HCl 3750 mg group, 14 (53.8%) in the colesevelam HCl 1875 mg group, and 8 (38.1%) in the placebo group. The most common system organ classes of adverse reactions were infections and infestations (23.9%), gastrointestinal disorders (14.1%), and nervous system disorders (7.0%). Of note, the AEs of vomiting, dyspepsia, and headache only occurred in female subjects in the colesevelam groups.

Age
There does not appear to be any clinically meaningful differences between the age subgroups (≤13 years vs >13 years of age) in the incidence rates or types of adverse reactions with colesevelam treatment.

For the subgroup of subjects ≤13 years of age, 34 of 79 (43.0%) subjects experienced an adverse reaction: 10 (38.5%) in the colesevelam HCl 3750 mg group, 11 (39.3%) in the colesevelam HCl 1875 mg group, and 13 (52.0%) in the placebo group. The most common system organ classes of TEAEs were infections and infestations (19.0%), gastrointestinal disorders (12.7%), general disorders and administration site conditions (6.3%), and respiratory, thoracic, and mediastinal disorders (6.3%).

For the subgroup of subjects >13 years of age, 49 of 115 (42.6%) subjects experienced an adverse reaction: 16 (42.1%) in the colesevelam HCl 3750 mg group, 20 (54.1%) in the colesevelam HCl 1875 mg group, and 13 (32.5%) in the placebo group. The most common

system organ classes of adverse reactions were infections and infestations (19.1%), gastrointestinal disorders (8.7%), and nervous system disorders (7.8%).

Race
A higher percentage of subjects in the Caucasian subgroup had adverse reactions than the non-Caucasian subgroup. The number of non-Caucasian subjects (n=25) was relatively small compared to the number of Caucasian subjects (n=169). No important differences between the race subgroups in the types of adverse reactions with colesevelam treatment were noted.

For the subgroup of Caucasian subjects, 76 of 169 (45.0%) subjects experienced an adverse reaction: 26 (44.8%) in the colesevelam HCl 3750 mg group, 28 (49.1%) in the colesevelam HCl 1875 mg group, and 22 (40.7%) in the placebo group. The most common system organ classes of AEs were infections and infestations (20.1%), gastrointestinal disorders (10.7%), and nervous system disorders (6.5%).

For the subgroup of non-Caucasian subjects, 7 of 25 (28.0%) subjects experienced an adverse reaction: 3 (37.5%) in the colesevelam HCl 1875 mg group and 4 (36.4%) in the placebo group. The most common system organ classes of TEAEs were infections and infestations (12.0%), respiratory, thoracic, and mediastinal disorders (12.0%), and gastrointestinal disorders (8.0%).

Body Mass Index
There does not appear to be any clinically meaningful differences between the BMI subgroups (<25 kg/m2 vs ≥25 kg/m2) in the incidence rates or types of adverse reactions with colesevelam treatment.

For the subgroup of subjects with a BMI <25 kg/m2, 63 of 142 (44.4%) subjects experienced an adverse reaction: 20 (45.5%) in the colesevelam HCl 3750 mg group, 21 (47.7%) in the colesevelam HCl 1875 mg group, and 22 (40.7%) in the placebo group. The most common system organ classes of AEs were infections and infestations (19.7%), gastrointestinal disorders (10.6%), general disorders and administrative site conditions (5.6%), nervous system disorders (5.6%), and respiratory, thoracic, and mediastinal disorders (5.6%).

For the subgroup of subjects with a BMI ≥25 kg/m2, 20 of 52 (38.5%) subjects experienced an AE: 6 (30.0%) in the colesevelam HCl 3750 mg group, 10 (47.6%) in the colesevelam HCl 1875 mg group, and 4 (36.4%) in the placebo group. The most common system organ classes of TEAEs were infections and infestations (17.3%), gastrointestinal disorders (9.6%), and respiratory, thoracic, and mediastinal disorders (7.7%).

Statin Status
The number of non-naïve to lipid-lowering medication subjects (n=47) was relatively small compared to the number of naïve to lipid-lowering medication subjects (n=147).There were no clinically meaningful differences between the statin status subgroups in the incidence rates of AEs or the types of AEs with colesevelam treatment.

For the subgroup of statin-naïve subjects, 66 of 147 (44.9%) subjects experienced an AE: 20 (40.8%) in the colesevelam HCl 3750 mg group, 25 (50.0%) in the colesevelam HCl 1875 mg

group, and 21 (43.8%) in the placebo group. The most common system organ classes of TEAEs were infections and infestations (18.4%), gastrointestinal disorders (11.6%), and respiratory, thoracic, and mediastinal disorders (6.1%).

For the subgroup of non-naïve subjects, 17 of 47 (36.2%) subjects experienced an AE: 6 (40.0%) in the colesevelam HCl 3750 mg group, 6 (40.0%) in the colesevelam HCl 1875 mg group, and 5 (29.4%) in the placebo group. The most common system organ classes of TEAEs were infections and infestations (21.3%), nervous system disorders (6.4%), gastrointestinal disorders (6.4%), and respiratory, thoracic, and mediastinal disorders (6.4%).

Tanner Stage at Baseline
The number of Tanner Stage II subjects (n=39) was relatively small compared to the number of Tanner Stage III to V subjects (n=155).No important differences between the Tanner stage subgroups in the incidence rates of AEs or the types of AEs with colesevelam treatment were noted.

For the subgroup of subjects with baseline Tanner stage II, 16 of 39 (41.0%) subjects experienced an AE: 5 (33.3%) in the colesevelam HCl 3750 mg group, 5 (33.3%) in the colesevelam HCl 1875 mg group, and 6 (66.7%) in the placebo group. The most common system organ classes of TEAEs were infections and infestations (20.5%), gastrointestinal disorders (15.4%), and respiratory, thoracic, and mediastinal disorders (10.3%).

For the subgroup of subjects with baseline Tanner stage III to V, 67 of 155 (43.2%) subjects experienced an AE: 21 (42.9%) in the colesevelam HCl 3750 mg group, 26 (52.0%) in the colesevelam HCl 1875 mg group, and 20 (35.7%) in the placebo group. The most common system organ classes of TEAEs were infections and infestations (18.7%), gastrointestinal disorders (9.0%), and nervous system disorders (7.1%).

7.5.2 Drug-Disease Interactions

No new information on the effect of drug-disease interactions on the safety and tolerability of Welchol was available for this sNDA.

7.5.3 Drug-Drug Interactions

No new information on the effect of drug interactions on the safety and tolerability of Welchol was available for this sNDA.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

Not applicable as the study is too short in duration and utilizes a pediatric population.

7.6.2 Human Reproduction and Pregnancy Data

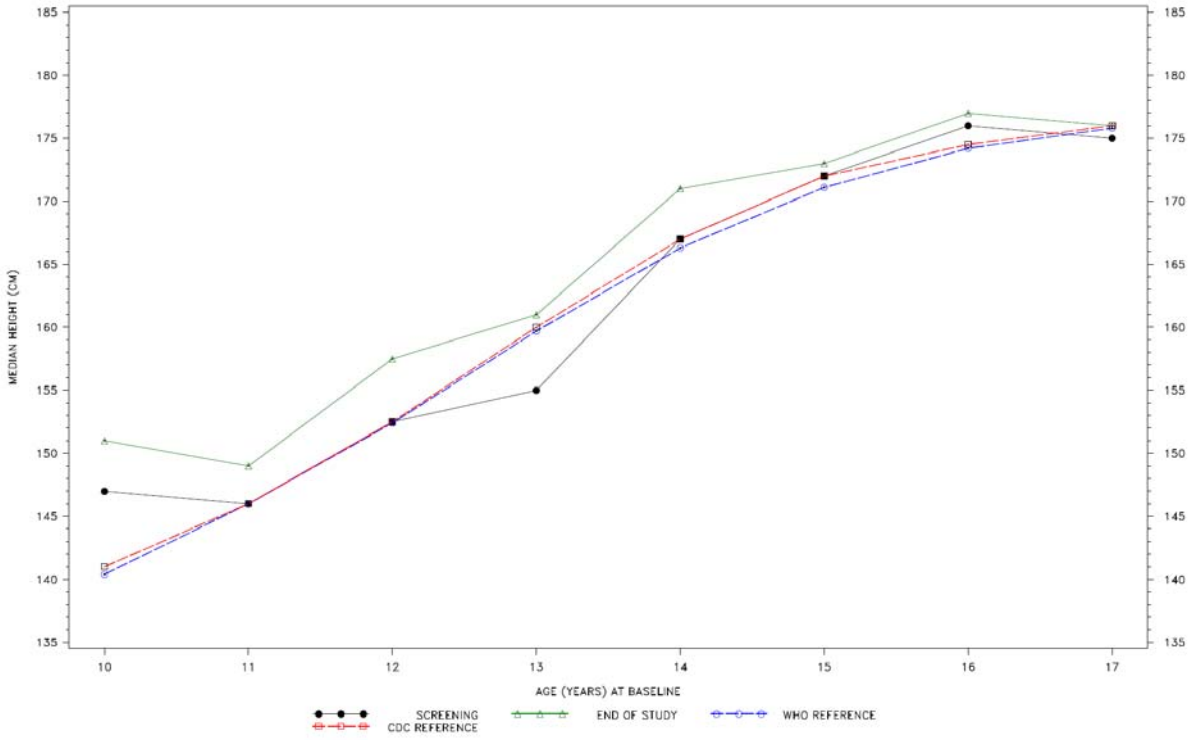
No new information on the effect of Welchol on human reproduction, pregnancy and lactation was available for this sNDA.

7.6.3 Pediatrics and Effect on Growth

Height

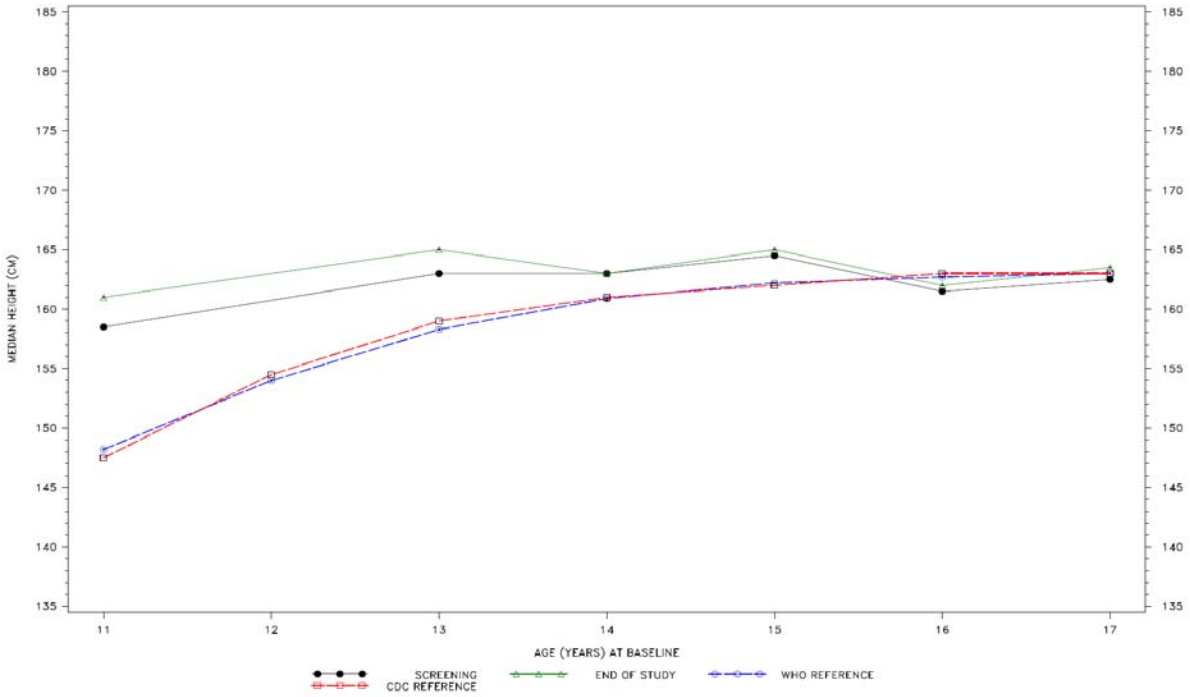
Figures 7.6.3.1 and 7.6.3.2 present median height by age for males and females in this study as well as the CDC and WHO reference standards. The study subjects had expected changes in height-velocity associated with normal maturation. Height-velocity assessments for males and females during the study were similar to both the CDC and WHO reference standards.

Figure 7.6.3.1: Median Height (cm) by Age (Years) – Randomized Population – Males



CDC = Centers for Disease Control and Prevention; WHO = World Health Organization.
Source: Applicant's Figure 12.1

Figure 7.6.3.2: Median Height (cm) by Age (Years) – Randomized Population – Females



CDC = Centers for Disease Control and Prevention; WHO = World Health Organization.
Source: Applicant's Figure 12.2

Tanner Stage

The table below shows shifts in Tanner Stage from screening to Week 26 endpoint. All but one subject either remained in the same Tanner Stage or advanced to a higher Tanner stage. One male subject (031-01) in the colesevelam HCl 3750 mg group who was Tanner stage III at screening was Tanner stage I at Week 26/Early Termination. This subject had no notable laboratory values or adverse events that were related to this change in Tanner stage. The applicant states that site personnel were queried about the difference between baseline and Week 26/Early Termination Tanner stage but no change was made.

Table 7.6.3.1: Shifts in Tanner Stage From Screening to Week 26 Endpoint – Safety Population for Period II

Treatment Group	Shift in Tanner Stage			
	II to III	III to IV	III to V	IV to V
Colesevelam HCl 3750 mg	7 (10.9)	5 (7.8)	1 (1.6)	5 (7.8)
Colesevelam HCl 1875 mg	5 (7.7)	5 (7.7)	1 (1.5)	2 (3.1)
Placebo	1 (1.5)	4 (6.2)	1 (1.5)	8 (12.3)

Subject (031-01) is not included in this table.
HCl = hydrochloride.
Source: Post-text Table 14.3.4.28

Source: Applicant Table 12.23

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No new overdose information for Welchol was available for this sNDA. There is no known drug abuse potential for Welchol. No studies to date have been conducted to evaluate the withdrawal effects of Welchol.

7.7 Additional Submissions

None

8 Postmarketing Experience

Welchol was approved for marketing in the US on 26 May 2000. The most recent Annual Periodic Drug Experience Report submitted to the FDA covers the time period of 26 May 2007 through 25 May 2008 and represents the fifth annual report for Welchol. There was 1 case reported from the Czech Republic as part of a Welchol clinical trial. The other reported adverse events were associated with Welchol in the US and Cholestagel® (tradename of Welchol) in Germany and the United Kingdom. During this reporting period, colesevelam HCl was launched under the tradename Cholestagel in the United Kingdom, Netherlands, Sweden, Norway, and Denmark in October 2007, Germany in February 2008, and Greece and Austria in April 2008. This report was based on safety information for Welchol received by Daiichi Sankyo, its affiliates, and licensing partner, Genzyme.

From May 2007 to 2008, Daiichi Sankyo received a total of 292 postmarketing cases reporting adverse events associated with the administration of Welchol. In one of the cases Welchol was not listed as the primary suspect drug; this case was also reported under the NDA for the primary suspect drug and is referred to as the non-most suspect case.

Of the 291 cases in which Welchol was listed as the primary suspect drug, 20 cases were submitted as initial 15-day alert reports (16 cases) and both initial and follow-up 15-day alert reports (4 cases). Of these 20 cases, 12 cases consisted of adverse events that were serious and unlabeled and 8 cases reported non-serious adverse events related to “difficulty swallowing” that were submitted as 15-day alert reports.

Two cases reported at least 1 serious, labeled event.

Of the 269 non-serious cases, 162 cases (158 initial and 4 follow-up) reported at least 1 unlabeled event and 107 cases (104 initial and 3 follow-up) reported only labeled events. The majority of the 291 cases originated from the US (287); the remaining 4 cases originated from other countries, all of which were serious and unlabeled: United Kingdom (2), Czech Republic (1), and Germany (1).

Distribution of Cases by System Organ Class

A total of 524 adverse events were reported in these 292 cases. The table below lists MedDRA (version 10.1) System Organ Classes (SOCs) that were reported in > 2% of the total number of events reported in these 292 cases.

Table 8.1. Summary of MedDRA SOCs System Organ Class Number (%) of Events

System Organ Class	Number (%) of Events
Gastrointestinal disorders	192 (37%)
Musculoskeletal and connective tissue disorders	77 (15%)
Investigations	75 (14%)
General disorders and administration site conditions	53 (10%)
Nervous system disorders	34 (6%)
Skin and subcutaneous tissue disorders	31 (6%)
Injury, poisoning and procedural complications	10 (2%)
Respiratory, thoracic and mediastinal disorders	9 (2%)
Renal and urinary disorders	8 (2%)

Source: Applicant Table 2 Module 5.3.6 Postmarketing Experience

Serious, Unlabeled Cases

Twenty cases were submitted as initial 15-day alert reports (16 cases) and both initial and follow-up 15-day alert reports (4 cases). Of these 20 cases, 12 cases consisted of adverse events that were serious and unlabeled and 8 cases reported non-serious adverse events related to "difficulty swallowing" that were submitted as 15-day alert reports. A total of 19 serious and unlabeled events were reported in these twelve 15-day alert cases. Table 8.2 lists the most frequently involved MedDRA (version 10.1) SOCs for the serious, unlabeled events that were reported in these 12 cases.

Table 8.2. Serious, Unlabeled MedDRA SOCs

System Organ Class	Number (%) of Events	System Organ Class	Number (%) of Events
Gastrointestinal disorders	6 (32%)	Blood and lymphatic system disorders	1 (5%)
Cardiac disorders	2 (11%)	Eye disorders	1 (5%)
General disorders and administration site conditions	2 (11%)	Hepatobiliary disorders	1 (5%)
Musculoskeletal and connective tissue disorders	2 (11%)	Investigations	1 (5%)
Respiratory, thoracic and mediastinal disorders	2 (11%)	Skin and subcutaneous tissue disorders	1 (5%)

Source: Applicant Table 4 Module 5.3.6 Postmarketing Experience

Table 8.3 lists MedDRA (version 10.1) Preferred Terms (PTs) for the 19 serious, unlabeled events that were reported in these 12 cases.

Table 8.3. Serious, Unlabeled MedDRA PTs

Preferred Term	Number (%) of Events	Preferred Term	Number (%) of Events
Diarrhoea	3 (16%)	Dyspnoea	1 (5%)
Angina pectoris	1 (5%)	Idiopathic thrombocytopenic purpura	1 (5%)
Angioedema	1 (5%)	Intraocular pressure increased	1 (5%)
Asthma	1 (5%)	Irritable bowel syndrome	1 (5%)
Biliary cirrhosis primary	1 (5%)	Muscle disorder	1 (5%)
Cardiac failure	1 (5%)	Myopathy	1 (5%)
Death	1 (5%)	Optic atrophy	1 (5%)
Diverticulum	1 (5%)	Vomiting	1 (5%)
Drug interaction	1 (5%)		

Source: Applicant Table 5 Module 5.3.6 Postmarketing Experience

GI

Four of these 12 cases reported events of gastrointestinal disorders. Case DSU-2007-00916 involved a 68-year-old female patient, with a history of diverticulosis and spastic colon, who began therapy with Welchol on an unknown date in 2007 and reported abdominal cramping, constipation (5 bowel movements per month), and a hospitalization for diverticulosis (serious, unlabeled event) and spastic colon (serious, unlabeled event). The patient also reported an aggravation of right arm myopathy (serious, unlabeled event). Welchol was discontinued on an unknown date and the outcomes of the events of diverticulosis, spastic colon, abdominal cramping, and constipation are unknown. The aggravation of myopathy remained ongoing. Case DSU-2008-00227 described a female patient of unknown age who was reportedly hospitalized for the events of vomiting (serious, unlabeled event), abdominal pain, and diarrhea (serious, unlabeled event) while taking WelChol. Therapy status and event outcome are unknown. The final two cases, DSU-2008-00275 and DSU-2008-00346, referred to male patients who began therapy with colesevelam and experienced diarrhea (serious, unlabeled event), gastrointestinal upset or abdominal pain, and nausea. In both cases, the events resolved and colesevelam was discontinued.

Drug Interaction

Case DSU-2008-00580 reported that a female patient of an unknown age was taking Welchol for treatment of diarrhea. The patient experienced an increase in blood pressure and subsequent heart failure (serious, unlabeled event) due to a possible drug interaction (serious, unlabeled event) among Welchol, an unspecified ACE inhibitor, and an unspecified beta blocker. The patient also reportedly experienced an out-of-range digoxin level, although it was not indicated that the patient was concomitantly taking digoxin. Welchol therapy was discontinued and the patient's blood pressure decreased. The outcome of the heart failure is unknown.

Muscle Problems

Case DSU-2007-00472 involved an elderly female with a history of myopathies with previous statin use. The patient experienced a reoccurrence of muscle problems after beginning therapy with Welchol. Welchol was discontinued and the outcome of the event is unknown.

Serious, Labeled Cases
Two cases (DSU-2008-00749 and DSU-2008-00755) containing 1 event each were classified as serious and labeled during this reporting period. The MedDRA PTs reported in these 2 cases were Pancreatitis (DSU-2008-00749) and Constipation (DSU-2008-00755).

Non-Serious, Unlabeled Cases
During the current reporting period, 163 non-serious cases (1 case was categorized as non most suspect) reported at least 1 adverse event assessed as unlabeled. Table 8.4 lists MedDRA (version 10.1) PTs that were reported in >2% of the 262 non-serious, unlabeled events reported in these 163 cases.

Table 8.4. Non-serious, unlabeled MedDRA PTs

Preferred Term	Number (%) of Events	Preferred Term	Number (%) of Events
Abdominal distension	12 (5%)	Headache	5 (2%)
Flatulence	9 (3%)	Low density lipoprotein increased	5 (2%)
Drug interaction	8 (3%)	Rash	5 (2%)
Dizziness	7 (3%)	Vomiting	5 (2%)
Diarrhoea	6 (2%)	Arthralgia	4 (2%)
Muscle spasms	6 (2%)	Blood cholesterol increased	4 (2%)
Pain in extremity	6 (2%)	Hyperhidrosis	4 (2%)
Blood creatine phosphokinase increased	5 (2%)	Muscular weakness	4 (2%)
Gastrointestinal disorder	5 (2%)	Weight decreased	4 (2%)

Source: Applicant Table 6 Module 5.3.6 Postmarketing Experience

Non-Serious, Labeled Cases
During the current reporting period, there were 107 cases reporting non-serious and labeled events. Table 8.5 lists MedDRA PTs that were reported in >2% of the 133 nonserious, labeled events reported in these 107 cases.

Table 8.5. Non-serious, labeled MedDRA PTs

Preferred Term	Number (%) of Events	Preferred Term	Number (%) of Events
Myalgia	28 (21%)	Drug interaction	3 (2%)
Constipation	26 (20%)	Dyspepsia	3 (2%)
Flatulence	10 (8%)	Fatigue	3 (2%)
Diarrhoea	8 (6%)	Abdominal distension	2 (2%)
Abdominal pain upper	7 (5%)	Back pain	2 (2%)
Stomach discomfort	6 (5%)	Hepatic enzyme increased	2 (2%)
Blood triglycerides increased	5 (4%)	Hypoglycaemia	2 (2%)
Nausea	5 (4%)	Pain	2 (2%)
Drug ineffective	4 (3%)	Rash	2 (2%)
Headache	4 (3%)		

Source: Applicant Table 7 Module 5.3.6 Postmarketing Experience

Drug Interactions

Fourteen cases, serious (1 case) and non-serious (13 cases), reported events involving drug interactions that were either labeled or unlabeled during this time period. Of the 14 cases, 6 non-serious cases reported drug interactions with Welchol that were considered labeled according to the US Product Label for this reporting period. Two of the 6 labeled cases described a possible interaction between Welchol and warfarin sodium. The remaining 4 labeled cases reported an interaction between Welchol and thyroid replacement hormone.

The remaining 8 cases (1 serious case and 7 non-serious cases) reported drug interactions with Welchol that were considered unlabeled by the applicant according to the US Product Label for this reporting period. Two of the 8 unlabeled cases involved drug interactions which resulted in altered digoxin levels. Two cases described unlabeled drug interactions between Welchol and a prescribed sleep-aid medication. The remaining 4 cases refer to isolated unlabeled events of drug interactions with Welchol: a female patient who experienced muscle pain while taking Welchol and calcium; a mother who attributed her unintended pregnancy to a drug interaction between Welchol and an unspecified oral contraceptive (this reviewer notes that the Welchol label dose state that Welchol reduced levels of oral contraceptives containing ethinyl estradiol and norethindrone); a 46-year-old male who experienced worsening depression and suspected an interaction among Welchol, escitalopram, and clonazepam, (the Welchol was discontinued and the events resolved); a patient experienced a drug interaction between an unspecified antibiotic and Welchol.

Difficulty Swallowing Welchol Tablet

During the current reporting period, there were 12 non-serious cases reporting events describing difficulty swallowing of Welchol tablets. Of these 12 cases, 8 cases were submitted as 15-day alert reports as requested by the FDA on February 5, 2008. The remaining 4 cases were received prior to this FDA request. These 12 cases involved the MedDRA PTs of Dysphagia (7), Foreign body trauma (3), Retching (1), and Oesphageal pain (1).

- Of the 7 cases categorized as MedDRA PT Dysphagia, 4 cases reported a difficulty swallowing the Welchol tablet without associated choking, gagging, or coughing; 2 cases reported that the tablets “got stuck in the throat” but were eventually able to be

swallowed. In 1 of these cases, the patient attempted to swallow all 3 tablets at the same time. The remaining case, reported difficulty swallowing Welchol tablets after they were cut in half. Welchol therapy was continued in 5 out of these 7 cases.

- Three cases categorized as MedDRA PT Foreign body trauma described lodging of the Welchol tablet in the throat. Case DSU-2007-00180 referred to a female patient who experienced a residual feeling of the tablet still being in her throat after drinking additional water in order to swallow the tablet. Case DSU- 2007-00929 referred to a male patient who experienced getting the tablet stuck in the throat and required an emergency room visit. In this case, the Welchol tablet was being cut in half. The remaining case (DSU-2007-00283) was reported by a pharmacist and referred to a female patient who experienced a lodging of the Welchol tablet in the throat. The indication for use and outcome of the event are unknown.
- One case referred to a male patient who reported experiencing gagging (MedDRA PT of Retching) on the Welchol tablet since the time of therapy initiation. The patient subsequently began to grind the tablets and take them with psyllium. Welchol therapy was continued and the event remained ongoing.
- One case of esophageal pain involved a female patient who experienced burning in the esophagus, severe gas, and stomach swelling. The events continued with reduction of the dosage of Welchol. The patient's relevant medical history included esophagitis. Welchol therapy was continued and the event remained ongoing.

Estimation of Patient Exposure

This is the fifth Annual Periodic Adverse Drug Experience Report for Welchol and covers the period of May 26, 2007 through May 25, 2008. There were (b) (4) prescriptions written in the U.S. (a one-month supply is assumed) during the current reporting period, compared with (b) (4) prescriptions written during the previous time period. This represents a (b) (4) % increase in the number of prescriptions written. There were 292 cases received during the current reporting period from the U.S., compared with 307 cases received during the previous time period. This represents a 5% decrease in the number of cases reported.

<u>OSE/Division of Pharmacovigilance (DPV I) Review of Postmarketing Reports</u>

OSE performed a review of dysphagia postmarketing reports in 2/2008[6] and updated that report in 2/2009[7]. Jo Wyeth's 2009 updated review is summarized below:

The 2008 OSE review identified 71 reports of dysphagia or esophageal obstruction associated with colesevelam. The sponsor deemed 69 of the 71 reports as having a nonserious outcome. However, the reports deemed nonserious included descriptions of individuals who sought medical intervention (endoscopy, Heimlich maneuver, emergency services summoned or obtained) for a potentially life-threatening "stuck" or "lodged" colesevelam tablet in the esophagus or throat area. OSE recommended the Office of New Drug Quality Assessment (ONDQA) evaluate the tablet for possible reformulation, and requested the sponsor submit all serious and nonserious colesevelam reports of dysphagia or suspected esophageal obstruction as expedited (15-Day Alerts) to OSE for a period of one year (31Dec2007-31Dec2008). The updated 2009 review notes that since the previous OSE review (31Dec2007) through 01Jan2009, FDA received 24 cases of suspected dysphagia or esophageal obstruction associated with colesevelam. The characteristics for these 24 cases are presented in the table below.

Table 8.6. Characteristics of AER Cases of Suspected Dysphagia or Esophageal Obstruction Associated With Colesevelam Tablets (Welchol), n=24. Source: AERS, 31Dec2007 – 01Jan2009		
Reported Characteristic		**Number of Cases**
Age (yrs)		
Average: 72	<60	2
Median: 71	60-70	6
Range: 59-86	70-80	4
Unknown age: 8	>80	4
Gender		
% Female: 71	Female	15
Unknown Gender: 3	Male	6
Reason For Use		
	Hyperlipidemia	9
	Diabetes, Type 2	1
	Fecal Incontinence	1
	Unknown Reason For Use	13
Colesevelam Dose (1 tablet = 625 mg)		
Median: 6 Tablets Daily	2 Tablets Daily	3
Range: 2 – 6 Tablets Daily	4 Tablets Daily	3
Unknown Dose: 7	6 Tablets Daily	11
Reported Dysphagia or Esophageal Obstruction Event		
	Difficulty swallowing tablet(s)	21
	Sensation of tablet "stuck" or "lodged" in throat	7
History of Dysphagia or Swallowing Tablets		7
Reports or Requests Information on Alternative Methods of Administering Tablets (Crushing, Splitting, Chewing, or Dissolving)		13

Table 8.6. Characteristics of AER Cases of Suspected Dysphagia or Esophageal Obstruction Associated With Colesevelam Tablets (Welchol), n=24. Source: AERS, 31Dec2007 – 01Jan2009

Reported Characteristic		**Number of Cases**
Outcomes		
	Emergency room visit	2
	Takes fewer tablets than prescribed	5
	Crushing tablets	1
	Unknown	16
Reporter Source		
	Healthcare Professional	13
	Consumer	11

The colesevelam reports of difficulty swallowing and or sensation of tablets "stuck" or "lodged" in the throat continue. Unlike the previous OSE review, no reports of hospitalization or endoscopy to remove lodged tablets were reported during this one-year time period. Two individuals sought medical attention. The first involved a 69-year-old man who had been taking two colesevelam tablets once daily for several years, but recently went to the emergency room when he "got a Welchol tablet lodged in [his] voice box." No treatment was required and the man continues taking colesevelam. The other report of an individual seeking medical attention describes a 74-year-old female who had been taking two colesevelam tablets twice daily for about 10 months. She experienced trouble swallowing the tablets and pain in her chest area, and summoned emergency response. In the emergency room, she underwent an esophagogastroduodenoscopy and was diagnosed with dysphagia and a spastic esophagus.

In conclusion, FDA continues to receive colesevelam reports of difficulty swallowing tablets or sensation of tablets being "stuck" or "lodged" in the throat. The cause of the difficulty swallowing or sensation of "stuck" tablets is not clear. However, the sponsor is developing a new formulation (powder for oral suspension), which will provide an option for patients experiencing these types of adverse events. OSE recommended that the sponsor continue to submit all suspected reports of dysphagia or esophageal obstruction associated with colesevelam as expedited (15-Day Alert) reports for an additional year.

9 Appendices

9.1 Literature Review/References

A literature search of the Pub Med database containing the term "colesevelam" results in 80 articles retrieved. Many of the recent articles are related to colesevelam use and improving glycemic control. Some of the articles published from October 2006 to December 2008 are listed below. None of the articles address pediatric use of colesevelam.

1. Bays HE, Cohen DE. Rationale and design of a prospective clinical trial program to evaluate the glucose-lowering effects of colesevelam HCl in patients with type 2 diabetes mellitus. Curr.Med.Res.Opin. 2007 Jul;23(7):1673-1684.
2. Bays HE, Goldberg RB. The 'forgotten' bile acid sequestrants: is now a good time to remember? Am.J.Ther. 2007 Nov;14(6):567-580.
3. Bays H, Jones PH. Colesevelam hydrochloride: reducing atherosclerotic coronary heart disease risk factors. Vasc Health Risk Manag 2007 Oct;3(5):733-742.
4. Bays H, Rhyne J, Abby S, Lai Y, Jones M. Lipid-lowering effects of colesevelam HCl in combination with ezetimibe. Curr.Med.Res.Opin. 2006 Nov;22(11):2191-2200.
5. Davidson MH. The use of colesevelam hydrochloride in the treatment of dyslipidemia: a review. Expert Opin.Pharmacother. 2007 Oct;8(15):2569-2578.
6. Florentin M, Liberopoulos EN, Mikhailidis DP, Elisaf MS. Colesevelam hydrochloride in clinical practice: a new approach in the treatment of hypercholesterolaemia. Curr.Med.Res.Opin. 2008 Apr 19;24(4):995-1009.
7. Fonseca VA, Rosenstock J, Wang AC, Truitt KE, Jones MR. Colesevelam HCl improves glycemic control and reduces LDL cholesterol in patients with inadequately controlled type 2 diabetes on sulfonylurea-based therapy. Diabetes Care 2008 Aug;31(8):1479-1484.
8. Goldberg RB, Fonseca VA, Truitt KE, Jones MR. Efficacy and safety of colesevelam in patients with type 2 diabetes mellitus and inadequate glycemic control receiving insulin-based therapy. Arch.Intern.Med. 2008 Jul 28;168(14):1531-1540.
9. Goldfine AB. Modulating LDL cholesterol and glucose in patients with type 2 diabetes mellitus: targeting the bile acid pathway. Curr.Opin.Cardiol. 2008 Sep;23(5):502-511.
10. Jacobson TA. Toward "pain-free" statin prescribing: clinical algorithm for diagnosis and management of myalgia. Mayo Clin.Proc. 2008 Jun;83(6):687-700.
11. Jacobson TA, Armani A, McKenney JM, Guyton JR. Safety considerations with gastrointestinally active lipid-lowering drugs. Am.J.Cardiol. 2007 Mar 19;99(6):47c-55c.
12. Knopp RH, Tsunehara C, Retzlaff BM, Fish B, Nguyen H, Anderson S, et al. Lipoprotein effects of combined ezetimibe and colesevelam hydrochloride versus ezetimibe alone in hypercholesterolemic subjects: a pilot study. Metabolism 2006 Dec;55(12):1697-1703.
13. Robinson DM, Keating GM. Colesevelam: a review of its use in hypercholesterolemia. Am J Cardiovasc Drugs 2007;7(6):453-465.

There are some articles that discuss the use of bile acid sequestrants in general for the management of hyperlipidemia in children and adolescents:

1. Kwiterovich PO Jr. Recognition and management of dyslipidemia in children and adolescents. J Clin Endocrinol Metab. 2008 Nov;93(11):4200-9. Epub 2008 Aug 12.

2. Holmes KW, Kwiterovich PO Jr. Treatment of dyslipidemia in children and adolescents. Curr Cardiol Rep. 2005 Nov;7(6):445-56.
3. Tonstad S, Thompson GR. Management of Hyperlipidemia in the Pediatric Population. Curr Treat Options Cardiovasc Med. 2004 Oct;6(5):431-437.

Additional literature references relevant to colesevelam coadministration are incorporated in various sections of this review.

9.2 Labeling Recommendations

This section summarizes the clinically meaningful changes to the label; minor editing changes and other changes are not included. The applicant's proposed changes and the Medical Officer's suggested revisions are organized by the sections of the label in which proposed changes appear. The applicant's requested additions to the label are in red and red strike-through marks designate their requested deletions to the label. The medical officer's comments are in *italics*. Double strike-through marks designate segments deleted from the applicant's proposal and underlined red color areas indicate reviewer's additions. At the time of finalization of this review, labeling negotiations were essentially complete; however, minor changes may occur, and one should refer to the final label attached to the approval letter.

(b) (4)

AFTER THIS PAGE, 3 PAGES WITHHELD IN FULL - (b)(4) - DRAFT LABELING

(b) (4)

9.3 Advisory Committee Meeting

There was no Advisory Committee meeting for this submission.

[1] National Cholesterol Education Program 1992 Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. Pediatrics 89(Suppl): 525–584
[2] Kwiterovich PO Jr. Recognition and management of dyslipidemia in children and adolescents. J Clin Endocrinol Metab. 2008 Nov;93(11):4200-9. Epub 2008 Aug 12.
[3] Liacouras CA, Coates PM, Gallagher PR, Cortner JA 1993 Use of cholestyramine in the treatment of children with familial combined hyperlipidemia. J Pediatr 122:477–482
[4] Tonstad S, Knudtzon J, Sivertsen M, Refsum H, Ose L 1996 Efficacy and safety of cholestyramine therapy in peripubertal and prepubertal children with familial hypercholesterolemia. J Pediatr 129:42–49
[5] Farah R, Kwiterovich PO, Neill CA 1977 A study of the dose-effect of cholestyramine in children and young adults with familial hypercholesterolemia. Lancet 1:59–63
[6] Wyeth J. Colesevelam (Welchol): review of dysphagia post-marketing reports (OSE RCM 2008-25). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research (US); 2008 Feb 21. pp 13.
[7] Wyeth J. Colesevelam (Welchol): Update on Dysphagia and Esophageal Obstruction. Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research (US); 2009 Feb

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Eileen Craig
6/11/2009 06:05:41 AM
MEDICAL OFFICER

Eric Colman
6/11/2009 10:22:32 AM
MEDICAL OFFICER
I concur with Dr. Craig's review