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2 SYNOPSIS

Protocol Number:	WEL-410
Investigational Product:	Welchol
Active Ingredient(s)/INN:	Colesevelam HCl
Study Title:	Randomized, Double-Blind, 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)
Investigators:	[redacted]
Study Centers:	41 clinical sites in Australia, Austria, Canada, Hungary, Israel, New Zealand, Norway, Slovakia, South Africa, the Czech Republic, the Netherlands, and the US
Publications (references):	none
Study Period:	110 weeks
Initiation Date:	5 November 2005
Completion Date:	18 December 2007
Phase of Development:	4
Study Objectives:	The objectives of this study were to evaluate the lipid-lowering efficacy and safety of colesevelam hydrochloride (HCl) (Welchol®) therapy administered to heterozygous familial hypercholesterolemia (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.

	Primary: For Period II (Day 1 to Week 8): To evaluate the low-density lipoprotein cholesterol (LDL-C)-lowering efficacy of colesevelam HCl administered to heFH subjects who were on a stable dose of statins or who were treatment naïve to lipid-lowering therapy. **Secondary:** For Period III (Week 8 to Week 26): To evaluate the long-term safety and efficacy of high-dose colesevelam HCl administered to heFH subjects while optimizing statin therapy for treatment to goal.
Methodology:	This was a 32-week, multi-center, randomized, double-blind, placebo-controlled, parallel-group, pediatric study consisting of 3 periods as follows: <u>Stabilization Phase – Period I (approximately 4 weeks)</u>: Period I was a single-blind stabilization period. All subjects received 6 placebo tablets daily. The objective was to evaluate the dosing compliance and tolerability to the tablets. <u>Double-Blind Treatment – Period II (Day 1 to Week 8)</u>: Period II was an 8-week, double-blind, randomized treatment period. Subjects were assigned randomly to 1 of 3 treatment groups: ∉ Placebo, ∉ Low-dose colesevelam HCl (1875 mg), or ∉ High-dose colesevelam HCl (3750 mg). Subjects continued to take their currently prescribed statin, or no statin if treatment naïve. Randomization was stratified by background statin therapy. <u>Open-Label Treatment – Period III (Week 8 to Week 26)</u>: 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 to the goal LDL-C of {110 mg/dL (2.85 mmol/L). 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 approved in the statin label. A 2-week follow-up visit occurred at the conclusion of Period III. **Duration of Treatment:** 32 weeks

Number of Subjects:	Planned: 132 randomized subjects Screened: 247 subjects Randomized: 194 subjects Completed: 173 subjects Discontinued: 21 subjects
Diagnosis and Main Criteria for Inclusion:	The study population comprised an approximately equal number of male and female subjects 10 to 17 years of age on a National Cholesterol Education Program Step I diet or equivalent diet, with a diagnosis of heFH who met LDL-C inclusion criteria (}130 mg/dL [3.37 mmol/L] for statin-stabilized subjects and }160 mg/dL [4.14 mmol/L] for naïve subjects). In addition, subjects must have met all other entry qualifications based on Tanner staging, medical history, physical examination, and laboratory tests. Female subjects must have also been at least 1-year post-menarche.
Investigational Product:	Colesevelam HCl 625 mg tablets (Lot # [redacted]
Comparator:	Colesevelam HCl placebo tablets (Lot # [redacted]
Criteria for Evaluation:	**Efficacy:** The primary efficacy parameter was the percent change in plasma LDL-C from study baseline (Day 1) to Week 8 of Period II. The other efficacy parameters included the following: ∉ Percent changes in total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), non-high-density lipoprotein cholesterol (non-HDL-C) apolipoprotein A-I (apo A-I), apolipoprotein B (apo B), and triglycerides (TG) from study baseline to Week 8 of Period II; ∉ Percent change in LDL-C from the start of Period III (Week 8) to Week 26; ∉ Percent changes in TC, HDL-C, non-HDL-C, apo A-I, apo B, and TG from the start of Period III to Week 26; ∉ Percent change in LDL-C from study baseline to Week 26; and ∉ Percent changes in TC, HDL-C, non-HDL-C, apo A-I, apo B, and TG from study baseline to Week 26. **Safety:** Safety assessments included adverse events, vital signs, physical examinations, serum pregnancy testing, Tanner

	staging, clinical hematology, blood chemistry, urinalysis, hormones, lipid-soluble vitamins A and E, high-sensitivity C-reactive protein (hsCRP), prothrombin time, and partial thrombin-plastin time.
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 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. For the primary efficacy parameter, the comparison between high-dose colesevelam HCl and placebo was performed first, using the method described above at a 2-sided significance level of 5%. If the first null hypothesis was rejected in favor of high-dose colesevelam HCl, then the second comparison between low-dose colesevelam HCl and placebo was performed, using the same method at a 2-sided significance level of 5%. If the first null hypothesis was not rejected in favor of high-dose colesevelam HCl in the first comparison, then the comparison between low-dose colesevelam HCl and placebo was not performed. If the parametric ANCOVA model was used, least-squares (LS) means, differences of LS means with associated standard errors, 95% confidence intervals for the differences of

	LS means, and p-values were provided. 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. Safety evaluations were based on the safety population, defined as all randomized subjects who had taken randomized study medication for Period II. For Period III, the safety population was defined as all subjects of the safety population who entered into Period III and took at least 1 dose of colesevelam HCl during Period III. The statistical assessments are presented by the actual treatment the subject received. 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, and clotting factors).
Efficacy Results:	Period II (Day 1 to Week 8) Table S1 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. 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. The mean percent change in LDL-C from study baseline (Day 1) 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 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). A moderate increase in TG was observed in the colesevelam HCl 3750 mg group; however, the increase in TG (5.1%) was not significantly higher than the increase in TG

for the placebo group.

Table S1. 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.

Period III (Week 8 to Week 26)
During Period III, clinically meaningful reductions were observed in LDL-C, TC, non-HDL-C, and apo B.

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%) during Period II, followed by the group of subjects who received colesevelam HCl 1875 mg (-11.6%). 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 in LDL-C of -1.9%.

The TC, non-HDL-C, and apo B reductions observed in Period III with colesevelam HCl 3750 mg treatment were similar to the patterns in LDL-C reduction. Subjects treated with colesevelam HCl 3750 mg for 18 weeks during Period III had a -6.3% change in TC, an -8.1% change in non-HDL-C, and an -8.0% change in apo B. As expected, the largest changes in TC (-10.2%), non-HDL-C (-12.8%), and apo B (-11.8%) during Period III occurred in the group of subjects who were treated with placebo during Period II.

From the start of Period III (Week 8) to Week 26 with LOCF, there was a median change in TG of 1.8%, a mean change in HDL-C of 2.9%, and a mean change in apo A-I of -1.6%.

Entire Study (Day 1 to Week 26)
Changes in lipid parameters were evaluated over the entire study. This assessment accounts for cumulative changes from both Period II and Period III. From study baseline (Day 1) to Week 26 with LOCF, the subjects who completed 8 weeks of double-blind treatment and received colesevelam HCl 3750 mg for an additional 18 weeks had a change in LDL-C of -14.0%, a change in TC of -8.0%, a change in non-HDL-C of -11.3%, and a change in apo B of -11.3%. In addition, there was a cumulative mean change in HDL-C of 8.1% and a cumulative mean change in apo A-I of 5.6%.

During the entire 26-week study, 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 (baseline LDL-C 199.6 mg/dL), 7 (12.5%) subjects whose Period II treatment was colesevelam HCl 1875 mg (baseline LDL-C 200.1 mg/dL), and 3 (4.8%) subjects whose Period II treatment was placebo (baseline LDL-C 195.9 mg/dL).

Subgroup Analyses

Period II (Day 1 to Week 8)

Several subgroup analyses were performed for changes in LDL-C during Period II. The subgroup categories evaluated included gender, age, race, body mass index (BMI), Tanner stage, statin status, and dosing schedule. These analyses did not reveal apparent subgroup differences in response to colesevelam HCl therapy. Specifically, following treatment with colesevelam HCl 3750 mg for 8 weeks, the mean percent changes in LDL-C achieved by males and females (-10.1% and -11.3%, respectively), subjects Ò13 years of age and >13 years of age (-11.4% and -10.0%, respectively), subjects at Tanner stage II and Tanner stage III to V (-13.9% and -9.5%, respectively), subjects with BMI ∅25 kg/m^2 and BMI {25 kg/m^2 (-10.9% and -10.4%, respectively), and subjects who took a divided dose and single evening dose (-11.9% and -9.3%, respectively) were of similar magnitude. In terms of LDL-C reduction, meaningful subgroup evaluations of race (Caucasian and non-Caucasian) could not be performed due to the small number of non-Caucasian subjects (167 Caucasian subjects and 24 non-Caucasian subjects). The small number of statin non-naïve subjects (145 statin-naïve subjects and 46 statin non-naïve subjects) also did not allow for meaningful comparisons between statin status subgroups.

Additional subgroup analyses were also performed for changes in LDL-C, TC, TG, HDL-C, non-HDL-C, apo A-I, and apo B during Period II for the subgroup categories of dosing schedule (divided dose [3 tablets noon/3 tablets evening] and single dose [6 tablets evening]) and statin status (statin naïve and statin non-naïve). During Period II, treatment with colesevelam HCl 3750 mg resulted in similar changes in LDL-C when taken either as a divided dose or as a single evening dose (-10.7% and -9.5% for LS mean, respectively). Furthermore, both the divided-dose and single-dose treatment regimens with colesevelam HCl 3750 mg resulted in similar changes in LS mean for TC (-5.8% and -4.5%, respectively), HDL-C (7.5% and 9.1%, respectively), non-HDL-C (-8.2% and -7.7%, respectively), apo A-I (10.5% and 10.8%, respectively), and apo B (-5.7% and -6.7%, respectively). Conclusions could not be made for the subgroup of statin status due to the relatively small number of subjects in the statin non-naïve subgroup (145 statin-naïve subjects and 46 statin non-naïve subjects).

	Period III (Week 8 to Week 26) Subgroup analyses were also performed for changes in LDL-C for Period III statin status subgroups (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. For the Period III statin status subgroups, the largest mean percent reductions in LDL-C were observed in subjects who changed statin dose or added a statin to the colesevelam HCl 3750 mg regimen during Period III (-19.7% in subjects whose Period II treatment was colesevelam HCl 3750 mg, -23.7% in subjects whose Period II treatment was colesevelam HCl 1875 mg, and -40.8% in subjects whose Period II treatment was placebo). For all Period III statin status subgroups, the largest mean percent changes in LDL-C were observed in subjects whose Period II treatment was placebo (-11.0% in the statin-naïve subgroup, -10.1% in the statin-naïve + statin-stable subgroup, and -40.8% in the changed statin dose + added statin subgroup). 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).
Safety Results:	No new safety issues were identified during the course of the study. Period I – Stabilization Period During Period I, 67 (34.5%) subjects had an adverse event. One subject discontinued from the study during Period II due to an adverse event (hypothyroidism) that started during Period I. Period II – Double-Blind Treatment Period Table S2 summarizes TEAEs during Period II of the study by system organ class and preferred term. During Period II, 83 of 194 (42.8%) subjects experienced a TEAE: 26 (40.6%) in the colesevelam HCl 3750 mg group, 31 (47.7%) in the colesevelam HCl 1875 mg group, and 26 (40.0%) in the placebo group. The most frequently reported TEAEs 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 TEAEs 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 TEAEs in the placebo group were ear infection (4.6%), nasopharyngitis (4.6%), and upper respiratory tract infection (4.6%). There were no reported TEAEs of choking or difficulty swallowing tablets.

Table S2. Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – Safety Population for Period II

	Colesevelam HCl 3750 mg n (%)	Colesevelam HCl 1875 mg n (%)	Placebo n (%)
Infections and infestations	12 (18.8)	12 (18.5)	13 (20.0)
Nasopharyngitis	4 (6.3)	4 (6.2)	3 (4.6)
Upper respiratory tract infection	1 (1.6)	1 (1.5)	3 (4.6)
Ear infection	0 (0.0)	1 (1.5)	3 (4.6)
Gastrointestinal viral	0 (0.0)	0 (0.0)	2 (3.1)
Influenza	2 (3.1)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	4 (6.3)	9 (13.8)	7 (10.8)
Vomiting	1 (1.6)	2 (3.1)	1 (1.5)
Diarrhea	1 (1.6)	0 (0.0)	2 (3.1)
Nausea	0 (0.0)	2 (3.1)	1 (1.5)
Respiratory, thoracic, and mediastinal disorders	3 (4.7)	8 (12.3)	1 (1.5)
Rhinitis	0 (0.0)	3 (4.6)	0 (0.0)
Pharyngolaryngeal pain	0 (0.0)	2 (3.1)	0 (0.0)
Nervous system disorders	2 (3.1)	4 (6.2)	5 (7.7)
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	4 (6.3)	3 (4.6)	1 (1.5)
Fatigue	2 (3.1)	3 (4.6)	1 (1.5)
Investigations	2 (3.1)	2 (3.1)	3 (4.6)
Blood CPK increased	1 (1.6)	2 (3.1)	0 (0.0)
Musculoskeletal and connective tissue disorders	1 (1.6)	2 (3.1)	4 (6.2)
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.
CPK = creatine phosphokinase; HCl = hydrochloride.

During Period II, 18 (9.3%) subjects experienced drug-related TEAEs: 4 (6.3%) subjects in the colesevelam HCl 3750 mg group, 7 (10.8%) subjects in the colesevelam HCl 1875 mg group, and 7 (10.8%) subjects in the placebo group. For subjects in both colesevelam HCl groups, the incidence of drug-related gastrointestinal adverse events was higher than

the placebo group: 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. The frequency of any particular type of drug-related TEAE was quite low; 2 or fewer subjects from any treatment group reported a specific drug-related TEAE. 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 TEAE. One (1.5%) subject had drug-related constipation in the colesevelam HCl 1875 mg group during Period II.

No subjects died during Period II. One subject (033-10) in the colesevelam HCl 1875 mg group had 2 treatment-emergent serious adverse events (SAEs) during Period II (contusion and renal hypoplasia). These treatment-emergent SAEs were considered by the investigator to be unrelated to study medication. Four subjects discontinued from the study due to adverse events (fatigue, nausea, hypothyroidism, and diarrhea). All of the subjects who discontinued from the study due to adverse events were being treated with either colesevelam HCl 1875 mg or colesevelam HCl 3750 mg. For 3 of the 4 subjects, the adverse events that led to discontinuation were considered by the investigator to be related to study medication (fatigue, nausea, and diarrhea). For 2 of the 4 subjects, the adverse events that led to discontinuation were gastrointestinal adverse events and related to study medication (nausea and diarrhea).

Period III – Open-Label Treatment Period

During Period III, 93 (50.5%) subjects experienced a TEAE. The most frequently reported TEAEs during Period III were headache (7.6%), nasopharyngitis (5.4%), and upper respiratory tract infection (4.9%). One (1.6%) subject had constipation in Period III.

During Period III, 11 (6.0%) subjects experienced drug-related TEAEs. Eight (4.3%) subjects experienced drug-related gastrointestinal TEAEs. The most common drug-related TEAEs were nausea (3 [1.6%] subjects) and abdominal pain (2 [1.1%] subjects).

No subjects died during Period III. Four subjects had a treatment-emergent SAE (gastroesophageal reflux disease, deliberate poisoning, idiopathic thrombocytopenia purpura, and nasopharyngeal cancer). None of the treatment-emergent SAEs were considered by the investigator to be related to

	study medication. One subject (018-14) who had the treatment-emergent SAE of nasopharyngeal cancer subsequently discontinued from the study during Period III. Five subjects discontinued from the study due to adverse events (nausea, flatulence, nasopharyngeal cancer, decreased appetite [Period II adverse event], and migraine). 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). For 2 of the 5 subjects, the adverse events that led to discontinuation were gastrointestinal adverse events and related to study medication (nausea and flatulence). No important differences in the frequency or types of TEAEs based on gender, age, BMI, statin status, and Tanner stage were noted. The Caucasian subgroup had a higher percentage of subjects with TEAEs than the non-Caucasian subgroup (45.0% vs. 28.0%); however, definitive conclusions cannot be made due to the relatively small number of subjects in the non-Caucasian subgroup (n=25 subjects). No important differences between the race subgroups in the types of TEAEs with colesevelam HCl treatment were noted. No clinically meaningful changes in hormones, vitamins, and clotting factors were noted. Estradiol measurements in female subjects showed significant variability, but the variability was not clinically meaningful and no measurements were outside the normal reference ranges. Subjects demonstrated the expected changes in height-velocity and Tanner staging associated with normal maturation. Height-velocity assessments during the study were similar to both the CDC and WHO reference standards. No unexpected, clinically important differences between the treatment groups in changes in safety laboratory parameters (including hsCRP), vital signs, or physical findings were noted.
Conclusions:	The results of this study indicate that colesevelam HCl is a safe and efficacious lipid-modifying treatment for pediatric subjects diagnosed with heFH who are currently taking a statin or who are naïve to statin therapy. During both the 8-week, double-blind and 18-week, open-label treatment periods, colesevelam HCl 3750 mg treatment resulted in clinically meaningful reductions in LDL-C, TC, non-HDL-C, and apo B, and a clinically meaningful increase in HDL-C.

	For subjects who were on stable background therapy (statin-naïve or statin-stable) and who received colesevelam HCl 3750 mg for 26 weeks, LDL-C levels were maintained. Statin status subgroup analyses demonstrated maintenance of the therapeutic effect of 26-week, high-dose colesevelam HCl treatment. The 3750 mg dose of colesevelam HCl was safe and well tolerated by pediatric subjects. The incidence of gastrointestinal disorders was higher in subjects treated with colesevelam HCl 3750 mg group, but consistent with the expected effects of this treatment regimen and distributed across different types of gastrointestinal adverse events. Constipation, choking, and difficulty swallowing study medication were not issues in this population of pediatric subjects. No effects of colesevelam HCl treatment on growth, sexual maturation, hormone levels, clotting parameter levels, or fat-soluble vitamin absorption were noted. No new safety concerns were identified during the study in this pediatric population.
Date of Report:	8 July 2008