DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-176/SE5-022
Drug Name:	Welchol® (colesevelam hydrochloride) Tablets
Indication(s):	Pediatric Heterozygous Familial Hypercholesterolemia
Applicant:	Daiichi Sankyo, Inc.
Date(s):	Received 12/10/08; user fee (6 months) 06/10/09
Review Priority:	Priority
Biometrics Division:	Division of Biometrics II (HFD-715)
Statistical Reviewer:	Cynthia Liu, MA
Concurring Reviewer(s):	Todd Sahlroot, Ph.D., Statistical Team Leader and Deputy Director of Biometrics II
Medical Division:	Division of Metabolic and Endocrine Products (HFD-510)
Clinical Team:	Eileen Craig, M.D., Medical Reviewer
	Eric Colman, M.D., Medical Team Leader and Deputy Director
Project Manager:	Kati Johnson
Keywords:	NDA review, clinical study, pediatric exclusivity

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Data from the WEL-410 trial have demonstrated that Welchol 3750 mg was effective in lowering LDL-C level from baseline by 12.5% compared to placebo at the end of 8-week double-blind randomized treatment period (primary efficacy endpoint), in pediatric patients aged between 10 to 17 years with heterozygous familial hypercholesterolemia (heFH). Welchol 3750 mg was also associated with statistically significant decreases in TC, non-HDL-C, and apo B, and increases in HDL-C and apo A-I during the 8-week double-blind treatment period. The efficacy was sustained throughout the 18-week open-label treatment period in which all patients received Welchol 3750 mg. Welchol 3750 mg resulted in a numerically increase in triglyceride by Week 8 as well as by Week 26, although the change was not statistically significantly different from placebo.

A borderline significant reduction in LDL-C from baseline at Week 8 was observed in patients taking Welchol 1875 mg compared to placebo (treatment difference = -6.3%). However, there were no statistically significant findings in all other lipids and apolipoproteins when Welchol 1875 mg was compared with placebo.

Data from the WEL-410 trial also showed that treatment effects relative to placebo in mean % change from baseline in LDL-C at Week 8 were consistent between the subgroups of statin (24% of the study population) and naïve (76% of the study population) patients. With such a small sample size for the statin subgroup, the additional LDL-C lowering effect from Welchol, if any, for the statin patients was not evaluable since the study did not have enough power for the assessment.

Overall, < 4% and < 8% of the study population achieved the LDL-C goal of < 110 mg/dL at the end of the double-blind treatment period and the open-label treatment period, respectively, and most of them had statins as their background medications.

Labeling Comments: The following bullets summarize this reviewer's comments for the sponsor's proposed labeling.

- It is misleading to state that the study was a (b) (4), randomized, double-blind, placebo-controlled study because the double-blind and placebo-controlled period was only 8 weeks.
- The mean baseline LDL-C value, 199 mg/dL, occurred at Day 1, (b) (4).
- In Table 9, p-values are presented for all the primary and secondary lipid and apolipoprotein variables. However, the multiplicity testing issue for the secondary variables was not pre-addressed in the protocol and/or statistical analysis plan. To be

consistent with the other tables under the section of clinical studies, a footnote with $p < 0.05$, rather than actual p-values, is recommended.

- It should be more specific that the results presented in Table 9 were based on the ITT population with LOCF.

1.2 Brief Overview of Clinical Studies

Welchol® (colesevelam hydrochloride) Tablets was approved under NDA 21-176 on 05/26/2000 for the reduction of elevated LDL-C in adult patients with primary hyperlipidemia (Fredrickson Type IIa), with a postmarketing commitment agreement to provide pediatric use information. The recommended dose of Welchol® Tablets in adults is 6 tablets once daily or 3 tablets twice daily (3750 mg in total). The sponsor (Daiichi Sankyo, Inc.) is now submitting a supplemental NDA (SE5-022) containing the results from a Phase 4 clinical trial (WEL-410) that was conducted to fulfill the postmarketing commitment and to respond a Pediatric Written Request (Amendment #3) issued on 04/02/2007.

The clinical study (11/05/2005 – 12/18/2007) included an 8-week randomized double-blind placebo-controlled period and an 18-week randomized open-label period, to evaluate the lipid-lowering efficacy and safety of colesevelam hydrochloride (HCl) administered to heFH patients, aged between 10 to 17 years, on a stable dose of statins or treatment naïve to lipid-lowering therapy. In the 8-week double-blind period, subjects were stratified by background statin use (yes or no) and randomized in a 1:1:1 ratio to receive placebo, low-dose colesevelam HCl (1875 mg), or high-dose colesevelam HCl (3750 mg). In the 18-week open-label period, all subjects were treated with the high-dose colesevelam HCl to the goal LDL-C of < 110 mg/dL, along with statin as necessary.

The primary efficacy endpoint was the percentage change from Day 1 (study baseline) in LDL-C at Week 8. The secondary efficacy variables included 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). The study was designed to support the proposed indication for colesevelam HCl which is to be used either alone or as an adjunctive therapy to statin in pediatric subjects with heFH.

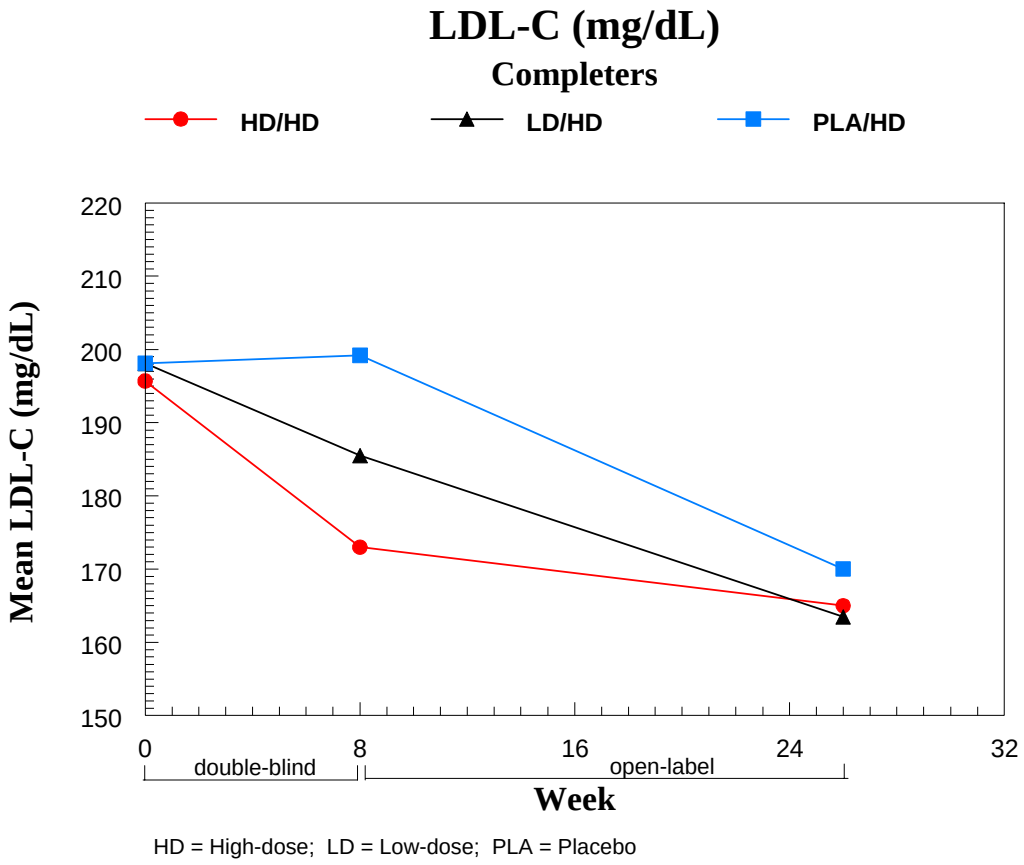
Although the Written Request (WR) asked for approximately equal numbers of males and females in this study, more male subjects (63%) were enrolled than female subjects (37%). Of the 194 randomized subjects, 87% of them were Caucasian and 76% of them were stain treatment naïve at screening.

1.3 Statistical Issues and Findings

In general, there were no serious statistical issues noted by this reviewer and the statistical analyses the sponsor performed met the statistical requirements listed in the WR.

As depicted in Text Figure 1, after 8 weeks of double-blind randomized treatment, the mean LDL-C values based on the ITT population with LOCF were in a dose-response fashion. The mean value at Week 8 was decreased from baseline for both the low- and high-dose colesevelam HCl groups, but was increased for the placebo group. The LS mean % changes from baseline to Week 8 for the high-dose, low-dose, and placebo groups were -10.0%, -3.8%, and +2.5%, respectively and the colesevelam HCl groups were both significantly different from the placebo group, although the significance in the low-dose group was only marginal (Text Table 1). Note that the % decrease in LDL-C from baseline to Week 8 in the low-dose group was only about 4%, which was not an impressive number, considering that 6% has been used previously as a norm for a clinically meaningful reduction.

Text Figure 1



HD = High-dose; LD = Low-dose; PLA = Placebo

Text Table 1 – Efficacy Results for % Change from Baseline to Week 8

(Period II – **ITT Population with LOCF**)

Treatment Difference	High-dose vs. Placebo			Low-dose vs. Placebo		
	LS Mean (SE)	95% CI	p-value	LS Mean (SE)	95% CI	p-value
LDL-C	-12.5 (2.9)	(-18.3, -6.8)	< 0.000	-6.3 (2.9)	(-12.1, -0.6)	0.03
TC	-7.4 (2.2)	(-11.8, -3.0)	0.001	-3.2 (2.2)	(-7.6, 1.2)	0.15
HDL-C	6.1 (2.3)	(1.6, 10.6)	0.008	2.4 (2.3)	(-2.2, 6.9)	0.31
non-HDL-C	-10.9 (2.8)	(-16.3, -5.5)	0.000	-5.1 (2.8)	(-10.6, 0.3)	0.06
Apo A-I	6.9 (2.4)	(2.0, 11.7)	0.006	4.0 (2.4)	(-0.9, 8.8)	0.11
Apo B	-8.3 (2.5)	(-13.2, -3.5)	0.001	-3.4 (2.5)	(-8.2, 1.5)	0.17
TG *	5.1 (76.52)	(-8.8, 20.0)	0.466	6.4 (70.65)	(-6.5, 20.3)	0.34

For LDL-C, TC, HDL-C, non-HDL-C, and TG, the sample sizes for the high-dose, low-dose, and placebo groups were 63, 63, and 65, respectively. For Apo A-I and Apo B, the sample sizes for the high-dose, low-dose, and placebo groups were 61, 62, and 63, respectively.

* TG was not normally distributed. Therefore, the sponsor reported median and interquartile range (IQR) instead of mean and SD or SE, and analyzed the data using Wilcoxon Signed-Rank test.

As also shown in Text Table 1 above, the LS mean % changes in TC, HDL-C, non-HDL-C, apo A-I, and apo B from baseline to Week 8 in the high-dose colesevelam HCl group were all highly significantly different from those in the placebo group, supporting the effectiveness of 3750 mg of colesevelam HCl in lipid management. However, the low-dose colesevelam HCl (1875 mg) did not exhibit such effects. No statistical differences between either colesevelam HCl group and the placebo group in TG were seen after 8 weeks of treatment, although a numerical increase in TG was observed in both the colesevelam HCl groups.

Further mean reductions in LDL-C, TC, non-HDL-C, and apo B occurred in all the 3 study groups after 18 weeks of open-label treatment period with high-dose colesevelam HCl. The reduction was especially evident for the original placebo-treated subjects and was minimal for the original high-dose colesevelam HCl-treated subjects (see Tables 7 and 8 in the main body of the report below). By Week 26, the mean LDL-C, TC, non-HDL-C, and apo B values were similar among the 3 study groups. In other words, regardless of what treatment the subjects received during the 8-week double-blind period, after 18 weeks of the high-dose colesevelam HCl treatment, the differences in efficacy among the study groups seen at Week 8 became minimal at Week 26 (see Text Figure 1 above for the example of LDL-C).

Most of the subjects in the 18-week open-label treatment period stayed with their original statin therapy (23.0%) or were still statin-naïve (61.8%). Approximately 14.0% of the subjects who were statin-naïve in the 8-week double-blind treatment period received a statin therapy along with the high-dose colesevelam HCl during the open-label treatment period.

Text Table 2 below shows that < 10% of the study population achieved the LDL-C goal of <110 mg/dL at the end of Period II (Week 8) and Period III (Week 26), and most of them were taking statin as the background medication.

Text Table 2 – No. of ITT Subjects Achieving the LDL-C Goal of < 110 mg/dL at the end of Periods II and III

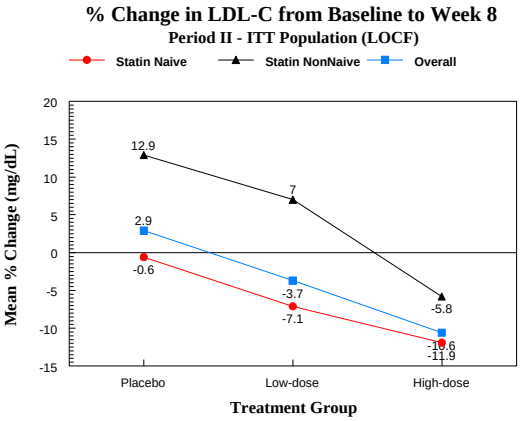
	High-dose	Low-dose	Placebo	Total
By Week 8	5 (3, 2)	2 (2, 0)	0	7/191 (3.7%)
By Week 26	4 (3, 1)	7 (4, 3)	3 (0, 3)	14/178 (7.9%)
(a, b) represents (no. of subjects with statin at screening, no. of subjects without statin at screening).				

Treatment effects on mean % change in LDL-C from baseline to Week 8 were consistent across the subgroups defined by age (≤ 13 years or > 13 years), gender, BMI (< 25 kg/m^2 or ≥ 25 kg/m^2), baseline Tanner stage (II or III-V), and dosing schedule (divided dose [3 tablets at noon/3 tablets in the evening] or single dose [6 tablets in the evening]), as no significant treatment-by-subgroup interactions were observed (all $p > 0.10$). No subgroup analysis of race was performed since the majority of the subjects were Caucasian (87%). These analyses are limited, however, by low statistical power.

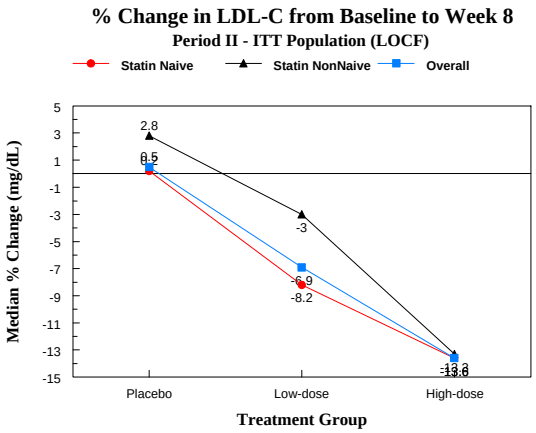
As depicted in Text Figures 2 (mean % change) and 3 (median % change), the LDL-C lowering effects after 8 weeks of double-blind treatment period were all larger across the 3 study groups for the naïve subjects than for the statin subjects. The treatment effects relative to placebo were, however, similar between the 2 subgroups of subjects, as there was no significant treatment-by-subgroup interaction ($p > 0.10$). Note that the results may not be reliable since the sample size for the statin subjects was small (24% of the study population) and they came to the study with lower LDL-C values at baseline (entry criterion was > 130 mg/dL) than the naïve subjects in general (entry criterion was > 160 mg/dL). The additional LDL-C lowering effect by colesevelam HCl for subjects taking statins as their background medications could not be evaluated since the study did not have enough power for the assessment.

In the final discussion and conclusion, the low-dose colesevelam HCl (1875 mg) will not be the focus of this review since (1) it is not a to-be-marketed dose for the proposed indication, (2) its treatment effect in LDL-C lowering was small (5% reduction for the completers), and (3) it did not show nominal significance for any of the secondary endpoints.

Text Figure 2



Text Figure 3



2. INTRODUCTION

2.1 Overview

Welchol® (colesevelam hydrochloride) Tablets was approved under NDA 21-176 on 05/26/2000 for the reduction of elevated low-density lipoprotein cholesterol (LDL-C) in adult patients with primary hyperlipidemia (Fredrickson Type IIa), with a postmarketing commitment agreement to provide pediatric use information. The recommended dose of Welchol® Tablets in adults is 6 tablets once daily or 3 tablets twice daily (3750 mg in total). The sponsor (Daiichi Sankyo, Inc.) is now submitting a supplemental NDA (SE5-022) containing the results from a clinical study (WEL-410) that was conducted to fulfill the postmarketing commitment and to respond a Pediatric Written Request (Amendment #3) issued on 04/02/2007.

The clinical study included a main 8-week, randomized, double-blind, placebo-controlled, 3-parallel-group, multicenter trial, to evaluate the lipid-lowering efficacy and safety of colesevelam hydrochloride (HCl) administered to pediatric patients with heterozygous familial hypercholesterolemia (heFH) on a stable dose of statins or treatment naïve to lipid-lowering therapy. The design highlights of the study are presented below.

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)	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)	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 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) 194 (173)
HCl = hydrochloride; heFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol.					

2.2 Data Sources

The clinical study report and electronic data files are located in the sub-folders of EDR **\\CDSESUB1\EVSPROD\NDA021176\0000**. The quality of the data sets was generally satisfactory.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

Study WEL-410 (11/05/2005 – 12/18/2007) was a Phase 4, 32-week, multicenter (41 sites), multinational (12 countries) trial, conducted in children aged between 10 to 17 years, who had heFH and were on a stable dose of a pediatric-approved statin monotherapy (i.e., atorvastatin, simvastatin, pravastatin, or lovastatin) or naïve to lipid-lowering treatment therapy. The study consisted of 3 periods: 4 weeks of stabilization phase (Period I), 8 weeks of double-blind treatment phase (Period II), and 18 weeks of open-label treatment phase (Phase III). Subjects returned for a follow-up visit 2 weeks after the end of Phase III. In Period I, all subjects were single-blinded and received 6 placebo tablets per day. In Period II, subjects were stratified by background statin therapy (any or none) and randomized in a 1:1:1 ratio to 1 of 3 treatment groups: placebo, low-dose colesevelam HCl (1875 mg = 3 x 625-mg tablet), or high-dose colesevelam HCl (3750 mg = 6 x 625-mg tablet). In Period III, all subjects were treated with the high-dose colesevelam HCl (3750 mg) to the goal LDL-C of <110 mg/dL, along with statin as necessary. If the LDL-C goal was not achieved, subjects were given an escalating dose of statin at the discretion of the investigator. Note that patients took 6 tablets either once a day or in divided doses of 3 tablets in the morning and 3 tablets in the evening with meals. The following table outlines the treatments in each of the 3 periods.

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

The primary efficacy endpoint was the percentage change from Day 1 (baseline) in LDL-C at Week 8 of Period II. The other efficacy endpoints included percentage 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 baseline to Week 8 of Period II; percentage changes in LDL-C, TC, HDL-C, non-HDL-C, apo A-I, apo B, and TG from Week 8 to Week 26 of Period III; and percentage changes in LDL-C, TC, HDL-C, non-HDL-C, apo A-I, apo B, and TG from baseline to Week 26. All the lipids and apolipoproteins were measured on Day 1, Week 8, and Week 26 (or upon early withdrawal). Additional measures at Week -4 and Week 17 were made for the lipids only.

3.1.2 Statistical Methods

The primary efficacy endpoint, percentage change in LDL-C from baseline to Week 8, was analyzed by the sponsor using an analysis of covariance (ANCOVA) model with treatment as a factor and baseline LDL-C value as a covariate. For the colesevelam HCl and placebo group comparisons, a step-down sequential testing approach was utilized. That is, the comparison between the low-dose colesevelam HCl and placebo was *only* conducted when the high-dose colesevelam HCl was shown to be significantly different from the placebo first in mean percentage change from baseline in LDL-C at Week 8. Note that the sponsor did not include the stratifying variable (statin use [yes or no] at screening) in the model, which was suggested in the Written Request (WR).

A similar model was used for the analyses of TC, HDL-C, non-HDL-C, apo A-I, and apo B. The Wilcoxon signed-rank test was used for the analysis of TG. Note that no p-value adjustments were made for multiplicity by the sponsor for the analyses of the secondary endpoints.

The primary analysis set was based on the intention-to-treat (ITT) population with last observation carried forward (LOCF) for missing values, which consisted of all randomized subjects who had taken at least 1 dose of the study medication and had a valid baseline and post-baseline lipid measurements for Period II. The ITT population for Period III comprised all the ITT subjects in Period II who had taken at least 1 dose of the Period III study medication and had at least 1 valid lipid measurement in Period III. All the efficacy analyses were evaluated at a 2-sided 5% significance level.

3.1.3 Subject Disposition

A total of 194 subjects were randomized into Period II: 65, 65, and 64 subjects in the placebo, low-dose colesevelam HCl, and high-dose colesevelam HCl groups, respectively. The overall withdrawal rate at the end of Period II was 4.1% (= 8/194), with the low-dose group showing the highest dropout rate among the 3 study groups (Table 1, copied from the sponsor's report). There were 2 subjects who discontinued after completing Period II but before entering Period III due to withdrawn consent and lost to follow-up. The overall withdrawal rate at the end of Period III was 10.8% (= 21/194), with the low-dose group again showing the highest dropout rate in Period III (Table 2, copied from the sponsor's report). The high withdrawal rate in the low-dose group in both periods and overall was mostly due to adverse events. In summary, 186 subjects (60 to 64 per group) completed Period II and 173 subjects (54 to 60 per group) completed Period III, which met the requirement of the WR.

Table 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

Table 2 – Subject Disposition – Period III – Randomized Population

	Treatment During Period II			Period III
Disposition	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

The ITT population for Period II comprised 65 placebo, 63 low-dose colesevelam HCl, and 63 high-dose colesevelam HCl treated subjects (total = 191). The ITT population for Period III included 178 ITT subjects from Period II.

3.1.4 Demographic and Baseline Characteristics

As shown in Table 3 (copied from the sponsor's report), the demographic and baseline characteristics of the randomized population were similar among the 3 study groups. The overall mean age at screening (when subjects provided informed consent) was 14 years, ranging from 10 to 17 years as required by the WR. However, 3 subjects became 18 years old at randomization. There were more male (63%) than female (37%) subjects enrolled, although the WR asked for approximately equal numbers of males and females in this study. Of the 194 randomized subjects, 87% of them were Caucasian and 76% of them were stain treatment naïve at screening. The overall mean BMI was 22.5 kg/m^2 at screening. Except for 1 female low-dose subject who had a Tanner stage II at screening, all others had a Tanner stage at least III at screening.

The overall mean ± SD LDL-C at baseline (Day 1 of Period II) was 199.1 ± 45.7 mg/dL, ranging from 101.9 to 347.9 mg/dL. For the statin subjects, the mean ± SD LDL-C at baseline was 164.2 ± 33.7 mg/dL, ranging from 101.9 to 245.2 mg/dL. For the naïve subjects, the mean ± SD LDL-C at baseline was 210.3 ± 43.4 mg/dL, ranging from 129.0 to 347.9 mg/dL. The LDL-C inclusion criterion was > 130 mg/dL at screening for statin subjects and > 160 mg/dL at screening for naïve subjects. The data showed that a few subjects had their LDL-C levels reduced after 4 weeks of the stabilization period (Period I).

Table 3 – 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

Table 3 – Demographic and Baseline Characteristics – Randomized Population (Continued)

Efficacy Parameter	Colesevelam HCl 3750 mg (N = 64)	Colesevelam HCl 1875 mg (N = 65)	Placebo (N = 65)
LDL-C (mg/dL)			
n	64	65	65
Mean (SD)	201.4 (50.26)	199.2 (43.68)	196.7 (43.56)
p-value [1]		0.8452	
HDL-C (mg/dL)			
n	64	65	65
Mean (SD)	45.5 (9.78)	49.2 (12.91)	45.2 (9.49)
p-value [1]		0.0689	
Total Cholesterol (mg/dL)			
n	64	65	65
Mean (SD)	265.6 (51.78)	267.6 (45.34)	260.9 (46.77)
p-value [1]		0.7165	
Triglycerides (mg/dL)			
n	64	65	65
Median (IQR)	93.8 (43.02)	96.3 (53.63)	95.2 (33.37)
p-value [1]		0.9479	
Non-HDL-C			
n	64	65	65
Mean (SD)	220.1 (52.21)	218.4 (43.84)	215.7 (46.66)
p-value [1]		0.8690	
Apolipoprotein A-I (mg/dL)			
n	63	65	63
Mean (SD)	137.0 (24.02)	143.3 (27.53)	136.7 (23.32)
p-value [1]		0.2499	
Apolipoprotein B (mg/dL)			
n	63	65	63
Mean (SD)	161.4 (33.36)	156.6 (27.14)	158.0 (33.58)
p-value [1]		0.6752	

1. P-values are presented for comparing baseline characteristics of 3 treatment groups.
HCl = hydrochloride; HDL-C = high-density lipoprotein cholesterol; IQR = interquartile range;
LDL-C = low-density lipoprotein cholesterol; non-HDL-C = non-high-density lipoprotein cholesterol; SD = standard deviation.
Source: Post-text Table 14.1.7

As expected and shown in Figures 1-4, across the 3 treatment groups, the statin subjects had lower mean LDL-C, TC, non-HDL-C, and apo B values at baseline than the naïve subjects. As presented in Figures 5-7, across the 3 treatment groups, the statin and naïve subjects had similar mean HDL-C, apo A-I, and TG values at baseline.

Figure 1

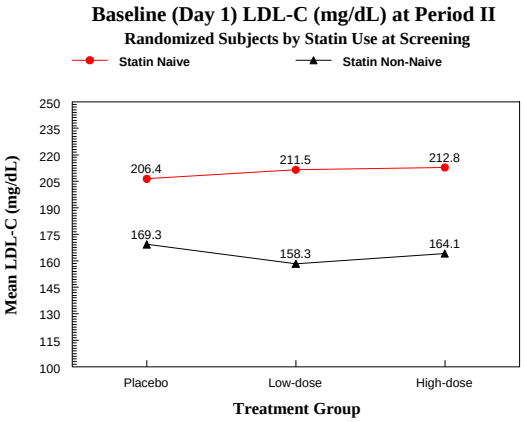


Figure 2

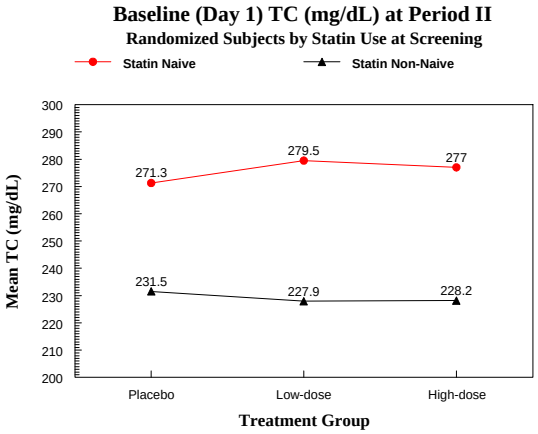


Figure 3

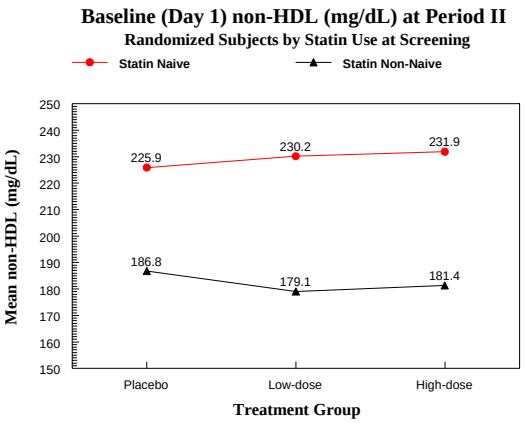


Figure 4

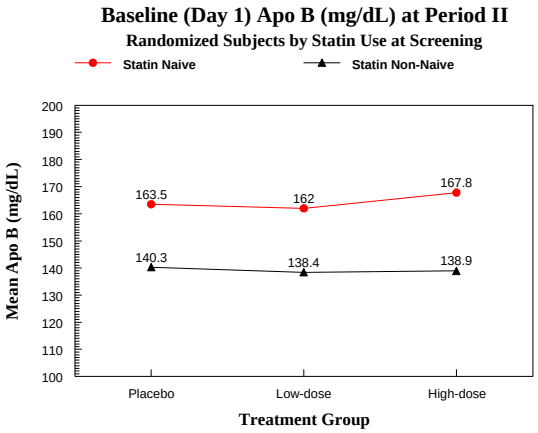


Figure 5

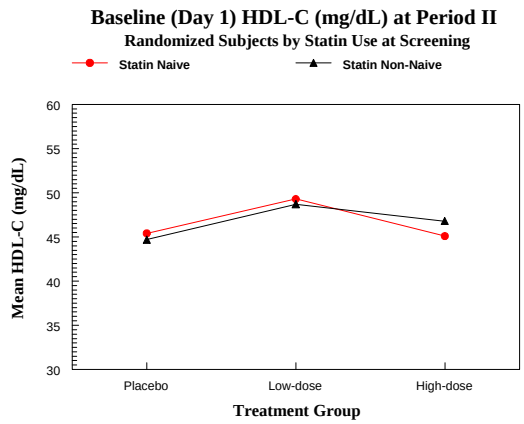


Figure 6

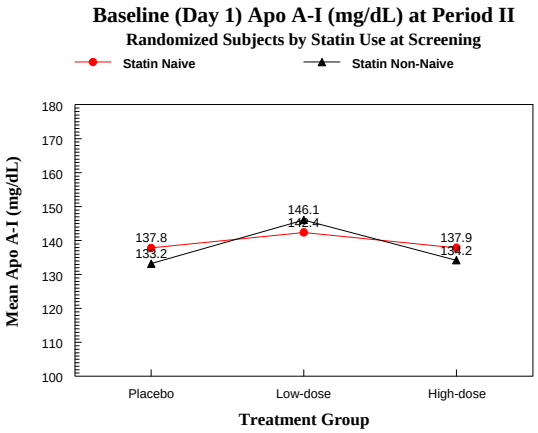
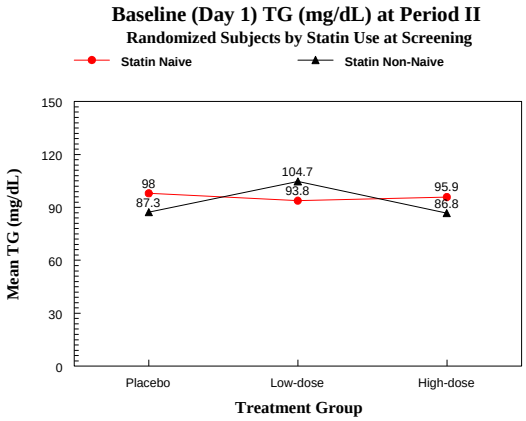


Figure 7



3.1.5 Efficacy Results and Discussion

Low-Density Lipoprotein Cholesterol (LDL-C). As shown in Table 4 (copied from the sponsor's report), the mean % changes in LDL-C from baseline to Week 8 based on the ITT population with LOCF (primary efficacy endpoint) were in a dose-response fashion. They were +2.9%, -3.7%, and -10.6% for the placebo, low-dose, and high-dose colesevelam HCl groups, respectively. The LS mean % change in the high-dose group was highly significantly different from that in the placebo group (treatment difference = -12.5%, $p < 0.0001$). However, the low-dose group was only marginally significantly different from the placebo (treatment different = -6.3%, $p = 0.0307$) according to the sponsor's sequential testing approach. When this reviewer used Dunnett's many-on-one t-test for the group comparisons, the LS mean % change in the low-dose group was not statistically different from that in the placebo group ($p = 0.0567$).

Table 4 – Summary Results for LDL-C (Period II – **ITT Population**)

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

This reviewer further analyzed the data from the completers and found that the LS mean % change from baseline in LDL-C at Week 8 in the low-dose group was significantly different from that in the placebo group at a lower p-value (Table 5, p = 0.0097). The significance was mainly caused by the exclusion of Subject No. 012-09 who was withdrawn due to non-compliance (see Table 1 above). The patient had baseline LDL-C at 101.9 mg/dL and Week 8 LDL-C at 183.0 mg/dL, resulting in a 79.5% increase from baseline. Nevertheless, the 5% reduction in LDL-C in the low-dose completers after 8 weeks of treatment was not a striking number, since a clinically meaningful reduction is often considered as ≥6%.

Table 5 – Summary Results for LDL-C (Period II – **Completers**)

Treatment Group	N	Day 1 Baseline Mean (SD)	Week 8 Mean (SD)	Percent Change From Baseline	
				Mean (SD)	LS Mean (SE)
Colesevelam HCl 3750 mg	62	202.7 (50.4)	178.1 (45.8)	-10.8 (19.4)	-10.3 (2.0)
Colesevelam HCl 1875 mg	60	200.6 (42.6)	187.8 (37.3)	-5.1 (15.3)	-5.0 (2.0)
Placebo	64	196.5 (43.9)	198.6 (36.3)	3.0 (16.6)	2.5 (2.0)
			Treatment Difference		
Treatment Comparison			LS Mean (SE)	95% CI	p-value
Colesevelam HCl 3750 mg vs. Placebo			-12.8 (2.8)	(-18.4, -7.2)	< 0.0001
Colesevelam HCl 1875 mg vs. Placebo			-7.5 (2.9)	(-13.1, -1.8)	0.0097
The comparison of low-dose vs. placebo by Dunnett's t-test showed p = 0.0184.					

Similar findings were observed when statin status (the stratifying factor) was added to the statistical model for both the ITT (with LOCF) and completer populations (see Appendix I).

Of the 191 ITT subjects in Period II, only 7 of them (3.7%) achieved the LDL-C goal of <110 mg/dL at the end of the period: 5 from the high-dose group (3 with statin and 2 without statin at screening) and 2 from the low-dose group (both with statin).

Secondary Efficacy Endpoints (Period II). As shown in Appendix II and Figures 8-12, the mean % changes in TC, HDL-C, non-HDL-C, apo A-I, and apo B from baseline to Week 8 based on the ITT population with LOCF were all in a dose-response fashion. The LS mean % changes of the high-dose groups in these endpoints were all significantly different from those of the placebo groups (Table 6). However, the low-dose groups in these cases did not show any statistical difference when compared with placebo. For TG, since the data were not normally distributed, the sponsor employed the Wilcoxon Signed-Rank test and found no statistically significant differences between either colesevelam HCl dose group and the placebo group in median % change from baseline to Week 8 in this case (Figure 13). A parametric test run by this reviewer also revealed the same findings.

Figure 8

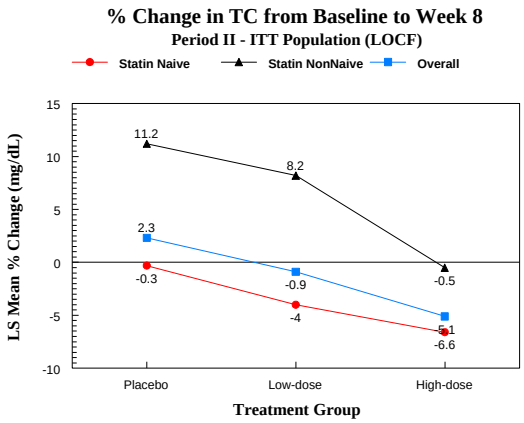


Figure 9

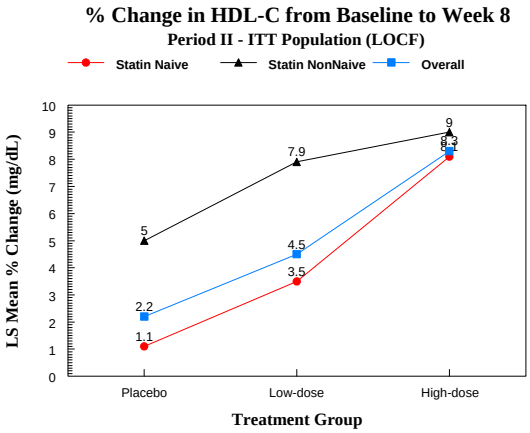


Figure 10

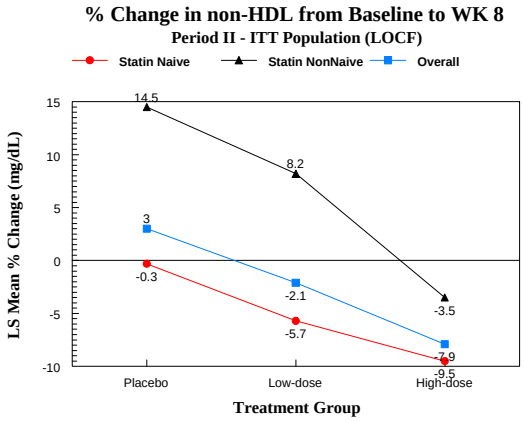


Figure 11

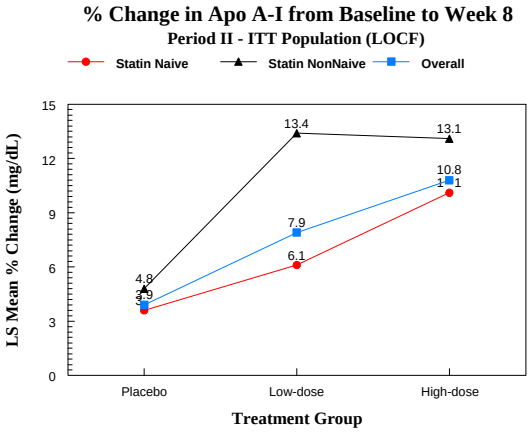


Figure 12

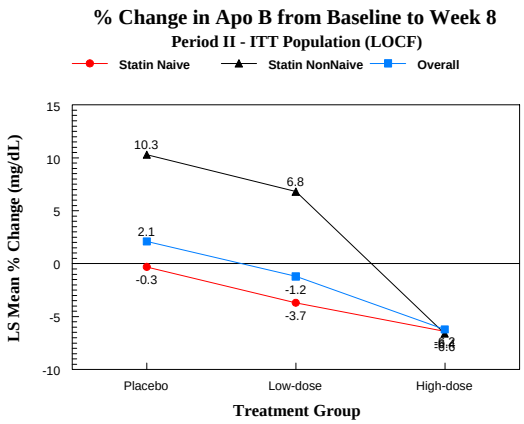


Figure 13

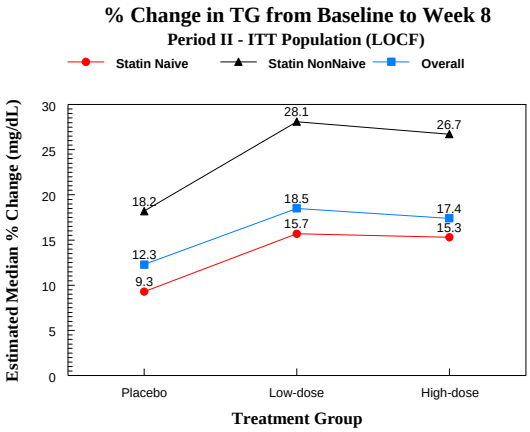


Table 6 – Summary Results of % Change from Baseline to Week 8 (LOCF) for Secondary Efficacy Endpoints (Period II – **ITT Population**)

Treatment Difference	High-dose vs. Placebo			Low-dose vs. Placebo		
	LS Mean (SE)	95% CI	p-value	LS Mean (SE)	95% CI	p-value
TC	-7.4 (2.2)	(-11.8, -3.0)	0.001	-3.2 (2.2)	(-7.6, 1.2)	0.15
HDL-C	6.1 (2.3)	(1.6, 10.6)	0.008	2.4 (2.3)	(-2.2, 6.9)	0.31
non-HDL-C	-10.9 (2.8)	(-16.3, -5.5)	0.000	-5.1 (2.8)	(-10.6, 0.3)	0.06
Apo A-I	6.9 (2.4)	(2.0, 11.7)	0.006	4.0 (2.4)	(-0.9, 8.8)	0.11
Apo B	-8.3 (2.5)	(-13.2, -3.5)	0.001	-3.4 (2.5)	(-8.2, 1.5)	0.17
TG *	5.1 (76.52)	(-8.8, 20.0)	0.466	6.4 (70.65)	(-6.5, 20.3)	0.34

For TC, HDL-C, non-HDL-C, and TG, the sample sizes for the high-dose, low-dose, and placebo groups were 63, 63, and 65, respectively. For Apo A-I and Apo B, the sample sizes for the high-dose, low-dose, and placebo groups were 61, 62, and 63, respectively.

* TG was not normally distributed. Therefore, the sponsor reported median and interquartile range (IQR) instead of mean and SD or SE, and analyzed the data using Wilcoxon Signed-Rank test. Also see Appendix II.

Similar results were also observed for these secondary efficacy endpoints when the completers were analyzed, except that the low-dose group showed a marginally significant difference when compared with the placebo for non-HDL-C (p = 0.0224).

Secondary Efficacy Endpoints (Period III). As stated in Section 3.1.1 above, all subjects in Period III received the high-dose colesevelam HCl (3750 mg) along with statins as necessary. After 18 weeks of open-label treatment period, the mean % changes in LDL-C, TC, HDL-C, non-HDL-C, apo A-I, and apo B from Week 8 (baseline for Period III) to Week 26 based on the ITT population with LOCF were -9.3%, -6.3%, +2.9%, -8.1%, -1.6%, and -8.0%, respectively. Note that the mean apo A-I value at Week 26 was lower than that at Week 8. The median % change from Week 8 in TG at Week 26 was +1.8%.

As shown in Tables 7 and 8 (copied from the sponsor's report), after 18 weeks of the high-dose colesevelam HCl treatment, the mean lipid and apolipoprotein values were similar among the groups of subjects who received the placebo, low-dose, and high-dose colesevelam HCl in Period II. As a result, the placebo group showed the greatest mean % decrease from Week 8, followed by the low-dose group, in LDL-C, TC, non-HDL-C, and apo B at Week 26. The high-dose group in these cases all had a minimal mean % decrease (e.g., -1.9% in LDL-C), implying that it was able to maintain the efficacy obtained in Period II.

Table 7 – Summary Results for Lipid Parameters (Period III – **ITT Population**)

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

Table 8 – Summary Results for Apolipoproteins Parameters (Period III – **ITT Population**)

Lipid Parameter Treatment Group	n	Week 8 Baseline Mean (SD)	Week 26 With LOCF Mean (SD)	Percent Change Mean (SD)
Apo A-I				
Colesevelam HCl 3750 mg in Period II	57	152.5 (23.36)	145.5 (26.54)	-4.2 (12.33)
Colesevelam HCl 1875 mg in Period II	52	151.8 (28.20)	148.7 (26.01)	-0.8 (15.24)
Placebo in Period II	54	140.4 (21.11)	139.1 (21.07)	0.3 (15.74)
Colesevelam HCl 3750 mg in Period III	163	148.3 (24.82)	144.4 (24.85)	-1.6 (14.51)
Apo B				
Colesevelam HCl 3750 mg in Period II	57	146.8 (29.48)	139.5 (31.93)	-3.9 (16.61)
Colesevelam HCl 1875 mg in Period II	52	150.7 (23.25)	137.1 (30.97)	-8.6 (17.10)
Placebo in Period II	54	156.5 (27.05)	137.1 (30.81)	-11.8 (16.41)
Colesevelam HCl 3750 mg in Period III	163	151.3 (26.95)	137.9 (31.09)	-8.0 (16.92)

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.
apo A-I = apolipoprotein A-I; apo B = apolipoprotein B; HCl = hydrochloride; LOCF = last observation carried forward; SD = standard deviation.
Sources: Post-text Tables 14.2.17 and 14.2.18

As shown in Table 9, about 14.0% of the subjects in Period III who were statin-naïve in Period II received a statin therapy in addition to the high-dose colesevelam HCl regimen according to the investigators' discretion. Most of the subjects were still either statin-naïve (61.8%) or statin-stable (23.0%) in Period III. Very few statin subjects had their statin doses changed in this period. However, that did not mean that the majority of the statin subjects were on their maximum statin doses.

Table 9 – Change in Statin Use Status from Period II to Period III (**ITT Population** for Period III)

	Treatment During Period II			Period III
	High-dose (N = 60) n (%)	Low-dose (N = 56) n (%)	Placebo (N = 62) n (%)	High-dose (N = 178) n (%)
Subjects naïve to lipid-lowering medication				
No change	36 (60.0)	37 (66.1)	37 (59.7)	110 (61.8)
Statin therapy added	10 (16.7)	6 (10.7)	9 (14.5)	25 (14.0)
Subjects non-naïve to lipid-lowering medication				
No change	14 (23.3)	11 (19.6)	16 (25.8)	41 (23.0)
Statin dose changed	0	2 (3.6)	0	2 (1.1)
The numbers were obtained based on the data set the sponsor submitted via e-mail on 04/22/2009.				

Of the 178 ITT subjects in Period III, 14 of them (7.9%) achieved the LDL-C goal of < 110 mg/dL at the end of the period: 4 from the high-dose group in Period II (3 with statin and 1

without statin at screening), 7 from the low-dose group in Period II (4 with statin and 3 without statin at screening), and 3 from the placebo group in Period II (all without statin at screening).

Secondary Efficacy Endpoints (Entire Study – Period II + Period III). After 8 weeks of double-blind and 18 weeks of open-label treatment periods, the overall mean % changes in LDL-C, TC, HDL-C, non-HDL-C, apo A-I, and apo B from Day 1 (baseline for the entire study) to Week 26 based on the ITT population with LOCF were -14.0%, -8.0%, +8.1%, -11.3%, +5.6%, and -11.3%, respectively. The overall median % change from Day 1 in TG at Week 26 was +11.5%.

As pointed out earlier, after 18 weeks of the high-dose colesevelam HCl treatment, the mean lipid and apolipoprotein values were similar among the groups of subjects who received the placebo, low-dose, and high-dose colesevelam HCl in Period II (Tables 10 and 11, copied from the sponsor's report). Since the Day 1 (baseline) mean values were also similar, the mean % changes from Day 1 to Week 26 were then similar as well. That is, regardless of what treatment the subjects received during Period II, after 18 weeks of the high-dose treatment, the differences in efficacy among the study groups seen at the end of Period II became minimal in Period III.

Table 10 – Summary Results for Apolipoproteins Parameters (Entire Study – **ITT Population**)

Lipid Parameter Treatment Group	n	Day 1 Baseline Mean (SD)	Week 26 With LOCF Mean (SD)	Percent Change Mean (SD)
Apo A-I				
Colesevelam HCl 3750 mg in Period II	57	138.1 (24.66)	146.6 (26.09)	7.2 (15.34)
Colesevelam HCl 1875 mg in Period II	52	143.5 (26.53)	148.7 (26.01)	4.9 (14.86)
Placebo in Period II	52	135.6 (24.02)	140.2 (20.55)	4.7 (12.95)
Colesevelam HCl 3750 mg in Period III	161	139.0 (25.13)	145.2 (24.52)	5.6 (14.40)
Apo B				
Colesevelam HCl 3750 mg in Period II	57	158.5 (30.94)	138.9 (32.35)	-11.2 (17.86)
Colesevelam HCl 1875 mg in Period II	52	155.9 (24.56)	137.1 (30.97)	-11.3 (18.71)
Placebo in Period II	52	157.0 (33.98)	137.2 (31.37)	-11.4 (16.86)
Colesevelam HCl 3750 mg in Period III	161	157.2 (29.94)	137.8 (31.41)	-11.3 (17.72)

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.
apo A-I = apolipoprotein A-I; apo B = apolipoprotein B; HCl = hydrochloride; LOCF = last observation carried forward; SD = standard deviation.
Sources: Post-text Tables 14.2.24 and 14.2.25

Table 11 – Summary Results for Lipid Parameters (Entire Study – **ITT Population**)

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

3.2 Evaluation of Safety

In consultation with the reviewing medical officer, there were no aspects of safety that required review by a statistician. See Dr. Eileen Craig's report for safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, and Age

Treatment effects on mean % change in LDL-C from Day 1 to Week 8 (Period II) were consistent across the subgroups defined by age (≤ 13 years or > 13 years) and gender, as no significant treatment-by-subgroup interactions were observed (both $p > 0.10$). Since 87.4%

of the ITT subjects in Period II were Caucasian, no meaningful comparison between subgroups of race could be done. Nevertheless, the mean % changes in LDL-C from Day 1 to Week 8 of the 3 study groups for the Caucasian population exhibited similar magnitudes to the ones for the whole study population. The summary statistics by these subgroups are presented in Appendix III.

4.2 Other Special/Subgroup Populations

Treatment effects on mean % change in LDL-C from Day 1 to Week 8 (Period II) were consistent across the subgroups defined by baseline BMI (< 25 kg/m^2 or ≥ 25 kg/m^2), baseline Tanner stage (II or III-V), and dosing schedule (divided dose [3 tablets at noon/3 tablets in the evening] or single dose [6 tablets in the evening]), as no significant treatment-by-subgroup interactions were observed (both $p > 0.10$). The summary statistics by these subgroups are presented in Appendix III.

Treatment effects on mean % change in LDL-C from Day 1 to Week 8 (Period II) were also consistent across the subgroups defined by statin use at screening (yes or no), as no significant treatment-by-subgroup interaction was observed ($p > 0.10$). Note that as shown in Table 12 below (copied from the sponsor's report), the LDL-C lowering effects across the 3 study groups after 8 weeks of double-blind treatment period were all larger for the naïve subjects than for the statin subjects. In fact, the Week 8 mean LDL-C values in the low-dose and placebo groups were both increased from their baselines for the statin subjects. The reviewer found that this perplexing finding was probably due to the large variation in the % change data in the small number of statin subjects. As one can see in Table 12, across the 3 study groups, the standard deviations of the % changes for the statin subjects were all much larger than those for the naïve subjects. Therefore, median % changes in LDL-C from Day 1 to Week 8 were evaluated. They were -13.3%, -3.0%, and +2.8% for the high-dose, low-dose, and placebo groups, respectively, for the statin subjects, and -13.6%, -8.2%, and +0.2%, respectively, for the naïve subjects.

Table 13 (copied from the sponsor's report) showed the mean % changes in LDL-C from Week 8 (baseline for Period III) to Week 26 for the subgroups of statin-naïve, statin-naïve + statin-stable, and changed statin dose + added statin subjects. As discussed for the whole study population, across the stain subgroups in Period III, the largest mean % reduction in LDL-C was from the placebo-treated subjects in Period II, followed by the low-dose-treated subjects. In addition, among the statin subgroups in Period III, the largest mean % reduction in LDL-C occurred in the subgroup of subjects who changed their statin dose or added a statin therapy in addition to the high-dose colesevelam HCl according to the investigators' discretion.

Table 12 – Summary Results for LDL-C by Statin Status Subgroups (Period II – **ITT Population**)

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

Table 13 – Summary Results for LDL-C by Statin Status Subgroups (Period III – **ITT Population**)

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

Note: Numbers of patients with statin in each period were not consistent among the sponsor's tables and data set. However, the discrepancies were small, which should not have any major impact on the results.

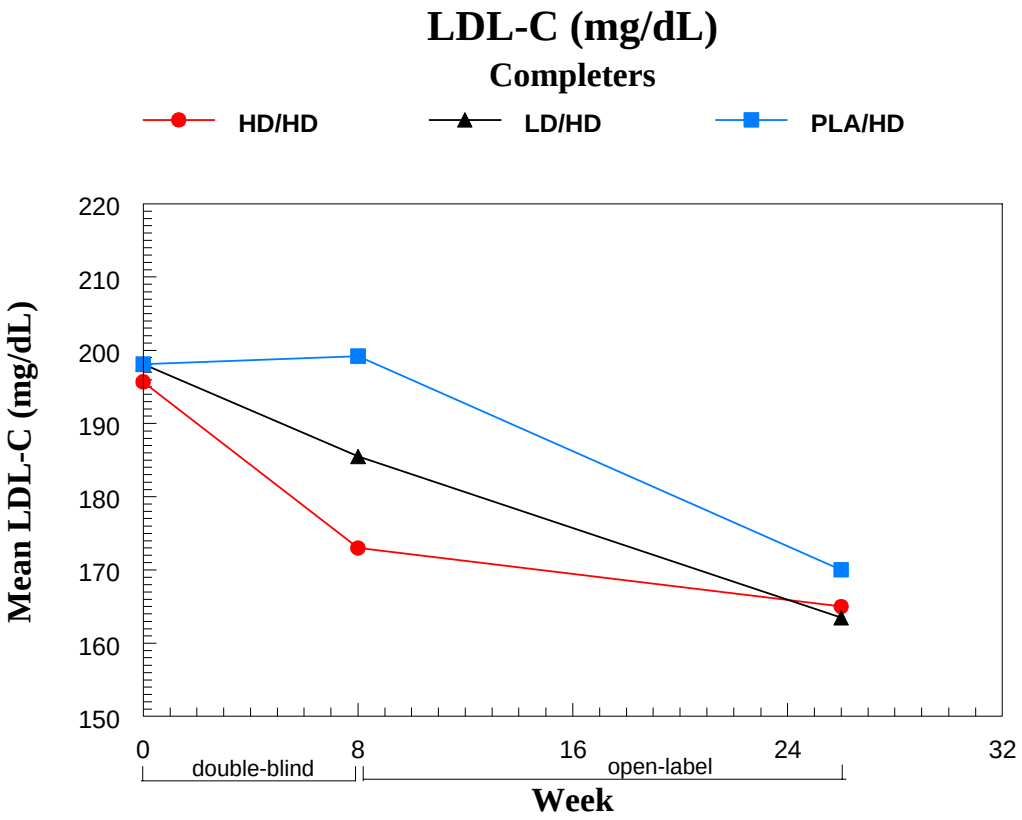
5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

In general, there were no serious statistical issues noted by this reviewer and the statistical analyses the sponsor performed met the statistical requirements listed in the WR.

As depicted in Figure 14, after 8 weeks of double-blind randomized treatment, the mean LDL-C values based on the ITT population with LOCF were in a dose-response fashion. The mean value at Week 8 was decreased from baseline for both the low- and high-dose colesevelam HCl groups, but was increased for the placebo group. The LS mean % changes from baseline to Week 8 for the high-dose, low-dose, and placebo groups were -10.0%, -3.8%, and +2.5%, respectively and the colesevelam HCl groups were both significantly different from the placebo group, although the significance in the low-dose group was only marginal (Table 14). Note that the % decrease in LDL-C from baseline to Week 8 in the low-dose group was only about 4%, which was not an impressive number, considering that 6% has been used previously as a norm for a clinically meaningful reduction.

Figure 14



HD = High-dose; LD = Low-dose; PLA = Placebo

As also shown in Table 14, the LS mean % changes in TC, HDL-C, non-HDL-C, apo A-I, and apo B from baseline to Week 8 in the high-dose colesevelam HCl group were all highly significantly different from those in the placebo group, supporting the effectiveness of 3750

mg of colesevelam HCl in lipid management. However, the low-dose colesevelam HCl (1875 mg) did not exhibit such effects. No statistical differences between either colesevelam HCl group and the placebo group in TG were seen after 8 weeks of treatment, although a numerical increase in TG was observed in both the colesevelam HCl groups.

Table 14 – Efficacy Results for % Change from Baseline to Week 8 (Period II – **ITT Population with LOCF**)

Treatment Difference	High-dose vs. Placebo			Low-dose vs. Placebo		
	LS Mean (SE)	95% CI	p-value	LS Mean (SE)	95% CI	p-value
LDL-C	-12.5 (2.9)	(-18.3, -6.8)	< 0.000	-6.3 (2.9)	(-12.1, -0.6)	0.03
TC	-7.4 (2.2)	(-11.8, -3.0)	0.001	-3.2 (2.2)	(-7.6, 1.2)	0.15
HDL-C	6.1 (2.3)	(1.6, 10.6)	0.008	2.4 (2.3)	(-2.2, 6.9)	0.31
non-HDL-C	-10.9 (2.8)	(-16.3, -5.5)	0.000	-5.1 (2.8)	(-10.6, 0.3)	0.06
Apo A-I	6.9 (2.4)	(2.0, 11.7)	0.006	4.0 (2.4)	(-0.9, 8.8)	0.11
Apo B	-8.3 (2.5)	(-13.2, -3.5)	0.001	-3.4 (2.5)	(-8.2, 1.5)	0.17
TG *	5.1 (76.52)	(-8.8, 20.0)	0.466	6.4 (70.65)	(-6.5, 20.3)	0.34

For LDL-C, TC, HDL-C, non-HDL-C, and TG, the sample sizes for the high-dose, low-dose, and placebo groups were 63, 63, and 65, respectively. For Apo A-I and Apo B, the sample sizes for the high-dose, low-dose, and placebo groups were 61, 62, and 63, respectively.

* TG was not normally distributed. Therefore, the sponsor reported median and interquartile range (IQR) instead of mean and SD or SE, and analyzed the data using Wilcoxon Signed-Rank test.

Further mean reductions in LDL-C, TC, non-HDL-C, and apo B occurred in all the 3 study groups after 18 weeks of open-label treatment period with high-dose colesevelam HCl. The reduction was especially evident for the original placebo-treated subjects and was minimal for the original high-dose colesevelam HCl-treated subjects (see Tables 7 and 8 above). By Week 26, the mean LDL-C, TC, non-HDL-C, and apo B values were similar among the 3 study groups. In other words, regardless of what treatment the subjects received during the 8-week double-blind period, after 18 weeks of the high-dose colesevelam HCl treatment, the differences in efficacy among the study groups seen at Week 8 became minimal at Week 26 (see Figure 14 above for the example of LDL-C).

Most of the subjects in the 18-week open-label treatment period stayed with their original statin therapy (23.0%) or were still statin-naïve (61.8%). Approximately 14.0% of the subjects who were statin-naïve in the 8-week double-blind treatment period received a statin therapy along with the high-dose colesevelam HCl during the open-label treatment period.

Table 15 below shows that < 10% of the study population achieved the LDL-C goal of <110 mg/dL at the end of Period II (Week 8) and Period III (Week 26), and most of them were taking statin as the background medication.

Table 15 – No. of ITT Subjects Achieving the LDL-C Goal of < 110 mg/dL at the end of Periods II and III

	High-dose	Low-dose	Placebo	Total
By Week 8	5 (3, 2)	2 (2, 0)	0	7/191 (3.7%)
By Week 26	4 (3, 1)	7 (4, 3)	3 (0, 3)	14/178 (7.9%)
(a, b) represents (no. of subjects with statin at screening, no. of subjects without statin at screening).				

Treatment effects on mean % change in LDL-C from baseline to Week 8 were consistent across the subgroups defined by age (≤ 13 years or > 13 years), gender, BMI (< 25 kg/m^2 or ≥ 25 kg/m^2), baseline Tanner stage (II or III-V), and dosing schedule (divided dose [3 tablets at noon/3 tablets in the evening] or single dose [6 tablets in the evening]), as no significant treatment-by-subgroup interactions were observed (all p > 0.10). No subgroup analysis of race was performed since the majority of the subjects were Caucasian (87%). These analyses are limited, however, by low statistical power.

As depicted in Figures 15 (mean % change) and 16 (median % change), the LDL-C lowering effects after 8 weeks of double-blind treatment period were all larger across the 3 study groups for the naïve subjects than for the statin subjects. The treatment effects relative to placebo were, however, similar between the 2 subgroups of subjects, as there was no significant treatment-by-subgroup interaction (p > 0.10). Note that the results may not be reliable since the sample size for the statin subjects was small (24% of the study population) and they came to the study with lower LDL-C values at baseline (entry criterion was > 130 mg/dL) than the naïve subjects in general (entry criterion was > 160 mg/dL). The additional LDL-C lowering effect by colesevelam HCl for subjects taking statins as their background medications could not be evaluated since the study did not have enough power for the assessment.

Figure 15

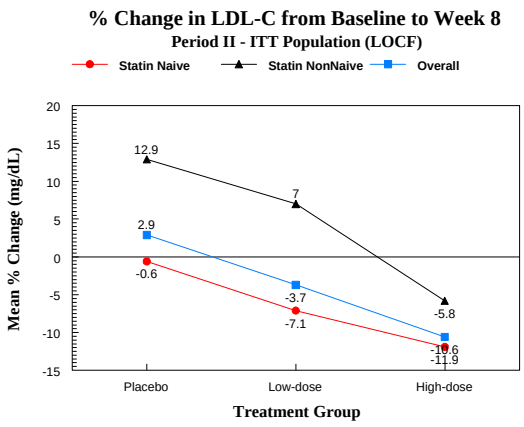
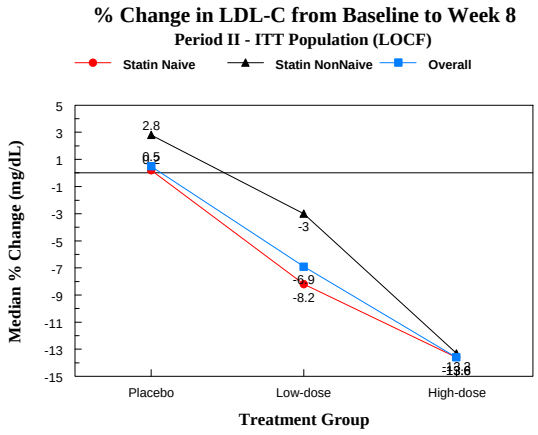


Figure 16



In the final discussion and conclusion, the low-dose colesevelam HCl (1875 mg) will not be the focus of this review since (1) it is not a to-be-marketed dose for the proposed indication, (2) its treatment effect in LDL-C lowering was small (5% reduction for the completers), and (3) it did not show nominal significance for any of the secondary endpoints.

5.2 Conclusions and Recommendations

Data from the WEL-410 trial have demonstrated that Welchol 3750 mg was effective in lowering LDL-C level from baseline by 12.5% compared to placebo at the end of 8-week double-blind randomized treatment period (primary efficacy endpoint), in pediatric patients aged between 10 to 17 years with heterozygous familial hypercholesterolemia. Welchol 3750 mg was also associated with statistically significant decreases in TC, non-HDL-C, and apo B, and increases in HDL-C and apo A-I during the 8-week double-blind treatment period. The efficacy was sustained throughout the 18-week open-label treatment period in which all patients received Welchol 3750 mg. Welchol 3750 mg resulted in a numerically increase in triglyceride by Week 8 as well as by Week 26, although the change was not statistically significantly different from placebo.

A borderline significant reduction in LDL-C from baseline at Week 8 was observed in patients taking Welchol 1875 mg compared to placebo (treatment difference = -6.3%). However, there were no statistically significant findings in all other lipids and apolipoproteins when Welchol 1875 mg was compared with placebo.

Data from the WEL-410 trial also showed that treatment effects relative to placebo in mean % change from baseline in LDL-C at Week 8 were consistent between the subgroups of statin (24% of the study population) and naïve (76% of the study population) patients. With such a small sample size for the statin subgroup, the additional LDL-C lowering effect from Welchol, if any, for the statin patients was not evaluable since the study did not have enough power for the assessment.

Overall, < 4% and < 8% of the study population achieved the LDL-C goal of < 110 mg/dL at the end of the double-blind treatment period and the open-label treatment period, respectively, and most of them had statins as their background medications.

5.3 Labeling Comments

The following bullets summarize this reviewer's comments for the sponsor's proposed labeling.

- It is misleading to state that the study was a (b) (4), randomized, double-blind, placebo-controlled study because the double-blind and placebo-controlled period was only 8 weeks.
- The mean baseline LDL-C value, 199 mg/dL, occurred at Day 1, (b) (4).
- In Table 9, p-values are presented for all the primary and secondary lipid and apolipoprotein variables. However, the multiplicity testing issue for the secondary variables was not pre-addressed in the protocol and/or statistical analysis plan. To be consistent with the other tables under the section of clinical studies, a footnote with $p < 0.05$, rather than actual p-values, is recommended.
- It should be more specific that the results presented in Table 9 were based on the ITT population with LOCF.

Primary Statistical Reviewer: Cynthia Liu, MA

Concurring Reviewer: Todd Sahlroot, Ph.D.
Statistical Team Leader and Deputy Director of Biometrics II

CC: HFD-510/KJohnson, EColman, ECraig
HFD-715/TPermutt, TSahlroot, CLiu
HFD-700/LPatrician

6. APPENDIX I

Statistical results below were based on an ANCOVA model with treatment and statin use as the fixed factors and baseline LDL-C value as the covariate.

Table 1 – Summary Results for LDL-C (Period II – **ITT Population**)

Treatment Group	N	Day 1 Baseline Mean (SD)	Week 8 LOCF Mean (SD)	Percent Change From Baseline	
				Mean (SD)	LS Mean (SE)
Colesevelam HCl 3750 mg	63	202.3 (50.1)	178.2 (45.5)	-10.6 (19.4)	-8.7 (2.2)
Colesevelam HCl 1875 mg	63	198.5 (44.0)	187.3 (37.0)	-3.7 (18.4)	-2.6 (2.2)
Placebo	65	196.7 (43.6)	198.7 (36.0)	2.9 (16.5)	3.7 (2.2)
			Treatment Difference		
Treatment Comparison			LS Mean (SE)	95% CI	p-value
Colesevelam HCl 3750 mg vs. Placebo			-12.5 (2.9)	(-18.2, -6.7)	< 0.0001
Colesevelam HCl 1875 mg vs. Placebo			-6.3 (2.9)	(-12.0, -0.5)	0.0322
Analysis results were based on an ANCOVA model with treatment and statin use as the fixed factors and baseline LDL-C value as the covariate. The comparison of low-dose vs. placebo by Dunnett's t-test showed p = 0.0594.					

Table 2 – Summary Results for LDL-C (Period II – **Completers**)

Treatment Group	N	Day 1 Baseline Mean (SD)	Week 8 Mean (SD)	Percent Change From Baseline	
				Mean (SD)	LS Mean (SE)
Colesevelam HCl 3750 mg	62	202.7 (50.4)	178.1 (45.8)	-10.8 (19.4)	-9.3 (2.2)
Colesevelam HCl 1875 mg	60	200.6 (42.6)	187.8 (37.3)	-5.1 (15.3)	-3.9 (2.2)
Placebo	64	196.5 (43.9)	198.6 (36.3)	3.0 (16.6)	3.5 (2.1)
			Treatment Difference		
Treatment Comparison			LS Mean (SE)	95% CI	p-value
Colesevelam HCl 3750 mg vs. Placebo			-12.8 (2.8)	(-18.3, -7.2)	< 0.0001
Colesevelam HCl 1875 mg vs. Placebo			-7.4 (2.8)	(-13.0, -1.8)	0.0101
Analysis results were based on an ANCOVA model with treatment and statin use as the fixed factors and baseline LDL-C value as the covariate. The comparison of low-dose vs. placebo by Dunnett's t-test showed p = 0.0193.					

7. APPENDIX II

Statistical results below were copied from the sponsor's report.

Table 11.2: Mean Percent Changes in Total 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	266.6 (51.49)	248.7 (45.27)	-5.4 (15.80)	-5.1 (1.58)
Colesevelam HCl 1875 mg	63	266.1 (45.28)	259.7 (37.66)	-1.1 (14.22)	-0.9 (1.58)
Placebo	65	260.9 (46.77)	265.1 (38.41)	2.9 (13.29)	2.3 (1.56)
			Treatment Difference		
Treatment Comparison			LS Mean (SE)	95% CI	p-value
Colesevelam HCl 3750 mg vs. Placebo			-7.4 (2.23)	(-11.8 , -3.0)	0.0011
Colesevelam HCl 1875 mg vs. Placebo			-3.2 (2.23)	(-7.6 , 1.2)	0.1514

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 14.2.3 and 14.2.9

Table 11.4: Mean Percent Changes in High-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	45.6 (9.81)	49.2 (10.96)	8.5 (14.72)	8.3 (1.63)
Colesevelam HCl 1875 mg	63	48.5 (11.92)	50.3 (13.54)	3.9 (12.45)	4.5 (1.64)
Placebo	65	45.2 (9.49)	45.9 (8.74)	2.5 (12.52)	2.2 (1.60)
			Treatment Difference		
Treatment Comparison			LS Mean (SE)	95% CI	p-value
Colesevelam HCl 3750 mg vs. Placebo			6.1 (2.28)	(1.6 , 10.6)	0.0081
Colesevelam HCl 1875 mg vs. Placebo			2.4 (2.30)	(-2.2 , 6.9)	0.3055

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 14.2.5 and 14.2.9

Table 11.5: Mean Percent Changes in Non-High-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	221.0 (52.09)	199.6 (47.33)	-8.4 (18.28)	-7.9 (1.96)
Colesevelam HCl 1875 mg	63	217.7 (44.17)	209.4 (37.50)	-2.1 (17.32)	-2.1 (1.96)
Placebo	65	215.7 (46.66)	219.2 (38.91)	3.4 (16.01)	3.0 (1.93)
			Treatment Difference		
Treatment Comparison			LS Mean (SE)	95% CI	p-value
Colesevelam HCl 3750 mg vs. Placebo			-10.9 (2.75)	(-16.3 , -5.5)	0.0001
Colesevelam HCl 1875 mg vs. Placebo			-5.1 (2.75)	(-10.6 , 0.3)	0.0635

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 14.2.6 and 14.2.9

Table 11.6: Mean Percent Changes in Apolipoprotein A-I (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	61	137.0 (24.41)	150.3 (24.05)	11.2 (16.79)	10.8 (1.75)
Colesevelam HCl 1875 mg	62	141.6 (25.61)	150.3 (27.75)	7.0 (13.96)	7.9 (1.74)
Placebo	63	136.7 (23.32)	141.0 (21.65)	4.4 (14.62)	3.9 (1.72)
			Treatment Difference		
Treatment Comparison			LS Mean (SE)	95% CI	p-value
Colesevelam HCl 3750 mg vs. Placebo			6.9 (2.45)	(2.0 , 11.7)	0.0055
Colesevelam HCl 1875 mg vs. Placebo			4.0 (2.45)	(-0.9 , 8.8)	0.1061

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 14.2.7 and 14.2.9

Table 11.7: Mean Percent Changes in Apolipoprotein B (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	61	162.7 (33.07)	149.8 (30.77)	-7.0 (14.45)	-6.2 (1.77)
Colesevelam HCl 1875 mg	62	156.4 (27.45)	153.1 (25.42)	-0.7 (16.52)	-1.2 (1.75)
Placebo	63	158.0 (33.58)	159.1 (27.74)	2.3 (14.78)	2.1 (1.73)
			Treatment Difference		
Treatment Comparison			LS Mean (SE)	95% CI	p-value
Colesevelam HCl 3750 mg vs. Placebo			-8.3 (2.48)	(-13.2 , -3.5)	0.0009
Colesevelam HCl 1875 mg vs. Placebo			-3.4 (2.46)	(-8.2 , 1.5)	0.1743

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 14.2.8 and 14.2.9

Table 11.3: Median Percent Changes in Triglycerides (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 Median (IQR)	Week 8 With LOCF Median (IQR)	Percent Change From Baseline	
				Median (IQR)	Estimated Median (IQR) [2]
Colesevelam HCl 3750 mg	63	85.0 (54.9)	95.6 (71.7)	12.5 (52.9)	17.4 (42.83)
Colesevelam HCl 1875 mg	63	83.2 (46.0)	91.2 (53.1)	16.9 (53.7)	18.5 (34.93)
Placebo	65	92.9 (39.8)	99.1 (45.1)	12.5 (53.8)	12.3 (36.23)
			Treatment Difference [1]		
Treatment Comparison			Median (IQR)	95% CI	p-value
Colesevelam HCl 3750 mg vs. Placebo			5.1 (76.52)	(-8.8 , 20.0)	0.4659
Colesevelam HCl 1875 mg vs. Placebo			6.4 (70.65)	(-6.5 , 20.3)	0.3405

1. For comparisons between 2 treatment groups, treatment difference and its 95% CI are estimated using Hodges-Lehmann estimator and Moses Method, and p-value is obtained from Wilcoxon Signed-Rank test.
2. Within the treatment group, treatment differences are estimated using the Hodges-Lehmann estimator and Tukey method.

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.
Triglycerides are not normally distributed. Median value is displayed. Interquartile range (IQR) is displayed to replace standard deviation or standard error.
Treatment difference = colesevelam HCl – placebo.
CI = confidence interval; HCl = hydrochloride; IQR = interquartile range; LOCF = last observation carried forward.
Sources: Post-text Tables 14.2.4 and 14.2.9

8. APPENDIX III

Statistical results below were copied from the sponsor's report.

Table 11.12: 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

Table 11.13: 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

Table 11.14: 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

Table 11.15: Mean Percent Changes in Low-Density Lipoprotein Cholesterol (mg/dL) From Study Baseline (Day 1) to Week 8 With LOCF – BMI 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
≥25 kg/m^2					
Colesevelam HCl 3750 mg	19	209.7 (54.41)	185.3 (49.72)	-10.9 (14.33)	0.0038
Colesevelam HCl 1875 mg	19	199.4 (52.01)	193.4 (44.49)	-1.6 (14.00)	0.6291
Placebo	11	227.1 (61.91)	217.9 (28.34)	0.4 (20.21)	0.9525
<25 kg/m^2					
Colesevelam HCl 3750 mg	44	199.1 (48.38)	175.1 (43.75)	-10.4 (21.32)	0.0023
Colesevelam HCl 1875 mg	44	198.1 (40.65)	184.7 (33.51)	-4.7 (20.03)	0.1304
Placebo	54	190.5 (36.57)	194.8 (36.36)	3.4 (15.77)	0.1160

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 14.2.30

Table 11.16: Mean Percent Changes in Low-Density Lipoprotein Cholesterol (mg/dL) From Study Baseline (Day 1) to Week 8 With LOCF – Tanner Stage at Baseline 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
Tanner Stage II					
Colesevelam HCl 3750 mg	15	196.9 (50.08)	166.8 (52.36)	-13.9 (25.94)	0.0571
Colesevelam HCl 1875 mg	15	221.3 (41.60)	207.9 (30.40)	-3.8 (17.04)	0.3964
Placebo	9	213.1 (55.53)	213.3 (35.30)	3.3 (19.95)	0.6351
Tanner Stage III to V					
Colesevelam HCl 3750 mg	48	204.0 (50.48)	181.7 (43.08)	-9.5 (17.02)	0.0003
Colesevelam HCl 1875 mg	48	191.4 (42.61)	180.9 (36.80)	-3.7 (18.93)	0.1833
Placebo	56	194.0 (41.33)	196.4 (35.87)	2.9 (16.05)	0.1889

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 14.2.31

Table 11.20: 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

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