3. If taking androgen, estrogen, progesterone, oral steroid, thiazide diuretic, or beta-blocker, the prescribed dose must have been stable for 30 days prior to drug treatment.
4. If women, have negative pregnancy tests during the diet period.
5. If women of childbearing potential, have an IUD or used hormonal, or barrier methods of contraception for the duration of the study period.

B. Exclusion Criteria:

1 Had tendinous xanthomas.
2. Had thyroid disease, clinically significant liver or renal disease, vasculitis, HIV infection, poorly controlled diabetes mellitus, poorly controlled hypertension, unstable cardiac disease, recent M. I. Or cardiac by-pass surgery, or any clinically significant unstable medical condition.
3. Has a hx. Of dysphagia or swallowing disorders or motility disorder of the intenstine, including gastroparesis, ileus, pseudo-obstruction, megacolon, or mechanical obstruction.
4. Had participated in a study of an investigational drug in the month prior to the start of the screening period . Used probucol in the year prior to screening or used fibrates in the month prior to screening.
5. Had active ethanol or drug dependence or abuse, excluding tobacco use.
6. Women who were pregnant or breast-feeding.
7. Had the following lab. abnormalities: hemoglobin<11.0 g/dL, ALT>ULN, TSH>ULN.
8. Any evidence of active malignancy, except for basal cell ca of skin.

III. Study Design and Procedures:

This was an open extension study which enrolled patients from GTC-48-301, from GTC-37-201, from GTC-37-202, and from GTC-37-203 for up to 50 weeks of treatment. Patients began dosing at 2 capsules (each containing 375 mg.) with meals twice a day at Day 0. The dose was to be titrated to a maximal dose of 5 capsules twice a day to achieve 15-30% reduction in LDL-C from the baseline value. If the patient did not reach a 15-30% reduction in LDL-C on the maximum dose of Colesevelam, combination therapy commenced with Colesevelam and either a statin or nicotinic acid. The study was divided into 5 periods:

Screening Wk -4	Diet Wks-4 to 0	Day 0 -Baseline	Drug Treatment	Follow-up
Confirm eligibility Med. Hx. & blood Tests	NCEP Step 1 diet Baseline lipids HCG	Baseline PE, lab and ;lipid profile	Clinic visit Wks 2, 4, 8,12, 20, 28, 36,, 42, & 50	Visit 52 for ADRs Lipid profile, lab Tests

The detailed study procedures are shown below:

Table III-1: Flow Chart

	Screen	Diet Period	Randomized	Treatment Period				
Week #		–1	Day 0	2- 4	8-12	20-42	50	52
Med./Medi-cation hx.	*							
PE/V Signs	*		*				*	
Chem.profi-le,CBC	*			*	*	*	*	*
PT,PTT,Vit. A, D & E					*	*	*	*
Serum HCG		*						
Fasting lipid profile	*	*	*	*	*	*	*	*
TSH/T4	*							
Diet info	*	*	*	*	*	*	*	
Dispense drugs			*	*	*	*	*	
Adverse events		*	*	*	*	*	*	*
Drug ac-countability			*		*	*	*	

III. A. Patient Characteristics: Patients were considered part of the Safety population (260 patients) if they took at least one dose of Colesevelam. The Intent-to-Treat population included those patients who had at least one valid post-baseline lipid evaluation. The demographic data between this study and the GTC-48-301 were similar. Since most of the patients were the extension patients from GTC-48-301.

B. Duration of Exposure: Summary of duration of exposure and Colesevelam daily dose are shown below:

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Table III-II: Duration of Exposure and Colesevelam Daily Dose for Day 0 to Week 50—ITT Population:

Duration of Exposure)			
	# of patients	Mean(days)	Std. Deviation
All Study Visits	255	303.6	96.4
CSV Only Visits	255	282.4	103.7
CSV with Statin Visits	38	141.9	69.2
Daily Dose			
	# of patients	Mean daily dose	
Entire Study	255	2.8 g	
Weeks 42-50	255	3.3 g	

Comments:

1. The percent of patients taking the maximum dose of Colesevelam (3.8 g/day) increased steadily throughout the study to a maximum of 50% of the patients for the study interval of Weeks 42-50. Because 50% of the patients did not achieve the maximum daily dose , many did not achieve a greater than 15% reduction in LDL-C.
2. For those patients who did not achieve greater than 15% reduction, 37 of the 38 patients used a statin and 1 used nicotinic acid as additional lipid lowering medication co-administered with Colesevelam.

IV. Results:

A. Efficacy: Change and percent change in LDL-C, total-C, HDL-C and TG were efficacy parameters.

1. The mean change and percent change in LDL-C from baseline (mean of values at Week -1 and Day 0) to the end of the treatment period (Week 50/Early Termination) are shown below:

Table IV-1: Mean and Median Change and Percent Change in LDL-C from Baseline to Endpoint ITT Population:

	N	Baseline (mg/dL)	Endpoint (mg/dL)	Change (mg/dL)	P-value*	Percent Change	P-value+
All Study Visits							
Mean	253	185.8	156.2	-29.6	<0.0001	-15.0	<0.0001
CSV Only Visits							
Mean	253	185.8	164.2	-21.6	<0.0001	-10.9	<0.0001

* P-values obtained from Wilcoxon Signed Rank test. From baseline to endpoint.

+ P-value obtained from paired t-test from baseline to endpoint.

Comments:

1. The mean percent change in LDL-C in CSV Only Visits was 10.9%. Since only 50% of the patients achieved the maximum dose of 3.8 g in the 42-50 weeks period, and the mean daily dose of this period was only 3.3 g/day, the finding of only 10.9% decrease is to be expected. It is also consistent with the finding of Protocol GTC-48-301 that only Colesevelam groups of > 3.8 g reached > 15.0% percent reductions.
2. For Total-C, HDL-C and TG, the mean/median changes for CSV Only Visits were –4.0%, +10.8% and +10% respectively. All these changes were statistically significant at P<0.0001 compared to the baseline values. The clinical significance of these changes is unknown.

B. Safety:

1. Death: There was one death in this study due to homicide.
2. Serious Clinical Adverse Events: There were 21 serious adverse events reported in 18 patients during the study. These included: one patient hospitalized with generalized edema, one developed breast cancer, two developed basal cell carcinoma of the forehead, one hospitalized for cellulitis in the left knee, one hospitalized with myocardial infarction, one suffered a right ankle fracture due to auto accident, one hospitalized for cerebrovascular accident, one diagnosed with prostate cancer, one hospitalized for GU surgery, and one hospitalized for multiple fractures due to a fall.. None was felt to be drug-related.

   Twenty-three patients withdrew from the study due to adverse events . 18 of the 22 serious events were due to GI as shown below:

Table IV-1: Patients Prematurely Discontinuing Treatment Due to Adverse Events:

Patient ID	Dose of CSV	Primary Reason for Discontinuation	Exposure To CSV (Days)
901.308	3.0 g	Dyspepsia, esophagitis	134
901.320	3.8 g	Generalized edema	295
902.006	3.0 g	Flatulence, nausea	93
903.006	1.5 g	Angina, myocardial infarct	9
903.015	1.5 g	Constipation, flatulence	20
903.017	1.5 g	Flatulence	61
903.312	1.5 g	Accidental injury	98
903.317	2.3 g	Constipation	49
905.008	2.3 g	Abdominal pain, constipation	339
905.011	1.5 g	Abdominal pain, constipation	281
905.017	1.5 g	Anemia	85
905.021	3.8 g	Constipation	270
905.318	1.5 g	Constipation	162
905.322	3.8 g	Abdominal pain, back pain	257
906.302	3.8 g	Dysphagia	160
906.308	3.0 g	Abdominal pain, flatulence	158
907.010	3.0 g	Dyspepsia	271
907.019	2.3 g	Diarrhea	42
907.020	1.5 g	Constipation	63
907.022	2.3 g	Constipation	50
907.024	1.5 g	Flatulence	3
908.314	2.3 g	Constipation	49
910.002	3.0 g	Depression, nervousness	236

3. Laboratory Adverse Events:
   a. There were no statistically significant changes in electrolytes, renal, hepatic, and iron parameters. No patient had marked changes of clinical concern.
   b. AST (SGOT), ALT (SGPT) and alkaline phosphatase showed a statistically significant mean increase from Day 0 to Endpoint in Colesevelam Only Visits. However, these changes were <2X ULN.and no patient had persistently elevation >3XULN. Combination therapy with Colesevelam and statins did not result in statistically significant change in mean ALT, AST, or alkaline phosphatase. And no patient developed persistently elevations of > 3XULN.
   c. There were no statistically significant changes in hematology parameters or chemistry parameters. No patient developed marked changes of clinical concern.
   d. There were no clinically significant change in vitamins and coagulation parameters from Day 0 to Endpoint. In patients treated with both Colesevelam and statins, there was a statistically significant decrease in PT and PTT.

However, all the values were still within the normal and no clinical venous thrombosis or bleeding were reported.

III. Reviewer's Evaluation:

A. Safety: This long-term study showed similar safety findings as the short-term, 24 -week study. There were no significant differences between treatment groups in number of patients experiencing serious adverse events. There were no clinically significant changes liver function tests, in fat-soluble vitamins and coagulation parameters.

B. Efficacy: In this extension study, only 50% of patients were titrated to the maximum prescribed dose of 3.8 g/day by the final treatment interval (Week 42 -50). At an average prescribed daily dose of 2.8 g, reductions in mean and median percent change in LDL-C were 10.9% and 11.5% respectively in the Colesevelam Only Visits. When Colesevelam was co-administered with a statin, the mean and median percent reductions in LDL-C were 15.0% and 14.5% respectively in All Study Visits. This study demonstrated the utility of combining Colesevelam with a statin in lowering LDL-C in patients with hypercholesterolemia. This combined therapeutic approach was additionally evaluated in the following 3 studies.

Protocols GTC-37-203, GTC-48-204 and GTC-48-405: These Phase II studies were designed to determine the safety and efficacy of Colesevelam in combination with HMG-CoA reductase inhibitors: lovastatin, simvastatin, and atorvastatin respectively.

Protocol GTC-48-204: : This was a multicenter, randomized, double-blind, placebo-controlled, parallel-design efficacy study.

I. Objectives:

The primary objectives of this study were to determine the efficacy and safety when Colesevelam at two dose levels and simvastatin at two dose levels were given separately and in various combinations during a 6-week treatment period.

II. Patient Selection: The *inclusion* and exclusion criteria were identical to the previous protocols (GTC-48-301 and GTC-37-901).

III. Study Design and Procedures:

Following screening, 598 patients with primary hypercholesterolemia entered the diet period. After a two-to-four weeks diet period, 258 patients meeting the entrance criteria were enrolled into one the following dosage groups:

1. Placebo.

2. Colesevelam 2.3 g/day.
3. simvastatin 10 mg/day.
4. simvastatin 20 mg/day.
5. Colesevelam 2.3 g and simvastatin 20 mg/day.
6. Colesevelam 3.8 g and simvastatin 10 mg/day.

The detailed study procedures are shown below:

Table III-1: Flow Chart

Study Period	Screening	Diet		Treatment		
Visit # Days	1	2 -28	3 Day 0	4 14±3	5 28±3	6 42±3
Med./Medication Hx.	*					
PE with vital signs			*			*
Chem. Profile & CBC	*		*			*
Serum HCG	*		*			*
Fasting lipid profile	*	*	*	*	*	*
Diet Instruction	*	*	*	*	*	*
Adverse Events concomit. Medicatios		*	*	*	*	*
Drug accountability				*	*	*

III A. Patient Accounting: Of the 258 patients randomized, 241 patients completed the study. The reasons for discontinuation included adverse event (13 patients), withdrawal of consent (2 patients), protocol violation (1 patient), and lost to follow-up (1 patient).

B: Patient Characteristics: The sponsor had performed ANOVA for continuous variables (age , height, weight, and body mass index) and Chi Square test for categorical variables (age category, gender, female menopausal and hormone supplement status, race and baseline LDL-C). The p-values were not statistically significant at $p<0.05$. The treatment groups were well matched

IV. Results:

A. Safety:

1. Death: One patient died one month after prematurely discontinuing from the study due to aspiration pneumonia secondary to cerebrovascular accident.
2. Serious Clinical Adverse Events: There were four additional serious adverse events during the study: One event (myocardial infarction) occurred during the diet phase of the study. One patient in the Placebo group experienced an accidental injury and one patient experienced abdominal pain. In the SIM 10 mg group, one patient experienced angina pectoris.
3. 13 patients prematurely withdrew from the study due to adverse events:

Table 111-3: Patient Withdrawals

Patient ID	Treatment Group	Reason for Discontinuation	Exposure (days)
001.012	Placebo	Dizziness	27
003.009	CSV 2.3 g/SIM 20 mg	Constipation	20
003.032	CSV 2.3 g/SIM 20 mg	Cerebrovascular accident	33
004.007	SIM 10 mg	Constipation,flatulence,nausea	10
004.018	CSV 2.3 g	Anxiety	6
004.018	CSV 2.3 g/SIM 20 mg	Abdominal pain, face edema, nausea, confusion	21
004.045	CSV 2.3 g	Lupus, constipation, flatulence	33
005.046	CSV 2.3 g	Constipation, insomnia, impotence	10
006.045	CSV 3.8 g	Diarrhea, nausea	30
006.047	Placebo	Diarrhea, flatulence, rectal hemorrhage	7
006.065	CSV 3.8 g/SIM 10 mg	Headache, pain, nausea	6
009.036	CSV 3.8 g	Headache, nausea	5
011.041	Placebo	Abdominal pain	14

4. Laboratory Adverse Events:
   a. There were statistically significant increases of 0.01 mg/dL in direct bilirubin in all the active treatment groups except the CSV 2.3 g group. No patient had marked elevation of bilirubin
   b. Similarly, the CSV 3.8 g and CSV 2.3 g/SIM 20 mg groups had statistically significant decrease in bicarbonate of 0.83 mEq/dL and 0.74 mEq/dL respectively. No patient had decrease of bicarbonate >1.0 mEq/dL.
   c. There were no statistically or clinically significant changes in hematology parameters.

B. Efficacy: The mean and median changes in LDL-C, total-C, HDL-C, and TG) from baseline to the end of the treatment period were the efficacy parameters. These changes are shown in the following tables:

Table III-4: Mean and Median Percent Change in LDL-C (mg/dL) from Baseline to Endpoint—ITT Population:

		Baseline		Endpoint		Percent Change		
Treatment	N	Mean	Median	Mean	Median	Mean	Median	P-value*
Placebo	33	183.6	182.0	176.8	177.0	-3.7	- 3.9	0.0044
CSV 2.3 g	36	186.2	183.0	169.3	166.5	-8.5	-9.1	<0.0001
CSV 3.8 g	37	197.7	187.0	167.1	155.0	-16.0	-15.9	<0.0001
SIM 10	35	183.3	172.5	135.6	127.0	-25.5	-30.3	<0.0001
SIM 20	39	180.1	176.5	119.3	118.0	-33.8	-33.3	<0.0001
CSV 2.3 g /SIM 20	37	191.3	183.5	111.2	103.0	-42.3	-41.6	<0.0001
CSV 3.8 g /SIM 10	34	196.0	179.0	115.8	104.0	-41.5	-41.8	<0.0001

* P-values obtained from Wilcoxon Signed-Rank test from baseline to endpoint.

Comments:

The mean and median percent changes in LDL-C from Baseline to Endpoint were statistically significantly different for all the treatment groups. In the CSV-only-treated groups only CSV>3.8 g resulted in >15.0% reduction. The sponsor had provided the paired comparisons between the treatment groups are shown below:

Table III-5: Percent Change in LDL-C (mg/dL) from Baseline to Endpoint, Paired Comparisons Between Treatment Groups—ITT Population:

Treatment	CV 2.3 g	CV 3.8 g	SIM 10	SIM 20	CV 2.3 g/ SIM 20 mg	CV 3.8 g/ SIM 10 mg
Placebo	0.0377	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
CSV 2.3 g		0.0135	<0.0001	<0.0001	**<0.0001**	<0.0001
CSV 3.8 g			0.0013	<0.0001	<0.0001	**<0.0001**
SIM 10				0.0546	<0.0001	**<0.0001**
SIM 20					**0.0010**	<0.0001
CSV 2.3g/ SIM 20						0.6744

Statistical Analysis using ANOVA. Table provided by the sponsor.

Comments:

1. The mean and median percent change in LDL-C levels at Endpoint for all the colesevelam, SIM and Combination-treated groups were statistically significantly different from placebo group(p-values of 0.0377 to <0.0001).
2. The more meaningful paired comparisons were between the combination treatment vs. the CSV or SIM treatment alone. The combination treatments of CSV 2.3 g/SIM 20 mg or CSV 3.8 g/SIM 10 mg were significantly different from the individual treatment with CSV (2.3/3.8 g) or SIM (10 mg/20 mg). The additive efficacy

between Colesevelam and simvastatin can be better appreciated from the percent of patients achieving a >40% reduction of LDL-C :

Placebo	CSV 2.3 g	CSV 3.8 g	SIM 10	SIM 20	CSV 2.3 g/ SIM 20 mg	CSV 3.8 g/ SIM 10 mg
0%	0%	0%	8.6%	28.2 %	59.5%	61.8%

Table III-5: Mean and Median Percent Change in Total-C (mg/dL) from Baseline to Endpoint—ITT Population:

		Baseline		Endpoint		Percent Change		
Treatment	N	Mean	Median	Mean	Median	Mean	Median	P-value*
Placebo	33	268.4	267.0	262.1	265.0	-2.2	- 3.1	0.0906
CSV 2.3 g	36	270.4	262.3	259.5	263.0	-3.9	-2.7	00047
CSV 3.8 g	37	281.7	273.0	257.2	253.0	-9.0	-8.7	<0.0001
SIM 10	35	265.1	257.5	215.1	210.0	-18.7	-21.3	<0.0001
SIM 20	39	262.2	236.0	200.5	202.0	-23.4	-23.5	<0.0001
CSV 2.3 g /SIM 20	37	273.6	275.5	194.2	190.0	-29.1	-29.0	<0.0001
CSV 3.8 g /SIM 10	34	274.3	262.8	197.1	188.0	-28.3	-29.7	<0.0001

* P-values based on paired t-test from base line to endpoint.

Comments:

1. The mean and median percent change from baseline to endpoint in total cholesterol was statistically significant for each of the active treatment groups.
2. Paired comparisons between the groups (provided by the sponsor) are as shown:

Treatment	CV 2.3 g	CV 3.8 g	SIM 10	SIM 20	CV 2.3 g/ SIM 20 mg	CV 3.8 g/ SIM 10 mg
Placebo	0.4631	0.0026	<0.0001	<0.0001	<0.0001	<0.0001
CSV 2.3 g		0.0190	<0.0001	<0.0001	<0.0001	<0.0001
CSV 3.8 g			<0.0001	<0.0001	<0.0001	<0.0001
SIM 10				0.0313	<0.0001	<0.0001
SIM 20					0.0071	0.0236
CSV 2.3g /SIM 20						0.7080

Statistical Analysis using ANOVA. Table provided by the sponsor.

Comments:

1. The mean and median percent change of total-C levels at Endpoint for all the colesevelam, SIM and Combination-treated groups were statistically significantly different from placebo group(p-0.0026--<0.0001) except for the CSV 2.3 g-group (p=0.4631).
2. The most pertinent comparisons were CSV 2.3 g/SIM 20 mg Vs. CSV 2.3 g (p<0.0001), and Vs. SIM 20 mg (p<0.0001); CSV 3.8 g/SIM 10 mg Vs. CSV 3.8 g

(p<0.0001), and Vs. SIM 10 mg (p<0.0001). The combination of Colesevelam and Simvastatin resulted in greater total-C lowering than either Colesevelam or Simvastatin alone.

Table III-6: Mean and Median Percent Change in HDL-C (mg/dL) from Baseline to Endpoint—ITT Population:

		Baseline		Endpoint		Percent Change		
Treatment	N	Mean	Median	Mean	Median	Mean	Median	P-value*
Placebo	33	49.9	47.5	48.7	48.0	-2.3	-2.9	0.2219
CSV 2.3 g	36	50.8	49.5	52.9	52.0	4.3	3.0	0.0043
CSV 3.8 g	37	49.8	49.0	50.6	49.0	1.9	1.6	0.3000
SIM 10	35	50.6	49.5	52.7	52.0	4.9	3.2	0.0177
SIM 20	39	50.0	47.5	52.8	52.0	6.5	7.3	0.0010
CSV 2.3 g /SIM 20	37	47.8	47.0	50.7	52.0	6.1	4.3	0.0017
CSV 3.8 g /SIM 10	34	51.7	49.3	56.7	53.0	10.2	10.2	<0.0001

* P-values obtained from Wilcoxon Signed Rank test from baseline to endpoint.

Comments:

1. The mean and median percent changes from baseline to endpoint in HDL-C were statistically significant for each of the active treatment groups except the CSV 3.8 g group (p=0.300.) The greatest increase in HDL-C of 10.2 was in the CSV 3.8 g/SIM 10 mg group. The clinical significance of increases in HDL-C is unknown.
2. The paired comparisons between the treatment groups are shown:

Treatment	CSV 2.3 g	CSV 3.8 g	SIM 10	SIM 20	CSV 2.3 g/ SIM 20 mg	CSV 3.8 g/ SIM 10 mg
Placebo	0.0118	0.1044	0.0062	0.0006	0.0011	<0.0001
CSV 2.3 g		0.3458	0.8041	0.3646	0.4487	0.0197
CSV 3.8 g			0.2361	0.0615	0.0876	0.0011
SIM 10				0.5172	0.6151	0.0380
SIM 20					0.8883	0.1356
CSV 2.3g/ SIM 20						0.1077

Statistical Analysis using ANOVA. Table provided by sponsor.

Comments:

1. The mean and median percent change of HDL-C levels at Endpoint for all the colesevelam, SIM and Combination-treated groups were statistically significantly different from placebo group(p-0.0118--<0.0001) except for the CSV 3.8 g-group (p=0.1044).
2. The pertinent comparisons were between the combination treatment vs. individual treatment. The combination of 2.3 g CSV/SIM 20 mg did not result in

statistically significant increase in HDL-C compared to either CSV 2.3 g or SIM 20 mg treatment alone. The combination of CSV 3.8 g/SIM 10 mg did result in statistically significant increase in HDL-C than CSV 3.8 g or SIM 10 mg (p=0.0011) or SIM 10 mg (p=0.0380) alone. The clinical significance of this increase of HDL-C is unknown.

Table III-7: Mean and Median Percent Change in TG (mg/dL) from Baseline to Endpoint—ITT Population:

		Baseline		Endpoint		Percent Change		
Treatment	N	Mean	Median	Mean	Median	Mean	Median	P-value*
Placebo	33	174.3	183.0	182.8	180.0	5.5	6.4	0.2553
CSV 2.3 g	36	167.2	163.3	186.7	174.0	12.6	11.4	0.0963
CSV 3.8 g	37	171.2	172.0	196.9	188.0	15.0	11.1	0.0070
SIM 10	35	156.3	152.5	134.3	125.0	-11.6	-17.1	0.0112
SIM 20	39	160.4	153.0	141.7	132.0	-9.7	-12.1	0.0028
CSV 2.3 g /SIM 20	37	175.4	172.0	161.9	160.0	-4.8	-11.9	0.0493
CSV 3.8 g /SIM 10	34	135.2	132.0	122.4	115.0	-3.2	-12.1	0.2013

* P-values obtained from Wilcoxon Signed-Rank test. from baseline to endpoint.

Comment: The mean and median percent changes from baseline to endpoint in TG were statistically significant for each of the active treatment groups except the CSV 2.3 g group (p=0.0963). The CSV-treated groups had increases in TG while the combination treatment groups had decreases in TG. The paired comparisons between the treatment groups are shown:

Treatment	CSV 2.3 g	CSV 3.8 g	SIM 10	SIM 20	CSV 2.3 g/ SIM 20 mg	CSV 3.8 g/ SIM 10 mg
Placebo	0.5561	0.1779	0.0047	0.0053	0.0178	0.0550
CSV 2.3 g		0.5812	0.0035	0.0041	0.0217	0.0470
CSV 3.8 g			0.0002	0.0002	0.0014	0.0039
SIM 10				0.4782	0.3242	0.5092
SIM 20					0.6512	0.6032
CSV 2.3g/ SIM 20						0.9633

Statistical Analysis using ANOVA. Table provided by the sponsor.

Comments:

The pertinent comparisons between CSV 3.8 g Vs. CSV 3.8 g/SIM 10 mg (p=0.0039) was statistically significant but SIM 10 mg Vs. CSV 3.8 g/SIM 10 mg (p=0.5092) was not statistically significant. The combination of CSV 2.3 g/SIM 20 mg was not statistically significantly different from SIM 20 mg alone; but there was

statistically significant decrease of TG than Coloesevelam 2.3 g alone. The clinical significance of this decrease of TG is unknown.

Sponsor's data on percent change in Lp(a), apoplipoproteins A-1 and B from Day 0 to Day 42 are not the pertinent comparisons. The relevant paired comparisons between the treatment groups on percent change in. Lipoprotein (a), and apolipoprotein A-1, apolipoprotein B were not performed by the sponsor.

Protocols GTC-37-203 and GTC-48-205 : These two protocols are identical to Protocol GTC-37-204 in terms of objectives, study design, patients' demographic and other characteristics, and statistical analysis. Since GTC-37-204 was previously extensively reviewed, only the most relevant efficacy and safety results will be reviewed here.

Protocol GTC-37-203: The treatment groups were:

1. Placebo: 26 patients,
2. Colesevelam 2.3 g: 29 patients,
3. Lovastatin 10 mg: 26 patients,
4. Colesevelam 2.3 g/Lovastatin 10 mg with evening meal:((combination meal) 27 patients,
5. Colesevelam 2.3 g/Lovastatin 10 mg at bedtime: (combination bed) 23 patients.

I. Results:

A. Safety:

1. There were no deaths in this study.
2. Five patients discontinued the study, all due to GI adverse events. 2 patients each from the combination-meal and combination-bed group and 1 patient from the CSV 2.3 g group.
3. No patients experienced serious adverse events during the study treatment and during the 30 days following study completion.
4. Clinical Laboratory parameters:

a. There were statistically significant decrease in the mean hematocrit in the combination -meal and combination-bed groups (.the decreases of 0.87% and 1.05% respectively). No patient had hematocrit <40% (normal range 42.00-54.00%).

b. There were no statistically or clinically significant changes in the mean coagulation parameters. 1 patient in the placebo group had PT of 10.4 seconds(normal 10.5-13.50 seconds). I patient each in the combination-meal and combination-bed groups had PTT of 20.0 second and 19,40 seconds respectively (normal 21.0-31.0 seconds).

c. Liver function tests:

(1). The combination-bed group experienced statically significant mean increases in AST/SGOT and ALT/SGPT. The CSV and the combination -meal groups experienced statistically significant mean increases in alkaline phosphatase. However, the increases were <2XULN and no patient had persistent elevations >3XULN.

(2). No patient had clinically significant increases in bilirubin which is a marker for more serious hepatic toxicity.

B. Efficacy: Only the relevant efficacy comparisons are shown:

Table I-1: Percent Change in Lipid Parameters from Baseline to Endpoint Paired Comparisons between Treatment Groups: ITT-Population:

Parameter (mg/dL) Treatment Groups/N	CSV 2.3 g	LOV 10 mg	CSV 2.3 g/ LOV Meal	CSV 2.3 g/ LOV Bed
LDL-C calculated				
Placebo	0.0146	<0.0001	<0.0001	<0.0001
CSV 2.3 g		<0.0001	<0.0001	<0.0001
LOV 10 mg			0.0002	0.0042
CSV/LOV Meal				0.4803
Total Cholesterol				
Placebo	0.1355	<0.0001	<0.0001	<0.0001
CSV 2.3 g		<0.0001	<0.0001	<0.0001
LOV 10 mg			0.0046	0.0046
CSV/LOV Meal				0.9095
HDL-C				
Placebo	0.1601	0.4118	0.3688	0.4621
CSV 2.3 g		0.5715	0.6178	0.5426
LOV 10 mg			0.9437	0.9521
CSV/LOV Meal				0.8974
Triglyceride				
Placebo	0.0874	0.6419	0.3611	0.5128
CSV 2.3 g		0.2159	0.4265	0.0209
LOV 10 mg			0.6564	0.1237
CSV/LOV Meal				

Table provided by the sponsor. Values in table based on using ANOVA for LDL-C and total-C; or Wilcoxon Rank-Sum test for HDL-C and TG.

Comments:

1. The mean and median percent change in LDL-C levels at Endpoint for all the colesevelam- and CSV/LOV Combination-treated groups were statistically significantly different from placebo group(p-values of 0.0146 to <0.0001).
2. The more meaningful paired comparisons were between the combination treatment vs. the CSV or LOV treatment alone. The combination treatments of CSV 2.3 g/ LOV 10 mg-meal and CSV 2.3 g/LOV 10 mg-bed were statistically significantly

different from individual treatment with CSV or LOV 10 mg-meal or CSV/LOV 10 mg-bed groups.

3. The mean and median percent change of total-C levels at Endpoint for all the colesevelam and Combination-treated groups were statistically significantly different from placebo group($p<0.0001$) except for the CSV 2.3 g-group ($p=0.1355$).
4. The most pertinent comparisons were CSV 2.3 g Vs. CSV 2.3 g/LOV 10 mg-meal ($p<0.0001$), and CSV 2.3 g vs. CSV 2.3 g/LOV 10mg-bed ($p=0.0046$) were statistically significant than the individual treatment alone.
5. The mean and median percent change of HDL-C and TG at Endpoint for all the colesevelam and Combination-treated groups were not statistically significantly different from placebo group. In the paired comparisons, only the CSV 2.3 g/LOV 10 mg-bed group showed statistically significant difference from the CSV 2.3 g treatment ($p=0.0209$).

Protocol GTC-48-205: The treatment groups were:

1. Placebo: 26 patients,
2. CSV 3.8 g: 19 patients,
3. Atorvastatin 10 mg: 16 patients,
4. CSV 3.8/ATO 10 mg: 18 patients,
5. Atorvastatin 80 mg: 20 patients.

I. Results:

A. Safety:

1. There were no deaths in this study.
2. Five patients discontinued the study, all due to GI adverse events. 2 patients in the ATO 10 mg group had stomach cramping,vomiting, constipation and bloating. 1 patient in the CSV 3.8 g group had stomach cramping and 1 patient in the CSV 3.8 g/ATO 10 mg group had nausea.
3. No patients experienced serious adverse events during the study treatment and during the 30 days following study completion.
4. Clinical Laboratory parameters:
   a. There were no statistically significant changes in hematology parameters or the coagulation parameters.
   b. No patient developed marked changes of clinical concern.

B. Efficacy: The efficacy results are shown in the following tables:

Table III-11: Percent Change in Lipid Parameters from Baseline to Endpoint Paired Comparisons between Treatment Groups: ITT-Population:

Parameter (mg/dL) Treatment Groups	CSV 3.8 g	ATO 10 mg	CSV 3.8 g/ ATO 10 mg	ATO 80 mg
LDL-C calculated				
Placebo	0.0010	<0.0001	<0.0001	<0.0001
CSV 3.8 g		<0.0001	<0.0001	<0.0001
ATO 10 mg			0.0124	0.0021
CSV 3.8g/ATO 10 mg				0.1247
Total Cholesterol				
Placebo	0.0010	<0.0001	<0.0001	<0.0001
CSV 3.8 g		<0.0001	<0.0001	<0.0001
ATO 10 mg			0.2479	0.0014
CSV 3.8 g/ATO 10 mg				0.0046
HDL-C				
Placebo	1.0000	0.5729	0.1398	0.9888
CSV 3.8 g		0.4153	0.0895	0.9490
ATO 10 mg			0.2042	0.5877
CSV 3.8 g/ATO 10 mg				0.1773
Triglyceride				
Placebo	0.8027	0.0313	0.8868	0.0006
CSV 3.8 g		0.0214	0.7018	0.0005
ATO 10 mg			0.0466	0.2018
CSV 3.8 g/ATO 10 mg				0.0012

Table provided by the sponsor. Values in table based on using ANOVA for LDL-C and total-C; or Wilcoxon Rank-Sum test for HDL-C and TG.

Comments:

1. The mean and median percent change in LDL-C levels at Endpoint for all the colesevelam- and CSV/ATO Combination-treated groups were statistically significantly different from placebo group (p-values of 0.0010 to <0.0001).
2. The more meaningful paired comparisons were between the combination treatment vs. the CSV or ATO treatment alone. The combination treatments of CSV 3.8 g/ ATO 10 mg was statistically significantly different from CSV 3.8 g group and from the ATO 10 mg group.
3. The mean and median percent change of total-C levels at Endpoint for all the colesevelam and Combination-treated groups were statistically significantly different from placebo group(p values of 0.0010 to <0.0001).

4. The most pertinent comparisons were between the combination treatment vs. the CSV or ATO treatment alone. The combination treatment of CSV 3.8 g Vs. CSV 3.8 g/ATO 10 mg was statistically significant different from CSV 3.8 g group but not from the ATO 10 mg group.
5. The mean and median percent change of HDL-C and TG at Endpoint for all the colesevelam and Combination-treated groups were not statistically significantly different from placebo group except for the ATO 80 mg group for TG.

Protocol GTC-44-201: All the previous protocols were performed with Colesevelam HCL capsules. Only this protocol was designed to test the tolerability of a tablet formulation in normal healthy volunteers.

I. Objectives:

The primary objectives of this study were to assess the tolerability and safety of Colesevelam tablets.

II. Patient Selection: Eligibility was based on health as judged from medical history, physical examination and clinical laboratory tests.

A. Inclusion Criteria:

1. Males and females 40 years of age or older.
2. Subjects willing to eat, on most days, at least 2 meals per day.
3. Subjects who are taking androgen, estrogen, progesterone, oral steroids, thiazide diuretics, or beta blockers were required to be on a stable prescribed dose for 30 days prior to screening.
4. Subjects had to have the following serum lab values within normal ranges: PT, PTT, WBC, RBC, absolute neutrophil count, HCT, Hb., MCV, MCH, platelet count, BUN, creatinine, AST, ALT, alkaline phosphatase, uric acid, calcium, phosphate, sodium, potassium, chloride, bicarbonate, glucose, albumin.

B. Exclusion Criteria: Identical to the previous protocol. (GTC-48-301).

III. Study Design and Procedures: This was an open-label, fixed dose safety and tolerability study. 20 male and female normal volunteers, aged 40 and older were enrolled. Colesevelam tablets were administered as 3 tablets taken twice daily (total dose of 3.8 g/day) for 28 days.

A. The first administration of the study drug was given at the clinic where the subjects remained for 4 hours to monitor any adverse events or difficulties with the tablets. Adverse events were assessed at baseline (day 0) and following 14 and 28 days of treatment.
B. Clinical chemistry, hematology, and coagulation parameters were assessed at screening (day –7) and at the end of the treatment period.
C. Tolerability was assessed at baseline when subjects took the first dose of Colesevelam tablets with the question, "Did you experience any difficulties with the tablets?" On day 7 of the treatment period, this question was asked again via

telephone. At clinic visits on days 14 and 28, the same question was repeated and the :yes" and "no" responses were recorded on the appropriate CRF.

IV. Results: 20 subjects entered the treatment phase of the study; one subject withdrew consent and one subject was incarcerated. 18 subjects completed the study.

A. The adverse experiences are shown in table III-1:

Table III-1: Reported Adverse Experiences:

Body System/Adverse Experience	Colesevelam 3.8 g (N=20)	
	# of subjects	# of types of AE
Skin and Appendages	1	1
Central and Peripheral Nervous System	2	2
Gastrointestinal System	14	10
Respiratory System	2	2
Urinary System	1	1

B. Clinical laboratory parameters: Possible treatment-related changes are shown below:

Table III-2: Shifts in Lab. Values from Screening (Day –7) to End-of - Study(Day 28):

Parameter	Colesevelam 3.8 g/day N=19	
Hematology: Hb. Hct, RBC,WBC,Platelet count	No clinically significant shifts	
Serum Chemistry	from H/Normal to low	from L/N to high
Glucose	0	1
SGPT (ALT)	0	1
CO2	0	3
Phosphorus	0	1
Uric Acid	0	1
Coagulation		
Prothrombin	1	0
Partial Thromboplastin Time	0	1
Lipid Profile		
Total Cholesterol	2	1
LDL Cholesterol	0	0
HDL Cholesterol	2	0
TG	1	3

H/normal to low=from high/normal to low; L/N to high=from low/normal to high.

Comments:

1. The clinical chemistry and coagulation values were still within normal/safe ranges and the shifts were clinically insignificant.

2. There were no significant changes in systolic or diastolic blood pressure, heart rate or body weight.

C. Responses to tablet tolerability are shown in Table III-3:

Table III-4 : Responses to Tolerability Question

Day of Study	Yes	No	Comments/Description of Difficulty
Day 0	1	19	"Noticeable sensation of tablet coating upon swallowing, and belching"
Day 7	0	19	NA
Day 14	0	19	NA
Day 28	2	18	"Tablets more noticeable when taken with liquids before starting a meal" "Difficulties with swallowing 3 tablets at the same time"

III. Reviewer's Evaluation:

A. Colesvelam hydrochloride tablet administration to normal men and women for 28 days taken as 3 tablets with either breakfast or lunch plus 3 tablets with dinner, to achieve a total dose of 3.8 g/day were well-tolerated. 14/20 subjects experienced 10 different types of GI adverse events. No specific incidence of "choking" or "tablet got stuck" were reported in this small study of 20 subjects of short duration..

B. No clinically significant changes in serum chemistry, hematology, blood coagulation profiles, vital signs or physical examination were observed.

C. LDL-C decreased by 12.4% and TG increased by 29.9% from baseline. For definitive bioequivalency comparison between the tablet and capsule formulations regarding efficacy, please refer to Biopharmacology Review of in-vitro binding studies.

Integrated Summary of Safety: This summary is based on the analysis of the Phase 2 and 3 studies reviewed above and additional data submitted by the sponsor in the Integrated Summary of Safety.

A. Number of patients: The 1350 patients included in the integrated safety analysis represent 98% of the total 1374 patients treated in Phase 2 and 3 clinical studies. The 952 patients exposed to colesevelam HCL alone or in combination with HMG-CoA reductase inhibitors represent 98% of the 976 patients exposed across multiple doses of colesevelam HCL in clinical studies.

B. Duration of exposure: The duration of exposure by treatment category is shown:

Duration of Exposure	# of patients completed study	Colesevelam Doses
4 Weeks: N=227	24	1.5 g to 3.8 g
	90	1.5 g
	79	2.3 g; 2.3 g/10 mg LOV
	34	3.8 g; 3.8 g/10 mg ATO.
6 Weeks: N=334	118	1.5g; 2.3g; 3.0g; 3.8g
	72	3.8 g (once or split dose)
	144	2.3 g; 2.3g/20 mg SIM; 3.8g/10 mg SIM
24 Weeks: N=379	379	2.3g; 3.0g; 3.8g; 4.5g
50 Weeks: N =186	186	1.5g to 3.8 g alone & in combination with HMG-CoA reductase inhibitors

C. Early termination during the treatment period:

The most frequent reason was an adverse event. Overall, of the 1350 patients treated (including placebo patients), 82 (6.1%) discontinued due to an adverse event. The CSV-treated patients did not have more early termination due to an adverse event.

The second most frequent reason was consent withdrawn. Overall, 52 (3.9%) terminated for consent withdrawn.

The other reasons for termination included noncompliance in 1 patient, protocol violation in 6 patients, death in 1 patient (homicide, in the CSV-extension study), another death in 1 placebo-treated patient due to cardiac arrhythmia , lost to follow up in 16 patients and other reasons in 6 patients.

Colesevelam HCL is a cross-linked polymer and is member of the class of bile acid sequestrants. Bile acid sequestrants are generally non-absorbed and complex with bile acids in the intestine, decreasing their absorption. Therefore the following safety issues are of particular interest:

A. Gastrointestinal Adverse Events: Not surprisingly, constipation or dyspepsia was the most common adverse event. The incidence by treatment category can be summarized in the following table:

Body System	Placebo N=258 N (%)	CSV only N=807 N (%)	CSV/HMG-CoA N=145 N(%)	HMG-CoA N=140 N(%)
Digestive:				
Dyspepsia/ Constipation	9 (3.5%)	67 (8.3%)	8 (5.5%)	7 (5.0%)

Comments:

1. Compared to placebo group, the percentage of patients experiencing dyspepsia/constipation was 8.3% in CSV-only-treated patients vs. 3.5% in the placebo-treated patients. This difference was statistically significant with p-value of 0.0079. The CSV/HMG-CoA reductase inhibitor combination-treated patients had a incidence of 5.5% which was also statistically significantly different from placebo-treated patients. Constipation and dyspepsia were for most part mild or moderate in intensity and did not result in discontinuation of therapy solely due to constipation /dyspepsia. Although the percentage of patients reporting dyspepsia did vary between the demographic subgroups, there was no evidence of a subgroup, with respect to age and/or gender, at particular risk for this adverse event. In general, there was a slightly higher incidence with higher doses (3.8 g to 4.5 g).
2. There was no increased risk of abdominal pain, bloating, gas, and nausea in CSV-treated patients.

B. Serum Vitamin and Coagulation Parameters: Absorption of fat-soluble vitamins is dependent on bile acids. Bile acid binding sequestrants have been associated with interference with fat-soluble vitamin absorption as in the case of cholestyramine. Vitamins A and E serum concentrations were obtained. Vitamin K was not measured directly since there is no reliable/practical assay for the measurement of Vitamin K in humans. Vitamin K status was indirectly assessed using the prothrombin time reflecting the concentration of vitamin K-dependent coagulation factors.

In summary, the CSV treatments were associated with statistically significant changes in some vitamin and coagulation parameters. The same degree of changes in vitamin levels were present in some placebo-treated patients . Thus, it is unlikely to be drug-related. Moreover, the magnitudes of the changes were small and the mean values remained within the normal range at endpoint. The patients with abnormal values were discussed in the individual study protocols reviewed in the preceding pages.

C. Drug-Drug Interactions: Since CSV is not absorbed, the potential mechanisms of interaction with other drugs is by affecting absorption, or by affecting excretion in the case of those drugs undergoing enterohepatic circulation. Cholestyramine has been reported to interact with warfarin, phenylbutazone, penicillin G, thyroid hormone, thiazide diuretics, amiodarone, cardiac glycosides, and phenobarbital. Colestipol has been reported to interact with propranolol, tetracycline, furosemide, penicillin G, gemfibrozil, clorothiazide, and digitoxin.

Pharmacokinetic effect of CSV on absorption of 7 drugs were studied: lovastatin, a HMG-CoA reductase inhibitor likely to be co-administered; digoxin and warfarin, agents with narrow therapeutic indices and both have been reported to interact with cholestyramine and colestipol; verapamil and metoprolol, commonly used in patients with cardiovascular disease; quinidine, an anti-arrhythmic with narrow therapeutic

index; and valproic acid, an anti-seizure agent that has been reported to interact with cholestyramine. For detailed evaluation of the pharmacokinetic studies, please see Biopharmacology Review.

In summary, Colesevelam therapy was found to have no significant effect on the bioavailability of digoxin, lovastatin, metoprolol, quinidine, valproic acid, and warfarin. Colesevelam therapy decreased the bioavailability of sustained-release verapamil by 11%, and the clinical significance of this finding is unclear.

D. Adverse Laboratory Parameters:

1. There were no clinically significant changes in mean hematology parameters or general chemistry parameters. The patients with abnormal values were discussed in the individual study protocols reviewed in the preceding pages.

2. Liver function tests: Mildly elevated liver function tests have been described with other bile acid sequestrants and have been attributed to increased bile acid synthesis and excretion rather than hepatic toxicity.
   a. There were statistically significant mean elevations of SGPT, SGOT, and Alkaline Phosphatase from baseline to endpoint in CSV-treated patients. These small mean elevations were <2x ULN). No patient developed persistently elevated SGOT, SGPT, and Alkaline Phosphatase >3xULN. No CSV-treated patient had increased bilirubin which is a marker of more severe hepatic toxicity.
   b. HMG-CoA reductase therapy is associated with elevation of liver function tests representing hepatic toxicity. In the combination studies with 3 HMG-CoA reductase inhibitors, there was no evidence of additive elevations of liver function tests. It should be pointed out that the doses of SIM (10 mg and 20 mg) and LOV (10 mg) and ATO (10 mg) were not maximal doses.
3. Changes in lipid profile: Therapy with bile acid sequestrants may increase VLDL production, (a major component of VLDL is TG), thereby increasing TG concentration. The mean percent increase in TG reached statistical significance in all the CSV-alone-treated groups from baseline to endpoint. Since patients with baseline TG >300 mg/dL were excluded from the study, no patient had TG >750 mg/dL. Greatly increased TG >1500-2000 mg/dL is associated with increased incidence of pancreatitis. There was no case of pancreatitis.

   During combination therapy with HMG-CoA reductase inhibitor therapy, TG were not increased but decreased since statins usually decrease TG.

In conclusion, Colesevelam HCL treatment, either as monotherapy or in combination with HMG-CoA reductase inhibitor, was well tolerated without serious clinically significant adverse effects, any clinically significant changes in safety laboratory tests, any prolongation of the prothrombin time or decreases in serum concentration of fat-soluble vitamins.

Integrated Summary of Efficacy: This summary is based on the analysis of individual monotherapy and combination therapy studies reviewed above and additional data submitted by the sponsor in the Integrated Summary of Safety.

1. Number of Patients Studied:

A. Monotherapy: Summary of clinical studies using colesevelam as monotherapy is shown below: Table modified from sponsor's tables:

Protocol	Study Design	Duration	Min-Max Dose (g)	Enrolled	Treated	Completed	Range for mean/ median % change
GTC-48-301	A randomized, double-blind Trail, CV vs. placebo	6 months	2.3 to 4.5	962	494	382	LDL-C: -9 to -18% -9 to -20% Total-C: -4 to -10% -5 to -10% HDL-C: +3 to +5% +3 to +4% TG: +8 to +14% +5 to +10%
GTC-48-302	A randomized, double-blind, placebo-controlled trial once/day vs. Split dose	6 weeks	3.8	177	98	90	LDL-C: -15 to -18% -14 to -19% Total-C: -8 to -9% -7 to -12% HDL-C: +4 to +9% +3 to +8% TG: +7 to +18% +6 to +15%
GTC-37-901	An extended use of CV in patients with primary hyper-Cholesterolemia	50 weeks	1.5 to 3.8 mean daily dose 2.8	272	260	186	LDL-C: -11% -12% Total-C: -4% -4% HDL-C: +13% +11% TG: +18% + 11%
GTC-37-201	A randomized, Double-blind, Placebo-Controlled trial	6 weeks	1.5 to 3.8	275	149	137	LDL-C: -4 to -15% -4 to -16% Total-C: -2 to -8% -3 to -9% HDL-C: +1 to +5% -2 to +4% TG: +2 to +23% +1 to +10%

In addition, Protocol GTC-37-202 was a randomized, double-blind, placebo-controlled trial of once/day vs. split dose in patients with primary hypercholesterolemia. 121 patients completed the 4-week study. The study dose was 1.5 g only and LDL-C reduction were –6 to –7%.

A. Combination Therapy: A summary of combination studies with HMG-Co-A reductase inhibitors is shown below:(Modified from sponsor's tables)

Protocol	Study Design	Duration	Min-Max Dose (g)	Enrolled	Treated	Completed	Range for mean/ median % change
GTC-37-203	A randomized, Double-blind, Placebo-controlled trial Of CV alone and in combination with LOV	4 weeks	CV 2.3 CV 2.3+ LOV 10 mg dosed Together or apart	202	135	126	LDL-C: -7 to-34% -8 to 33% Total-C: -3 to-21% -4 to-21% HDL-C: +3 to 5% +2 to 5% TG: -3 to +14% -2 to +16%
GTC-48-204	A randomized, double-blind, Placebo-controlled trial Of CV &SIM alone and in combination with SIM	6 weeks	CV 2.3, 3.8 CV 2.3+ SIM 20 mg CV 3.8+ SIM 10 mg	589	238	241	LDL-C: -8 to–42% -9 to-42% Total-C: -4 to–29% -3 to-30% HDL-C::+2 to 10% +2 to 10% TG: -5 to +15% -12 to +11%
GTC-48-205	A randomized, double-blind, Placebo-controlled trial Of CV&ATO alone and in combination	4 weeks	CV 3.8 CV 3.8+ ATO 10 mg	194	94	89	LDL-C:-12 to–48% -12 to-49% Total-C: -6 to–31% -6 to-29% HDL-C: +5 to10% +3 to11% TG: +2 to 17% -1 to +10%

II. Efficacy: The primary efficacy endpoint was the percent of mean LDL-C reduction. The secondary efficacy endpoints were mean percent reductions in total-C, HDL-C, TG, and apolipoprotein B, Lp(a), and apolipoprotein A-1. The data were presented and discussed in the individual study protocols. The relevant lipid and lipoprotein data can be summarized :

A. Monotherapy Efficacy The responses to the proposed 3.8 g and 4.5 g daily doses can be summarized from GTC-48-301, the pivotal dose-ranging study:

Percent Change in :Lipid/Lipoprotein B from Baseline to Endpoint:

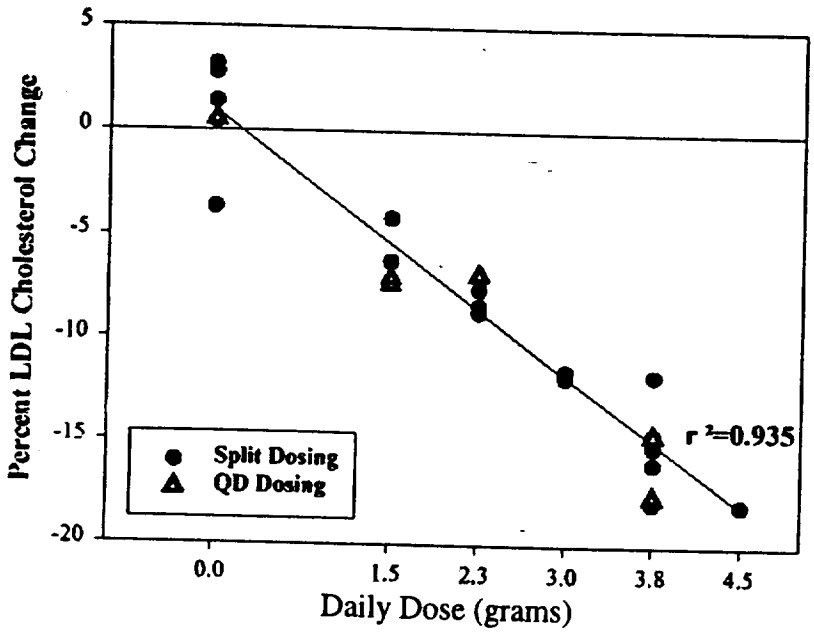
Percent Change/Lipid/Lipoprotein Parameter	Colesevelam Daily Dosage/# of patients	
	3.8 g	4.5 g
LDL-C	-14.6/95	18.0/94
Total-C	-7.1/95	-9.8/94
HDL-C	+2.9/95	+2.6/94
TG	+9.9/95	+9.4/94
Apolipoprotein B	-11.9/80	-12.1/75

Comments:

1. The main efficacy endpoint was percent LDL-C reduction which were –14.6 and - -18.0% respectively for 3.8 g and 4.5 g daily dose.
2. As expected the apolipoprotein B showed corresponding reductions of –11.9 and –12.1% over the same dose range.
3. The clinical significance of the reduction of total-C is unknown. Similarly the clinical significance of the increases in TG and HDL-C is unknown.

The cumulative mean percent change in LDL-C in all the clinical studies was provided by the sponsor and is shown:

Figure A-1: Cumulative Mean Percent Change in LDL-C: >



The main efficacy endpoint was the LDL-C. Colesevelam treatment decreased LDL-C in an apparent dose dependent fashion. According to the sponsor, "when the data were plotted using a linear regression analysis, the coefficient of determination r^2 ,calculated for this linear regression ,was 0.935. The coefficient of determination is the square of the Pearson correlation coefficient, and can be interpreted as the proportion of the variability among the observed values of y that is explained by the linear regression of y on x." There were no difference between once a day dosing or split dosing between breakfast and dinner.

B. Combination therapy with HMG-Co-A reductase inhibitors: The data from studies GTC-37-203, GTC-48-204 and GTC-48-205 can be summarized :

HMG-CoA Reductase Inhibitor dose	Colesevelam Dose	% LDL-C reduction: Colesevelam	% LDL-C reduction: HMG-CoA reductase inhibitor	% LDL-C reduction: Colesev+HMG-CoA Reductase inhibitor
Lovastatin 10 mg	2.3 g dosed together	7%	22%	34%
Lovastatin 10 mg	2.3 g dosed apart	7%	22%	32%
Simvastatin 20 mg	2.3 g/day	8%	34%	42%
Simvastatin 10 mg	3.8 g/day	16%	26%	42%
Atorvastatin 10 mg	3.8 g/day	12%	38%	48%

Comments:

1. There are two types of interactions between bile acid sequestrants and HMG-CoA reductase inhibitors. There is a pharmacodynamic interaction between the two classes of drugs because of their complementary effects in cholesterol homeostasis. However, bile acid sequestrants are reported to decrease serum levels of HMG-CoA reductase inhibitors due to altered absorption. The combination studies' data clearly demonstrated the additive therapeutic effect of lowering LDL-C.
2. There were similar increased changes in total-C, HDL-C in the combination studies, whether these were additive effects or not were not evaluated. The effects on TG in the combination studies reflected the result of the opposing effects of bile acid sequestrants and HMG-CoA reductase inhibitors.

Review of Financial Disclosure Forms:

The sponsor certified that he has not entered any financial arrangement with the listed investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a).

Labeling Review:
Additions are bolded and underlined. Deletions are noted by single strike-out.

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Draft

Labeling

[ ]

Conclusion and Recommendation:

This NDA should be approved.

/S/

S.W. Shen, M.D.
Medical Officer, HFD-510
4/24/00

CC:
Original NDA
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APPEARS THIS WAY
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