CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-445

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-445	Submission Date(s): Dec. 27, 2001
Brand Name	ZETIA™
Relevant IND(s)	[redacted]
Generic Name	Ezetimibe
Reviewer	Wei Qiu, Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	DPE II
ORM division	Metabolic and Endocrine Drug Products
Sponsor	MSP Singapore Co., LLC
Submission Type	Original NDA
Formulation; Strength(s)	Tablets; 10 mg
Indication	Hypercholesterolemia when administered alone or with an HMG-CoA reductase inhibitor; Hypercholesterolemia in patients with homozygous familial hypercholesterolemia; Elevated sitosterol and campesterol in patients with homozygous sitosterolemia.

II. Executive Summary

The MSP Singapore Co. LLC, a joint venture between Merck & Co., Inc. and Schering Corporation, submitted an original New Drug Application (NDA) for ZETIA™ (ezetimibe) tablets for the treatment of the followings:

- Primary hypercholesterolemia (heterozygous familial and non-familial), when administered alone or with an HMG-CoA reductase inhibitor, as an adjunct to diet and exercise;
- Hypercholesterolemia in patients with homozygous familial hypercholesterolemia (HoFH), as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable, and
- Elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolemia.

Both HoFH and homozygous sitosterolemia are rare forms of dyslipidemia which share grim prognoses in terms of the development of premature artherosclerosis, myocardial infarction, and death caused by coronary heart disease. While there is no approved pharmacological therapy for sitosterolemia, current standard therapy for HoFH (LDL apheresis and high-dose statin administration) is often inadequate. Ezetimibe is a proposed new or alternative therapeutic option for these serious diseases.

Ezetimibe, [redacted] is a member of a new class of lipid lowering compounds that are inhibitors of intestinal absorption of cholesterol. These agents block the intestinal absorption of dietary and biliary cholesterol. The specific molecular mechanism of action has not yet been

identified for this class of agents. The proposed dosing regimen is 10 mg once daily. Ezetimibe is proposed as a monotherapy or combination therapy with an HMG-CoA reductase inhibitor for incremental effect.

Clinical pharmacology section includes 32 studies. Of these 32 studies, there were 5 BA/descriptive pharmacokinetics studies, 6 studies in special populations, 18 drug interaction studies and 3 others. The pharmacokinetic results are summarized as follows:

The proposed to-be-marketed formulation was used in all Phase III clinical trials. Following oral administration of ^{14}C-ezetimibe (20 mg), total ezetimibe (ezetimibe + conjugated ezetimibe) accounted for approximately 93% of the total radioactivity in plasma. Approximately 78% and 11% of the administered radioactivity were recovered in the feces and urine, respectively. After oral administration, ezetimibe was rapidly and extensively conjugated to the phenolic glucuronide (conjugated ezetimibe), a major metabolic pathway. The mean peak plasma concentrations (Cmax) of conjugated ezetimibe and ezetimibe were achieved at 2 and 10 hours, respectively. Conjugated ezetimibe was a pharmacologically active metabolite. There was no substantial deviation from dose proportionality between – and 20 mg. Food had no effect on the oral bioavailability of ezetimibe when administered as a 10 mg tablet. Ezetimibe and conjugated ezetimibe were bound 99.7% and 88 to 92% to human plasma proteins, respectively. Both ezetimibe and conjugated ezetimibe were slowly eliminated with half-lives of 22 hours.

Elderly subjects had 2-fold greater plasma concentrations than younger subjects. Patients with severe chronic renal insufficiency had 50% higher exposure to ezetimibe and total ezetimibe compared to healthy subjects. After single dose administration, patients with various degrees of liver dysfunction had 1.8- to 4.2-fold increase in plasma ezetimibe and total ezetimibe concentrations, which was related directly with the severity of liver disease. Patients with moderate chronic liver disease had 4-fold higher exposure to ezetimibe and total ezetimibe compared to healthy subjects after multiple dosing.

Gemfibrozil and fenofibrate coadministration with ezetimibe increased the exposure to total ezetimibe approximately 1.7-fold and 1.5-fold, respectively. Concomitant cholestyramine administration decreased the mean exposure to total ezetimibe by 55%.

A. Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation 2 (OCPB/DPE-2) has reviewed NDA 21-445 submitted on 27 Dec 2001 and finds it acceptable. Labeling comments should be conveyed to the sponsor as appropriate.

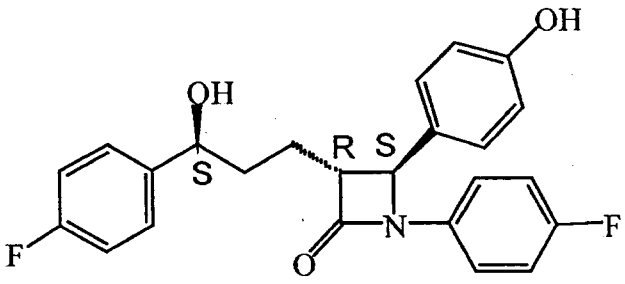
B. Phase IV Commitments

None.

III. Table of Contents

IV. Summary of CPB Findings

Zetia™ (Ezetimibe) tablet was developed as a new class of lipid lowering agents that inhibit the intestinal absorption of cholesterol. The proposed dosing regimen is 10 mg once daily. The proposed to-be-marketed formulation is the same as that used in Phase III clinical trials.



$C_{24}H_{21}F_2NO_3$ MW 409.4

Figure 1. Chemical Structure of Ezetimibe

Pharamcokinetics

The absolute bioavailability of ezetimibe (SCH 58235) cannot be determined since this compound is virtually insoluble in aqueous media. Ezetimibe is rapidly absorbed and extensively conjugated to an active phenolic glucuronide (ezetimibe-glucuronide) (SCH 60663) after oral administration with the mean Cmax of total ezetimibe achieved at 2-3 hour post dose. The Cmax of ezetimibe was attained at 10 hour post dose. The UDP-glucuronosyltransferase enzymes UGT1A1, UGT1A3, and UGT2B15 have been shown to be responsible for the glucuronidation of ezetimibe. The plasma concentration-time profiles exhibited multiple peaks, suggesting enterohepatic recycling. Dose proportionality for ezetimibe was established between [redacted] and 20 mg. Linearity was established for total and conjugated ezetimibe between [redacted] and 20 mg. Food did not alter the bioavailability of ezetimibe.

The in vitro protein binding to human plasma ranged from 99.5 to 99.8% for ezetimibe, and 87.8 to 92.0% for ezetimibe-glucuronide. The in vivo human plasma protein binding for ezetimibe was not determined. For total ezetimibe the mean in vivo protein binding ranged from 93.9 to 94.5%.

Ezetimibe is primarily metabolized via glucuronide conjugation with subsequent biliary and renal excretion. A schematic pathway for the proposed biotransformation of ezetimibe in humans is provided in Figure 2.

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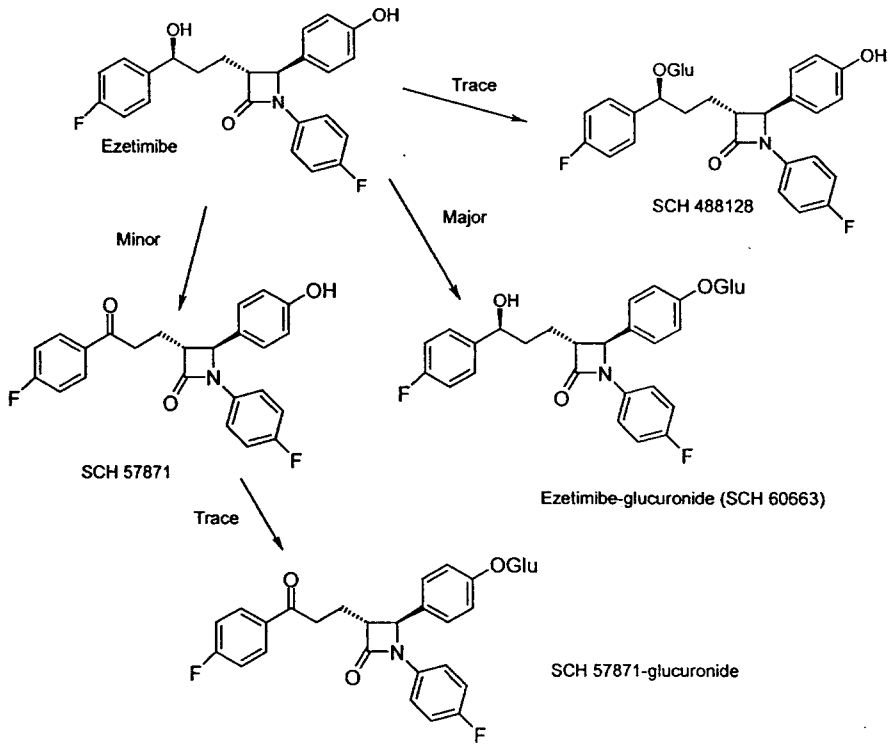

Figure 2. Proposed biotransformation pathway for ezetimibe in humans.

After oral administration of 20 mg ^{14}C-ezetimibe, the majority (78%) for the ezetimibe-derived radioactivity was eliminated in the feces, with 11% excreted in the urine. The majority of the radioactivity in feces was associated with ezetimibe. The majority of the radioactivity in urine was associated with ezetimibe-glucuronide. The systemic exposure (based on AUC) to ezetimibe and ezetimibe-glucuronide was approximately 93% of the systemic exposure to drug-derived radioactivity in plasma. The majority (90%) of the radioactivity in plasma was associated with ezetimibe-glucuronide, with ezetimibe accounting for the majority of the balance of drug-derived radioactivity. Both parent drug and ezetimibe-glucuronide were slowly eliminated, with half-lives of ezetimibe and conjugated ezetimibe of 22 hours. Following once daily multiple dosing, conjugated ezetimibe and ezetimibe accumulated 2 to 3 fold.

PK in Special Populations

The pharmacokinetics of ezetimibe was similar between males and females. After a daily dose of 20 mg ezetimibe for 10 consecutive days, females had slightly higher (13-22%) mean Cmax and AUC values of ezetimibe and total ezetimibe than males.

Meta analysis results showed that the pharmacokinetics of ezetimibe was similar between Caucasians and Blacks.

Systemic exposure (Cmax and AUC) to total and conjugated ezetimibe was significantly greater (2-fold) in elderly subjects (≥ 65 years) than that in the young (18-45 years). The mean AUC and Cmax values of total and conjugated ezetimibe in children (10-18 years) were similar to those in adults.

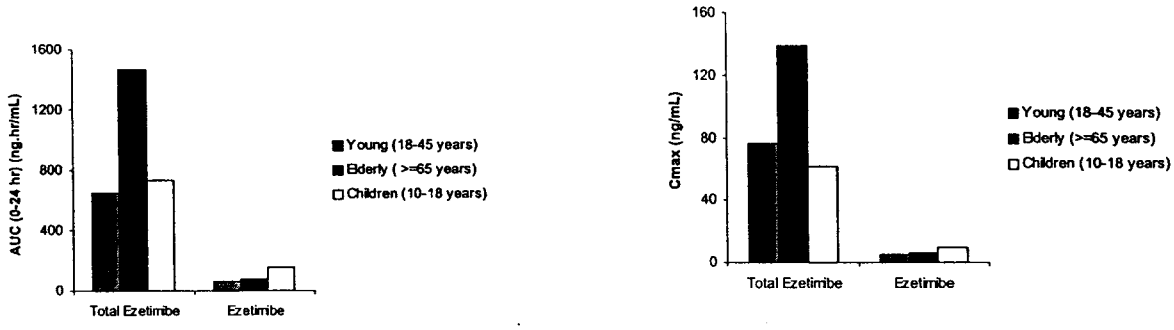

Figure 3. Comparison of pharmacokinetic parameters of ezetimibe in young, elderly and children.

Patients with severe chronic renal insufficiency had approximately 50% higher exposure (AUC) to ezetimibe and total ezetimibe compared to healthy subjects when ezetimibe was administered at a 10 mg single dose. Severe chronic renal insufficiency did not affect the protein binding of total ezetimibe. One patient exhibited significantly greater exposure than those for the rest of the patients. The AUC values of total ezetimibe and ezetimibe were 9-fold and 4-fold greater than those in other patients, possibly due to concomitant cyclosporine administration.

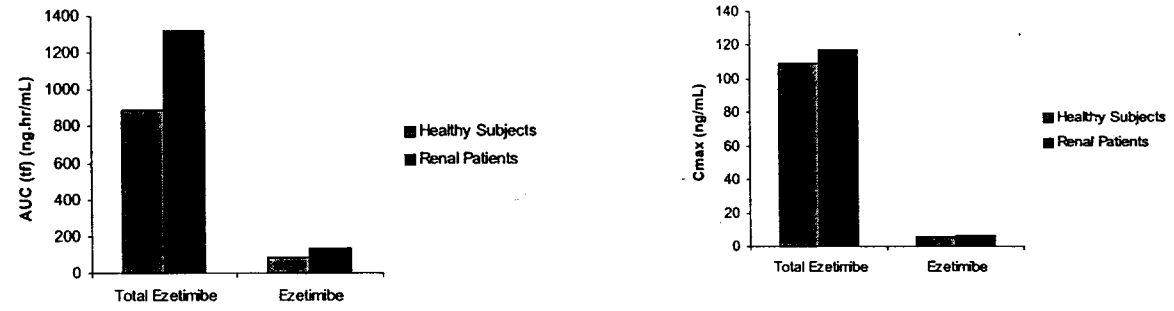

Figure 4. Comparison of pharmacokinetics parameters of ezetimibe in healthy subjects and patients with severe chronic renal insufficiency.

Patients with moderate and severe liver disease had 3- to 6-fold greater exposures to all ezetimibe analytes compared to healthy subjects when ezetimibe was given a 10 mg single dose. The AUC values of total ezetimibe for patients with mild liver impairment were 1.7-fold greater than those in healthy volunteers. Multiple dose study consistently demonstrated that patients with moderate chronic liver disease had 4-fold greater exposures (AUCs) to all ezetimibe analytes than those in healthy subjects.

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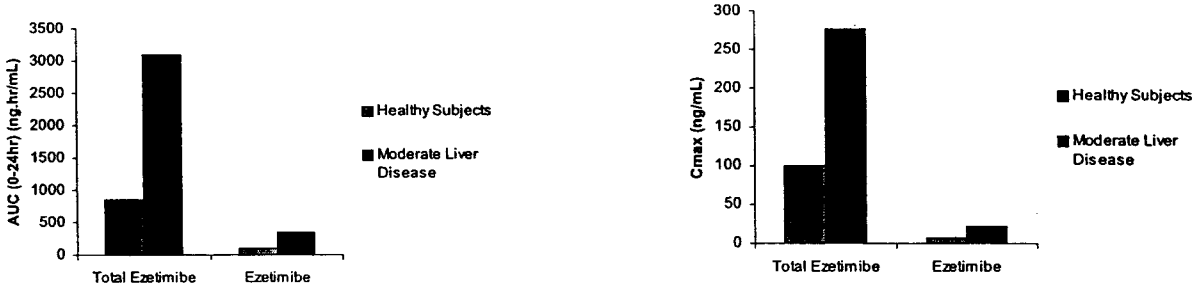

Figure 5. Comparison of pharmacokinetics parameters of ezetimibe following multiple dose administration in healthy subjects and patients with moderate liver disease.

Drug-Drug Interaction

Multiple-dose administration of Ezetimibe 20 mg given orally once daily for 7 days had no effect on the metabolic activities of CYP1A2, CYP2D6, CYP3A4, CYP2C8/9, or N-acetyltranferase enzymes using a "cocktail" approach. This "cocktail" included dextromethorphan (30 mg), caffeine (200 mg), tolbutamide (500 mg), dapsone (100 mg) and IV midazolam (0.05 mg/kg).

• *Effect of ezetimibe on other drugs:*

Multiple doses of Ezetimibe given 10 mg once daily for 7 – 14 days had no significant effect on AUC and Cmax values of gemfibrozil, fenofibric acid, simvastatin, lovastatin, pravastatin, atorvastatin, cerivastatin, fluvastatin, digoxin, ethinyl estradiol and levonorgestrel.

Multiple doses of ezetimibe given 10 mg once daily for 7-10 days did not alter the pharmacokinetics and pharmacodynamics of digoxin, warfarin, and glipizide.

• *Effect of other drugs on Ezetimibe:*

Multiple doses of gemfibrozil given 600 mg twice daily for 7 days increased the exposure to total ezetimibe and ezetimibe approximately 1.7-fold and 1.4-fold based on AUC values, respectively.
Multiple doses of fenofibrate given 200 mg once daily for 14 days increased the AUC and Cmax values of total ezetimibe 1.5-fold and 1.6-fold, respectively, with no effect on exposure to ezetimibe.
Multiple doses of cholestyramine given 4 g twice daily for 14 days decreased the AUC values of ezetimibe and total ezetimibe approximately 80% and 55%, respectively.
Multiple doses (7- 14 days) of lovastatin (20 mg daily), pravastatin (20 mg once daily), atorvastatin (10 mg once daily), cerivastatin (0.3 mg once daily), fluvastatin (20 mg once daily), cimetidine (400 mg twice daily), single dose of Supralox® antacid 20 mL or single dose of glipizide 10 mg did not alter the overall exposure to total ezetimibe (<20%).

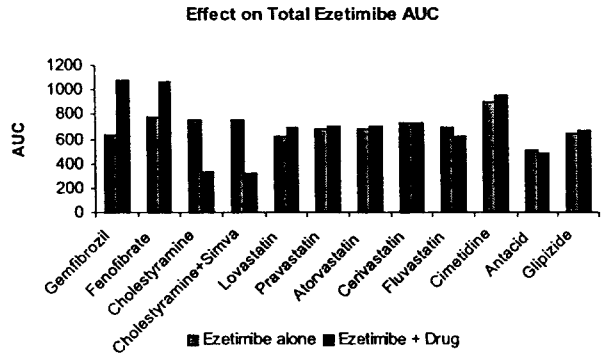

Figure 6. Effect of Drug Coadministration on Total Ezetimibe AUC

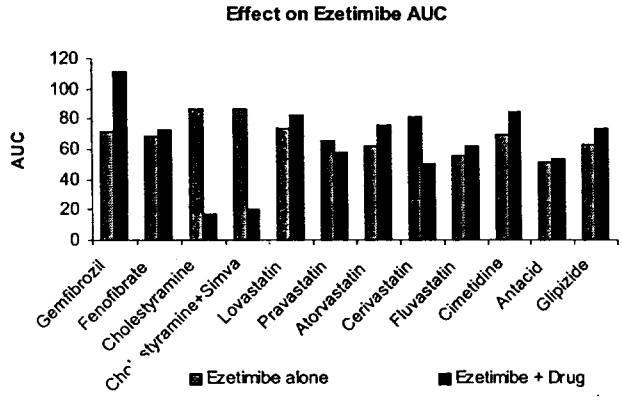

Figure 7. Effect of Drug Coadministration on Ezetimibe AUC

PK/PD Relationship

The degree of decrease in plasma concentrations of LDL-C was directly related to the dose of ezetimibe. Plasma LDL-C decreased as ezetimibe dose increased up to 10 mg. Doses beyond 10 mg failed to provide further benefit significantly.

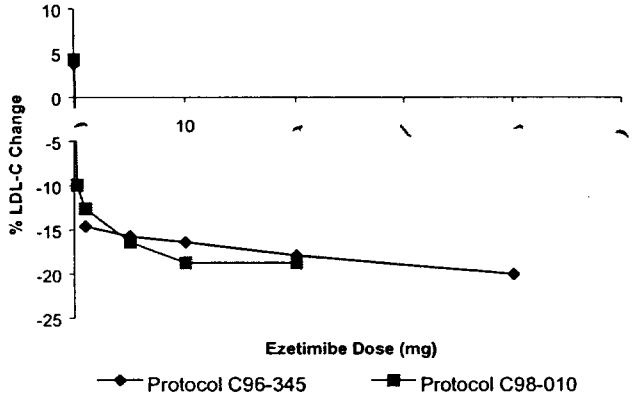

Figure 8. Dose-Response Relationship of LDL-C Lowering Effect of Ezetimibe

In Vitro Dissolution

The dissolution method is apparatus 2, paddles at 50 rpm and a dissolution medium of [redacted]. The dissolution specification is not less than [redacted] (Q) in 30 minutes.

V. QBR

A. General Attributes

QA1. What are the highlights of the chemistry and physical-chemical properties of the drug substance?

Molecular Formula:	$C_{24}H_{21}F_2NO_3$
Molecular Weight:	409.4
Chirality:	Ezetimibe has three chiral centers and therefore eight isomers are possible. Ezetimibe is the isomer with the stereochemical configuration [redacted]
Dissociation Constant:	The pKa of the phenol group is [redacted] Ezetimibe tertiary nitrogen is not ionizable.
Partition Coefficient (log Ko/w):	[redacted]
Solubility:	[redacted] forms are insoluble in aqueous solvents and non-polar solvents such as hexane; soluble in acetonitrile and USP ethanol.
Particle Size:	Typically, the drug substance has a median particle size in the range of [redacted] and the distribution contains [redacted] (by volume) of particles [redacted] (by volume) of particles [redacted] at the time of manufacturing.

[redacted]

QA2. What is the formulation of the drug product?

The unit composition for the proposed commercial formulation (Formula #3346) of Ezetimibe tablets, 10 mg is described below.

Table 1. Composition of Ezetimibe Tablets (Formula #3346)

Ingredients	mg/Tablet
Ezetimibe, [redacted]	10.0
Lactose Monohydrate NF	[redacted]
Microcrystalline Cellulose NF	
Povidone [redacted] USP	
Croscarmellose Sodium NF	
Sodium Lauryl Sulfate	
Magnesium Stearate NF	
TOTAL WEIGHT	**100.0 mg**

The proposed commercial formulation for ezetimibe is a capsule shaped immediate release tablet. Each tablet is manufactured via [redacted] employing [redacted] The to-be-marketed tablet formula was used in all Phase III clinical safety and efficacy studies.

QA3. What is the proposed mechanism of drug action?

The specific molecular mechanism of action has not yet been identified. The sponsor stated that ezetimibe inhibited intestinal dietary and biliary cholesterol absorption. This is the first drug in the class.

The activities of ezetimibe and conjugated ezetimibe, the phenolic glucuronide of ezetimibe, as cholesterol absorption inhibitors, were evaluated in different animal models. The activity of ezetimibe was also evaluated in human.

In hamster model, conjugated ezetimibe was given once daily by oval gavage in corn oil. The conjugated ezetimibe and ezetimibe were found to have ED_{50} of 0.17 and 0.04 mg/kg/day, respectively. The activity of conjugated ezetimibe was also evaluated in an acute rat cholesterol absorption model where the enterohepatic circulation was interrupted. The results showed that whether drug was delivered as the parent compound ezetimibe or as the glucuronide, absorption of cholesterol was significantly inhibited. Cholesterol absorption was further determined in rats following intraduodenal administration of the conjugated ezetimibe, in the presence and absence of D-glucaro-1,4-lactone (GL) (2 x 250 mg/kg), a deglucuronidation blocking agent. No significant differences in cholesterol absorption inhibition by conjugated ezetimibe were found between the comparable vehicle and GL dose groups. Overall, the pre-clinical results indicate that both ezetimibe and the conjugated ezetimibe have intrinsic activity as a cholesterol absorption inhibitor.

The effect of ezetimibe on intestinal cholesterol absorption was also evaluated in patients with mild-to-moderate hypercholesterolemia. The fractional cholesterol absorption was determined for each patient during the second week of each treatment period using the "continuous-feeding dual-isotope method". For this purpose patients took tracer capsules ($[^2H_6]$cholesterol and $[^2H_4]$sitostanol) 3 times daily for 7 days during the second week of each treatment period. Stool samples were collected daily over the final 4 days of each treatment period for measurement of fractional cholesterol absorption. The ratio of deuterated-cholesterol relative to deuterated-sitostanol was measured in stool samples by
The results showed that after 2 weeks of treatment, the geometric mean values for fractional cholesterol absorption were 22.7% for ezetimibe 10 mg and 49.8% for placebo. The geometric mean ratio (ezetimibe 10 mg/placebo) was 0.46 (90% CI: 0.35, 0.60). These results indicate that treatment with ezetimibe 10 mg/day for 2 weeks reduced fractional cholesterol absorption by 54% as compared with placebo.

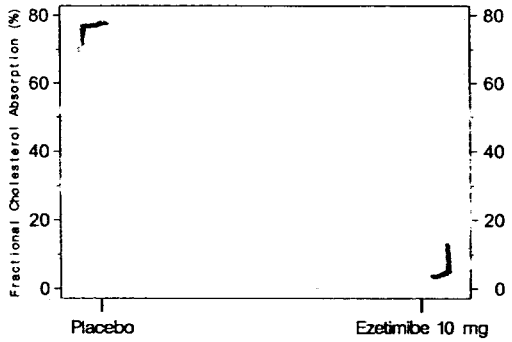

Figure 9. Fractional Cholesterol Absorption Values After 2 Weeks of Treatment With Placebo or Ezetimibe 10 mg for Each Patient

B. General Clinical Pharmacology

QB1. What are the characteristics of the exposure-response relationships for efficacy?

The degree of decrease in plasma concentrations of LDL-C was directly related to the dose of ezetimibe. The plasma LDL-C decreased 16-19% as the ezetimibe dose increased up to 10 mg. Doses beyond 10 mg failed to provide further LDL lowering significantly.

The dose-response relationship of ezetimibe in lowering LDL cholesterol compared to placebo was evaluated in two Phase II studies. In the pilot study C96-411/C96-345, the patients with primary hypercholesterolemia were administered orally in doses of [redacted] 10 mg, [redacted] and [redacted] once daily for 8 weeks. The results showed all active treatments decreased LDL-C significantly compared with placebo, the mean decreases ranging from approximately 15%-20% for ezetimibe [redacted] mg.

Table 2. Percent Changes (S.E.M.) from Baseline to Treatment Endpoint in Plasma Concentrations of Various Lipid-Related Variables in The Intent-to-Treat Data Set (C96-345)

Variables	Placebo (n=17)	Ezetimibe [redacted] (n=17)	Ezetimibe [redacted] (n=20)	Ezetimibe 10 mg(n=18)	Ezetimibe [redacted] (n=16)	Ezetimibe [redacted] (n=18)
Direct LDL-C	+3.8 (2.5)	-14.6 (2.4)	-15.7 (1.6)	-16.4 (2.2)	-17.9 (2.0)	-20.0 (2.0)
Total C	+0.9 (2.1)	-10.3 (1.8)	-11.8 (1.2)	-10.4 (1.9)	-14.2 (1.9)	-15.8 (1.8)

A confirmatory study (C98-010) evaluate the efficacy of ezetimibe in lowering LDL cholesterol compared to placebo when administered orally, once daily for 12 weeks in patients with primary hypercholesterolemia. The dose-response relationship of the LDL-C lowering effect of ezetimibe was determined over a range of [redacted] mg to 10 mg. Results showed that all active treatments decreased direct LDL-C significantly compared with placebo. Ezetimibe [redacted] mg to 10 mg was effective in reducing the mean plasma concentration of LDL-C by approximately 10% to 19% at the end of treatment. Figure 8 illustrates the results from these two studies.

Table 3. Percent Changes (S.E.M.) from Baseline to Study Endpoint in Plasma Concentrations of Various Lipid-Related Variables in the Intent-to-Treat Data Set (C98010)

Variables	Placebo (n=52)	[redacted] mg (n=47)	[redacted] (n=49)	[redacted] (n=49)	10 mg (n=46)
Direct LDL-C	+4.3 (1.4)	-9.9 (1.5)	-12.6 (1.5)	-16.4 (1.4)	-18.7 (1.5)
Total C	+2.2 (1.1)	-6.8 (1.2)	-10.3 (1.2)	-12.6 (1.1)	-12.6 (1.2)

QB3. What are the characteristics of the exposure-response relationships for safety?

Ezetimibe was well tolerated and had an overall adverse event profile similar to that of placebo.

The characteristics of the exposrue-repsonse relationships for safety of ezetimibe were evaluated in two Phase I studies and two Phase II studies. The results of the two Phase I studies showed that there were no apparent increase in the overall incidence of adverse events as the dose of ezetimibe increased up to [redacted] mg after multiple dose administration to healthy subjects. The results of two Phase II studies showed that ezetimibe was well tolerated and had an overall adverse event profile similar to that of placebo in subjects with primary hypercholesterolemia.

Phase I study I96-088 evaluated the safety and tolerability of ezetimibe when administered orally at single doses of [redacted], 10, [redacted] mg to healthy male volunteers. Of the 30 subjects who received ezetimibe, 6 (20%) reported adverse events, which was similar to the incidence rate (4/15; 27%) observed for the subjects receiving placebo. There was no apparent increase in the overall incidence of adverse events as the dose of ezetimibe increased from [redacted] mg to [redacted] mg. Phase I study I96-139 assessed the safety and tolerability of ezetimibe when administered orally at multiple doses of 10 [redacted] and [redacted] mg to healthy male volunteers for 14 days. Of the 27 subjects

who received ezetimibe, 11 (41%) reported adverse events, which was similar to the incidence rate (5/9; 56%) observed for the subjects receiving placebo. There was no apparent increase in the overall incidence of adverse events as the dose of ezetimibe increased from 10 mg to [redacted] mg. One subject (No. 26, [redacted] mg) discontinued treatment when his SGPT values reached 3x the upper reference limit. Ten of the 35 subjects enrolled (8 active, 2 placebo) had noteworthy elevations in liver function test.

Phase II study C96345 evaluated the safety of ezetimibe when administered orally in doses of [redacted] 10 mg, [redacted] once daily for 8 weeks to subjects with primary hypercholesterolemia. Six subjects discontinued treatment because of adverse events: 1 each treated with placebo or ezetimibe [redacted] mg; and 2 each treated with lovastatin 40 mg or ezetimibe 10 mg. The subject treated with ezetimibe [redacted] mg had mild urticaria (hives plus rash) that resolved with diphenhydramine.

Table 4. Number (%) of Subjects Reporting the Treatment-Emergent Adverse Events (C96345)

Adverse Events		Ezetimibe				Lovastatin
	Placebo (n=17)	[redacted] mg (n=17)	[redacted] mg (n=20)	10 mg (n=18)	[redacted] mg (n=16)	[redacted] mg (n=18)	40 mg (n=18)
Upper respiratory tract infection	0	4(24)	1(5)	1(6)	4(25)	1(6)	1(6)
Infection, viral	4(24)	1(6)	1(5)	1(6)	2(13)	1(6)	2(11)
Headache	1(6)	1(6)	2(10)	2(11)	0	2(11)	2(11)
Arthralgia	1(6)	0	0	3(17)	1(6)	2(11)	1(6)
myalgia	1(6)	1(6)	2(10)	1(6)	1(6)	1(6)	0

Phase II study C98010 confirmed the safety of a range of doses as determined by a pilot study (C96345) of ezetimibe when administered orally, once daily for 12 weeks, to subjects with primary hypercholesterolemia. Three subjects discontinued treatment because of adverse events: 1 treated with placebo (elevated liver enzymes: Day 65), 1 treated with ezetimibe [redacted] mg (arthralgia, edema dependent, paroniria, and skin disorder [red blotches on face]; Day 43), and 1 treated with ezetimibe [redacted] mg (thrombocytopenia; Day 35).

Table 5. Number (%) of Subjects Reporting the Most Common Treatment-Emergent Adverse Events (C98010)

		Ezetimibe			
	Placebo (n=52)	[redacted] mg (n=47)	[redacted] mg (n=49)	[redacted] mg (n=49)	10 mg (n=46)
Headache	4(8)	2(4)	2(4)	2(4)	5(11)
Arthralgia	3(6)	2(4)	2(4)	5(10)	3(7)
Infection, viral	2(4)	1(2)	1(2)	6(12)	4(9)
Upper respiratory tract infection	2(4)	3(6)	7(14)	0	2(4)

QB4. What is the safety profile of ezetimibe monotherapy and combination with statins in animals and humans?

Ezetimibe monotherapy revealed some toxicity in animals in heart (e.g., mononuclear cellular infiltration, enlarged heart with thickening of the right ventricular wall, nodularity of the left arterioventricular valve, and altered shape of the aortic valve), lymph nodes (e.g., accumulation in plasma cells, lymphoid mesenteric hyperplasia, mesenteric & mandibular hemorrhage/erythrophagocytosis, brown pigment accumulation), kidney, and bone marrow. According to pharma/tox reviewer, these target organ toxicities were observed at >10X human doses, suggesting sufficient safety margin in humans. No significant neoplastic or non-neoplastic tumor findings were observed at 160-220X and 14X the human exposures in mice and rats respectively. There were no clinical issues with monotherapy according to medical reviewer.

With the comination therapy, the target organs of toxicity in rats were liver (increase in liver enzymes ALT and/or AST, CGT), stomach and skeletal muscles. The combination of ezetimibe

and statins in rats generally increased the exposure of both the drug and statins (or their active hydroxy acids) by approximately 2-fold and toxicity could be explained based on a metabolic drug interactions. In dogs, the combination of ezetimibe and simvastatin or lovastatin resulted in the increased exposures to ezetimibe and simvastatin or lovastatin. The combination with statins had low or non-existent safety margins in rats and dogs to humans. In general, an increase in incidences/severity of the toxicity is observed in the target organ with the combination; but new toxicities have not been identified. The pharma/tox reviewer indicated that the toxicity profile appeared to be associated with statins. The combination did not show mutagenic/clastogenic potential. The clinical stuides of ezetimibe and statin combination did not seem to show major adverse events related to above toxicities in animals according to medical reviewer.

QB5. What is the feature of pharmacokinetics?

The absorption, distribution, metabolism and excretion of ^{14}C-ezetimibe were characterized following a single oral 20-mg dose to eight healthy male subjects (C97136).

Table 6. Mean (%CV) pharmacokinetic parameter of ezetimibe and radioactivity in plasma (C97136)

Parameter	Unit	Plasma Ezetimibe			Unit	Radioactivity
		Ezetimibe	Conjugated Ezetimibe	Total Ezetimibe		Plasma
Cmax	ng/mL	5.21 (52)	61.2 (51)	64.2 (51)	ng equiv/g	75.1 (47)
Tmax	hr	9.88 (114)	2.31 (66)	2.31 (66)	hr	2.63 (63)
AUC(tf)	ng.hr/mL	86.4 (56)	636 (33)	726 (30)	ng equiv.hr/g	780 (42)

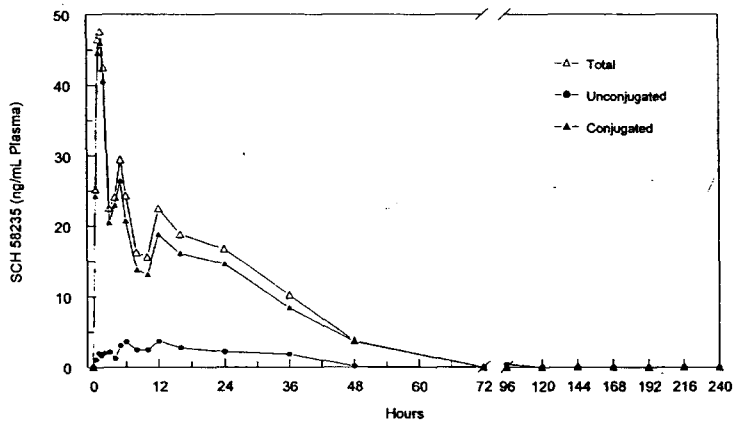

Figure 10. Mean plasma ezetimibe concentrations following a single oral administration of 20 mg ^{14}C-ezetimibe to eight healthy male volunteers (C97136).

Ezetimibe was rapidly absorbed following oral administration with mean Cmax of total ezetimibe and radioactivity achieved, on average, at 2-3 hour post-dose. Thereafter, concentrations rapidly declined, and then increased exhibiting multiple peaks, consistent with enterohepatic recycling. Plasma concentrations of ezetimibe and total ezetimibe were quantifiable until about 24-48 hr post-dose.

Ezetimibe was rapidly and extensively metabolized via glucuronide conjugate. The exposure (AUC) to ezetimibe represented approximately 10% of the exposure to total ezetimibe, suggesting extensive conjugation. The major route of elimination of drug-derived radioactivity following oral administration of ^{14}C-ezetimibe was via the feces and ranged from 62.6 to 87.4% of administered dose. Ezetimibe was the major component in feces and accounted for about 69% of the administered dose. The presence of ezetimibe in feces may be due to unabsorbed drug or to the hydrolysis of conjugated ezetimibe to ezetimibe during intestinal transit. An average of 11.3%

of the dose was excreted in the urine. Conjugated ezetimibe was the major component in urine (about 9% of the administered dose). Total recovery of radioactivity at 240 hr post-dose averaged 89.0% of the administered dose. There was no evidence that ezetimibe undergoes —— —— following oral administration to humans. The cumulative excretion data are illustrated in Figure 11.

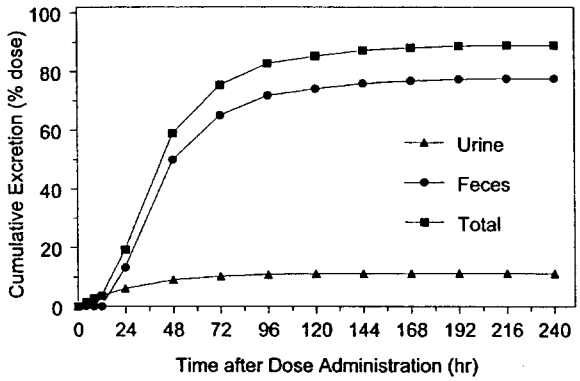

Figure 11. Cumulative recovery of radioactivity of ezetimibe in healthy male volunteers.

QB6. What are the in vitro binding characteristics of ezetimibe to plasma proteins?

The in vitro ezetimibe plasma protein binding in human ranged from 99.5% and 99.7% at ezetimibe concentrations ranging between 5 and 200 ng/mL (Sn98269). The range of in vitro binding of conjugated ezetimibe to human plasma proteins at concentrations of 2 to 2000 ng/mL was 87.8 to 92.0% (Sn99393).

QB7. Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The linearity for total and conjugated ezetimibe and proportionality for ezetimibe were established based on the log-transformed dose and AUC values over the ezetimibe dose range of —— mg (P00750).

Table 7. Mean (%CV) pharmacokinetic parameters of ezetimibe (P00750)

	Ezetimibe			Conjugated Ezetimibe			Total Ezetimibe		
	— mg	10 mg	— mg	— mg	10 mg	— mg	— mg	10 mg	— mg
Cmax	2.14	3.41	6.06	48.6	71.1	115	50.1	73.6	119
	(64)	(51)	(66)	(38)	(43)	(40)	(38)	(43)	(40)
AUC(0-24hr)	21.9	41.0	76.0	218	400	743	240	440	819
	(53)	(43)	(46)	(43)	(37)	(42)	(41)	(35)	(39)

Table 8. Statistical Comparison of the Log-transformed AUC values of Ezetimibe (P00750)

	P-value[a]		
Parameter	Total Ezetimibe	Conjugated Ezetimibe	Ezetimibe
Lack of fit[b]	0.7623	0.7623	0.8224
Intercept[c]	0.000	0.000	0.000
Slope[d]	0.0002	0.0001	0.1337

[a]: Based on log-transformed data
[b]: Test for deviation from linearity
[c]: Test for intercept = 0
[d]: Test for slope = 1

QB8. How do PK parameters change following chronic dosing?

After chronic dosing, the mean accumulation ratios of total, conjugated and ezetimibe were approximately 2-3 fold regardless of gender or age.

In **healthy volunteers**, the mean accumulation ratios of total ezetimibe, conjugated ezetimibe, and ezetimibe AUC values after multiple dose administration of 10 mg ezetimibe for 14 days were 1.6, 1.6, and 2.3, respectively (P01912).

Table 9. Mean (%CV) Single dose and multiple dose pharmacokinetic parameters (P01912)

Parameter	Total Ezetimibe		Conjugated Ezetimibe		Ezetimibe	
	Day 1	Day 14	Day 1	Day 14	Day 1	Day 14
Cmax	84.2 (64)	100 (47)	82.7 (65)	95.4 (48)	3.50 (36)	7.20 (57)
AUC(0-24hr)	529 (39)	853 (47)	489 (41)	760 (49)	40.6 (33)	93.2 (56)
R (AUC)	–	1.61	–	1.55	–	2.29

In **males**, the mean accumulation ratios of total ezetimibe, conjugated ezetimibe, and ezetimibe AUC values after multiple dose administration of — mg ezetimibe for 10 days were 1.75, 1.73, and 2.04, respectively (C98-107). In **females**, the mean accumulation ratio of total ezetimibe, conjugated ezetimibe, and ezetimibe were 1.97, 1.94, and 2.36, respectively (C98-107). In **elderly** (≥ 65 years), the mean accumulation ratio of total ezetimibe, conjugated ezetimibe, and ezetimibe AUC values were 1.72, 1.83, and 1.72, respectively (C98-115). In **adolescents** (10-18 years), the mean accumulation ratios of total ezetimibe, conjugated ezetimibe, and ezetimibe after multiple dose administration of 10 mg ezetimibe for 7 days were 1.82, 1.72, and 2.32, respectively (P00774).

QB9. What is the inter-subject variability of PK parameters in volunteers and patients?

In healthy volunteers, plasma ezetimibe concentrations exhibited moderate inter-subject variability. The coefficients of variation for the mean AUC values ranged from 35 to 60%. Patients with severe chronic renal insufficiency or chronic liver disease had similar inter-subject variability.

C. Intrinsic Factors

QC1. How does gender influence exposure?

Females had slightly higher (13-22%) mean Cmax and AUC values of all ezetimibe analytes than males after administration of 20 mg (2x10 mg tablets) ezetimibe once daily for 10 days (C98-107). This difference may partly be attributed to the difference in body weight. The average body weight for male and female subjects were 76 lbs and 67 lbs, respectively. In terms of adverse events, only females reported gastrointestinal adverse events.

Table 10. Mean (%) Day 10 pharmacokinetic parameters of ezetimibe for male and female subjects (C98-107)

Parameter	Gender	Total Ezetimibe	Conjugated Ezetimibe	Ezetimibe
Cmax (ng/mL)	Male	156 (34)	149 (36)	10.1 (34)
	Female	187 (53)	178 (53)	12.2 (39)
Tmax (hr)	Male	1.04 (48)	1.08 (43)	7.88 (84)
	Female	1.08 (68)	1.08 (68)	7.04 (71)
AUC(0-24 hr) (ng.hr/mL)	Male	1523 (39)	1374 (42)	149 (31)
	Female	1740 (37)	1556 (39)	185 (34)

QC2. How does age influence pharmacokinetics of ezetimibe?

Elderly (≥ 65 years) had 2-fold higher total ezetimibe concentrations than the young (18-45 years) (C98-115). The elderly subjects had similar body weights as those of young subjecdts (77 lbs vs. 80 lbs). Adolescents (10-18 years) had similar exposure to total ezetimibe but had 1.3 to 2.7 fold greater exposures to ezetimibe than those in adults (P00774). The average body weight of adolescents was 61 lbs.

Table 11. Mean (%CV) Pharmacokinetic Parameters of ezetimibe (C98-115)

Parameter	Age Group	Total Ezetimibe		Conjugated Ezetimibe		Ezetimibe	
		Day 1	Day 10	Day 1	Day 10	Day 1	Day 10
Cmax (ng/mL)	Young	66.6 (54)	76.2 (73)	65.6 (53)	74.1 (74)	3.35 (61)	4.87 (42)
	Elderly	113 (43)	139 (44)	111 (43)	135 (45)	4.21 (56)	5.73 (36)
Tmax (hr)	Young	1.42 (58)	1.00(80)	1.42 (58)	1.0 (80)	7.33 (29)	8.50 (20)
	Elderly	1.54 (54)	1.83 (112)	1.54 (54)	1.83 (112)	8.17 (30)	8.33 (52)
AUC(0-24hr) (ng.hr/mL)	Young	503 (65)	646 (63)	467 (69)	589 (66)	36.3 (42)	57.4 (43)
	Elderly	905 (46)	1461 (52)	853 (46)	1380 (54)	51.9 (58)	80.0 (36)
T1/2eff(hr)	Young	–	12.8 (40)	–	13.8 (25)	–	19.2 (33)
	Elderly	–	20.7 (53)	–	20.6 (54)	–	24.4 (43)

Table 12. Mean (%CV) Day 7 Pharmacokinetic parameters of Ezetimibe in Healthy Adolescent Volunteers (P00774)

Parameter	Total Ezetimibe	Conjugated Ezetimibe	Ezetimibe
Cmax (ng/mL)	61.8 (39)	54.8 (40)	9.71 (51)
Tmax (hr)	1.47 (118)	1.47 (118)	11.8 (58)
AUC(0-24 hr) (ng.hr/mL)	736 (43)	581 (46)	155 (49)
T1/2eff (hr)	21.5 (45)	19.8 (45)	29.3 (50)

QC3. How does renal function influence the pharmacokinetics of ezetimibe?

Patients with severe renal disease had mean exposures to all ezetimibe analytes 1.5-fold greater than those in healthy subjects (P00749). The mean ezetimibe terminal half-life was approximately 22 hours in healthy subjects and 30 hours in patients with severe renal insufficiency. Severe chronic renal insufficiency did not affect the protein binding of total ezetimibe.

Table 13. Mean (%CV) Pharmacokinetic Parameters of Ezetimibe 10 mg Tablet (P00749)

Parameter	Total Ezetimibe		Conjugated Ezetimibe		Ezetimibe	
	Healthy	Patients	Healthy	Patients	Healthy	Patients
Cmax (ng/mL)	109 (39)	117 (35)	106 (40)	113 (35)	5.12 (44)	6.65 (56)
Tmax (hr)	1.0	1.0	1.0	1.0	6.0	4.5
AUC(tf) (ng.hr/mL)	894 (33)	1317 (28)	805 (36)	1181 (30)	86.5 (56)	137 (60)
T1/2(hr)	22.1 (46)	30.1 (44)	22.8 (44)	30.4 (43)	22.4 (52)	28.9 (59)

Group 1 subjects had creatinine clearance greater than 80 mL/min/1.73 m^2 while Group 2 subjects had creatinine clearance between 10 - 29 mL/min/1.73 m^2.

Table 14. Statistical comparison of PK parameters for healthy subjects and patients with chronic renal insufficiency (P00749)

Parameter	Analyte	Point Estimate[a] (%)	90% CI
Cmax	Total Ezetimibe	108	79-147
	Conjugated Ezetimibe	108	78-148
	Ezetimibe	124	80-191
AUC	Total Ezetimibe	150	117-190
	Conjugated Ezetimibe	149	113-197
	Ezetimibe	155	97-248

[a]: Expressed as a percent of the corresponding value for subjects with chronic renal insufficiency to that in healthy volunteers.

One patient receiving multiple medications, including cyclosporine, had a 9-fold and 4-fold greater exposures to total ezetimibe and ezetimibe compared to the mean values of the patient group, respectively, possibly due to concomitant cyclosporine administration.

QC4. How does liver function influence the pharmacokinetics of ezetimibe?

After a single 10 mg dose of ezetimibe, the AUC values of total ezetimibe was increased 1.7-fold and 4-fold in patients with mild hepatic insufficiency and moderate (including severe) hepatic impairment compared to healthy subjects, respectively (P00251). This increase in ezetimibe

concentrations was observed for both ezetimibe and glucuronidated drug, and was not associated with an increase in the elimination half-life. Multiple dose study showed that the mean AUC values of total ezetimibe and ezetimibe were increased 4-fold in patients with moderate hepatic insufficiency compared to healthy subjects (P01912). Mean protein binding were 93.9% and 93.3% in healthy subjects and subjects with moderate chronic liver disease, respectively.

Table 15. Mean (%CV) Pharmacokinetic Parameters of Ezetimibe 10 mg Tablets (P00251)

Analyte	Parameter	Group 1 Mild[a] (n=4)	Group 2 Moderate[a] (n=4)	Group 3 Severe[b] (n=4)	Group 4 Healthy[c] (n=8)
Total Ezetimibe	Cmax (ng/mL)	141 (32)	181 (22)	189 (27)	98.2 (50)
	Tmax[d] (hr)	1.25	1.75	4	1
	AUC(tf)(ng.hr/mL)	1543 (16)	3001 (17)	3682 (36)	916 (43)
Conjugated Ezetimibe	Cmax (ng/mL)	138 (32)	171 (24)	178 (31)	95.3 (50)
	Tmax[d] (hr)	1.25	1.75	3	1
	AUC(tf)(ng.hr/mL)	1468 (14)	2685 (16)	3418 (41)	864 (45)
Ezetimibe	Cmax (ng/mL)	4.10 (37)	13.07 (41)	16.2 (43)	3.86 (118)
	Tmax[d] (hr)	6	10	7	6
	AUC(tf)(ng.hr/mL)	75.8 (54)	316 (51)	265 (57)	54.6 (36)

[a]: three males/one female
[b]: four males
[c]: Eight males
[d]: Median
Group 1: Mild hepatic impairment (Pugh score 5 to 6); n=4 (three males/one female)
Group 2: Moderate hepatic impairment (Pugh score 7 to 9); n=4 (three males/one female)
Group 3: Severe hepatic impairment (Pugh score 10 to 15); n=4 (four males)
Group 4: Healthy volunteers with no evidence of hepatic impairment; n=8 (eight males)

Table 16. Mean (%CV) Pharmacokinetic Parameters of Ezetimibe (P01912)

Analyte	Parameter	Day 1		Day 14		Day 14	
		Healthy (n=11)	Patient (n=11)	Healthy (n=11)	Patient (n=11)	Relative BA[a] (%)	90% CI
Total Ezetimibe	Cmax (ng/mL)	84.2 (64)	248 (48)	100 (47)	276 (32)	296	213-411
	Tmax[b] (hr)	1.0	2.0	1.0	3.0	--	--
	AUC(0-24hr)(ng.hr/mL)	529 (39)	2287 (33)	853 (47)	3089 (37)	380	259-558
Conjugated Ezetimibe	Cmax (ng/mL)	82.7 (65)	239 (49)	95.4 (48)	257 (33)	290	207-405
	Tmax[b] (hr)	1.0	2.0	1.0	3.0	--	--
	AUC(0-24hr)(ng.hr/mL)	489 (41)	2118 (35)	760 (49)	2749 (36)	383	260-564
Ezetimibe	Cmax (ng/mL)	3.5 (36)	16.0 (41)	7.20 (57)	22.3 (57)	326	212-500
	Tmax[b] (hr)	6.0	5.0	8.0	5.0	--	--
	AUC(0-24hr)(ng.hr/mL)	40.6 (33)	170 (43)	93.2 (56)	341 (75)	345	209-568

[a]: Ratio of the mean value for subjects with moderate hepatic impairment to the mean value for healthy subjects
[b]: Median

QC5: How do subject demographics influence pharmacokinetics of ezetimibe (Meta analysis)?

Data from twelve multiple dose Phase I studies conducted under similar study conditions and pharmacokinetic sampling schemes were combined to explore the effects of subject demographics on the pharmacokinetics of ezetimibe (SN 01483). The combined data set consisted of 154 subjects who received a daily dose of ezetimibe 10 mg for at least 7 days. There were 41 (27%) females and 37 (24%) non-Caucasians.

No difference was detected between Blacks and Caucasians.
Body weight was not statistically significant for exposures to total ezetimibe or ezetimibe.

Table 17. Comparison of pharmacokinetics of ezetimibe

Variable	Total Ezetimibe				Ezetimibe			
	AUC(0-24hr)		Cmax		AUC(0-24hr)		Cmax	
	%	p-value	%	P-value	%	p-value	%	p-value
Blacks vs. Caucasians	-12	0.12	-5	0.50	1	0.93	15	0.10
Body Weight[a]	-2	0.49	-2	0.44	-2	0.57	-4	0.21
Adolescent vs. Young	-3	0.77	-24	0.008	76	<0.0001	55	<0.0001
Elderly vs. Young	108	<0.0001	79	<0.0001	24	0.1	15	0.28
Females vs. Males	18	0.03	25	0.006	42	<0.0001	30	0.002

[a] Estimates are based on effect of body weight for every 10 kg.

D. Extrinsic Factors

QD1. How does food affect the pharmacokinetics of ezetimibe?

Food had no effect on the overall oral bioavailability (AUCs) of all ezetimibe analytes when administered as to-be-marketed ezetimibe 10 mg tablets. The Cmax values of ezetimibe was increased by 38% and decreased by 18% with consumption of high fat or non-fat meals, respectively (P00751). The Cmax values of total and conjugated ezetimibe were not affected by food.

Table 18. Statistical Comparison of Log-transformed Cmax and AUC values of Ezetimibe (P00751)

Analyte	Parameter	Treatment Ratio	Point Estimate(%)	90% CI
Total Ezetimibe	Cmax	High Fat/Fasted	103	84-126
		Nonfat/Fasted	103	84-127
	AUC(tf)	High Fat/Fasted	99	91-108
		Nonfat/Fasted	92	85-100
Conjugated Ezetimibe	Cmax	High Fat/Fasted	98	80-119
		Nonfat/Fasted High	102	83-125
	AUC(tf)	Fat/Fasted	99	91-108
		Nonfat/Fasted	92	85-100
Ezetimibe	Cmax	High Fat/Fasted	138	112-170
		Nonfat/Fasted High	82	66-101
	AUC(tf)	Fat/Fasted	100	92-109
		Nonfat/Fasted	89	82-97

QD2. Is there an in vitro basis to suspect in vivo drug-drug interaction?

The in vitro experiments using human liver microsomes suggested that ezetimibe was a metabolism-based inhibitor of CYP3A (IC_{50} = 0.25 μM). Ezetimibe was not a substrate of CYP enzymes.

Ezetimibe is a substrate and an inhibitor of Pgp transporter in vitro. In a hamster cell line, the Vmax value was approximately 270% of basal activity and the Km value was 21 μM. The well-known substrate quinidine has a Km value of 7.7 μM and a Vmax value of about 240% of control activity. Ezetimibe inhibited the hamster MDR1 mediated efflux of daunorubicin and rhodamine with IC_{50} values of 24 μM and 184 μM, respectively. Ezetimibe was less potent than cyclosporin A (IC_{50}=7 μM), nicardipine (IC_{50}=8 μM), or terfenadine (IC_{50}=7 μM), but was comparable to ketoconazole (IC_{50}=30 μM) in the inhibition of daunorubicin efflux in the CR1R12 cell line. The results with the human MDR1 transporter were similar as ezetimibe exhibited an IC_{50} of 25 μM for DNR transport.

Ezetimibe was extensively conjugated to the phenolic glucuronide (SCH 60663, ezetimibe-glucuronide). The UDP-glucuronosyltransferase enzymes UGT1A1, UGT1A3, and UGT2B15 have been shown to be responsible for the glucuronidation of ezetimibe. Incubation of various concentrations of ezetimibe (1-150 μM) with UGT1A1 and UGT1A3 SUPERSOMES®

demonstrated that the apparent Km values for SCH 60663 were 64.3 and 41.7 μM, respectively. Vmax values for SCH 60663 were 0.71 and 0.48 nmol/mg protein/min, respectively.

In conclusion, there is in vitro basis to suspect in vivo drug-drug interaction.

QD3. Is the drug an inhibitor and/or an inducer of CYP enzymes in vivo?

Ezetimibe had no significant effect on the activity of CYP1A2, CYP2C8/9, CYP2D6, CYP3A4 or N-acetyltransferase, suggesting no induction or inhibition of common CYP450 drug metabolizing enzymes (I97-137).

The effect of ezetimibe (20 mg daily) on the activity of CYP1A2, 2C8/9, 2D6 and 3A4 and N-acetyltransferase was examined in healthy male volunteers using a "cocktail" approach. The oral "cocktail" included caffeine (200 mg), tolbutamide (500 mg), dextromethorphan (30 mg), IV midazolam (0.05 mg/kd), and dapsone (100 mg).

Table 19. Effect of Ezetimibe on the activity of CYP1A2, 2C8/9, 2D6, and 3A4 and N-acetyltransferase

Enzyme Activity	Matrix	Parameter	Treatment	Mean value	%CV	p-value	Point Estimate[a](%)	CI[b]
CYP1A2	Plasma	AUC ratio[c]	Ezetimibe placebo	0.79 0.69	64 48	0.517	114	77-151
CYP2C8/9	Urine	Urinary ratio[d]	Ezetimibe placebo	865 823	33 26	0.228	105	98-112
CYP2D6	Urine	Urinary ratio[e]	Ezetimibe placebo	$9.15x10^3$ $9.44x10^3$	87 132	0.878	97.0	64-130
CYP3A4 (total)	Urine	Urinary ratio[f]	Ezetimibe placebo	5.17 5.47	47 52	0.513	94.7	80-109
CYP3A4 (hepatic)	Serum	AUC(tf)[g] (ng.hr/mL)	Ezetimibe placebo	84.7 85.8	34 24	0.672	96.3	82-113
N-acetyl transferase	Plasma	AUC(024h)[h] (ng.hr/mL)	Ezetimibe placebo	14694 15722	11 20	0.270	94.7	87-103

[a]: Expressed as a percent of Treatment A (Ezetimibe 20 mg) to Treatment B (Placebo)
[b]: 90% confidence interval of mean differences, a=0.1
[c]: AUC ratio of 1,7-paraxanthine to caffeine, n=12
[d]: Urinary ratio of carboxytolbutamide plus 4-hydrxytolbutamide to tolbutamide, n=10
[e]: Urinary ratio of dextromethorphan to dextrophan, n=11
[f]: Urinary ratio of dextromethorphan to 3-methoxymorphinan, n=10
[g]: AUC of midazolam, n=12
[h]: AUC(0-24 hr) of dapsone, n=12.

QD4. How does ezetimibe interact with other lipid lowering agents?

Gemfibrozil and fenofibrate significantly increased the oral bioavailability of total ezetimibe by a factor of 1.6-fold and 1.5-fold, respectively. Cholestyramine significantly decreased the exposure to total ezetimibe by 55%. There was no significant interaction between ezetimibe and some statins (lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, and cerivastatin).

Gemfibrozil: Gemfibrozil (600 mg twice daily) significantly increased the mean exposure to total and conjugated ezetimibe 1.7-fold based on AUC values (P00252). Ezetimibe AUC and Cmax values increased 37% and 33% after coadministration with gemfibrozil, respectively. Ezetimibe (10 mg once daily) had no effect on the pharmacokinetics of gemfibrozil.

Table 20. Mean (%CV) Day 7 pharmacokinetic parameters for ezetimibe (P00252)

	Parameter	Ezetimibe alone (n=12)	Eze + Gemfibrozil (n=12)	Relative BA[a](%)	90% CI
Total Ezetimibe	Cmax(ng/mL)	75.4 (53)	135 (37)	191	149-245
	AUC(0-24hr)(ng.hr/mL)	637 (44)	1071 (45)	164	142-190
Conjugated Ezetimibe	Cmax(ng/mL)	70.2 (54)	128 (38)	196	152-253
	AUC(0-24hr)(ng.hr/mL)	552 (52)	972 (47)	169	142-201
Ezetimibe	Cmax(ng/mL)	7.12 (64)	9.68 (67)	133	111-160
	AUC(0-24hr)(ng.hr/mL)	72.2 (47)	111 (68)	137	109-173

[a]: Base on log-transformed data. Ratio of the mean value for Ezetimibe

Fenofibrate: Fenofibrate (200 mg once daily for 14 days) significantly increased the mean exposure to total ezetimibe 1.5-fold (P00753). Ezetimibe (10 mg once daily for 14 days) had no effect on the pharmacokinetics of fenofibrate.

Table 21. The mean (%CV) day 14 pharmacokinetic parameters and statistical comparisons of the log-transformed Cmax and AUC values for ezetimibe (P00753)

Analyte	Parameter	Ezetimibe alone (n=8)	Eze + Fenofibrate (n=8)	Relative BA[a](%)	90% CI
Total Ezetimibe	Cmax(ng/mL)	70.1 (36)	114 (34)	164	117-230
	AUC(0-24hr)(ng.hr/mL)	785 (54)	1070 (32)	148	99-219
Conjugated Ezetimibe	Cmax(ng/mL)	66.5 (37)	110 (35)	168	119-237
	AUC(0-24hr)(ng.hr/mL)	717 (58)	997 (34)	152	101-230
Ezetimibe	Cmax(ng/mL)	4.50 (41)	5.13 (47)	114	79-164
	AUC(0-24hr)(ng.hr/mL)	68.6 (37)	72.9 (48)	106	72-154

[a]: Base on log-transformed data. Ratio of the mean value for Ezetimibe plus fenofibrate to ezetimibe alone.

Cholestyramine: Cholestyramine (4g twice daily for 14 days) significantly decreased the systemic exposure (based on AUC) to ezetimibe, conjugated ezetimibe, and total ezetimibe 80%, 51%, and 55%, respectively (P00776).

Table 22. Statistical Comparison of the Log-Transformed Cmax and AUC Values for Total Ezetimibe, Conjugated Ezetimibe and Ezetimibe (P00776)

Analyte	Parameter	Comparison	Relative BA[a](%)	90% CI
Ezetimibe	Cmax	C/B	26.5	19-36
	AUC(0-24hr)	C/B	19.6	15-26
Conjugated Ezetimibe	Cmax	C/B	101	73-140
	AUC(0-24hr)	C/B	48.6	38-62
Total Ezetimibe	Cmax	C/B	96.4	70-132
	AUC(0-24hr)	C/B	44.5	36-55

[a]: Ratio of the mean value for Treatment C (Cholestyramine + Ezetimibe) to Treatment B (Ezetimibe Alone).

The pharmacokinetic data from this study were consistent with the in vitro binding phenomenia of ezetimibe and ezetimibe-glucuronide to cholestyramine. Both ezetimibe and ezetimibe-glucuronide were highly bound to cholestyramine with the extent of binding ranging between 92.3 and 95.8% for ezetimibe and between 89.3 and 92.7% for ezetimibe-glucuronide (Sn01005).

Simvastatin: Ezetimibe — to 10 mg once daily for 14 days) had no significant effect on the pharmacokinetics of simvastatin (10 mg once daily for 14 days) (I98311). The relative bioavailability of simvastatin and hydroxysimvastatin after oral administration of 10 mg simvastatin in combination with either — or 10 mg ezetimibe as compared to 10 mg simvastatin alone based on both log-transformed Cmax and AUC values ranged from 96 to 138%.

Table 23. Mean (%CV) pharmacokinetic parameters for simvastatin (Simva) and hydroxysimvastatin (OH-simva) (I98311)

Treatment	Cmax (ng/mL)		AUC(0-24hr)(ng.hr/mL)		T1/2 (hr)	
	Simva	OH-Simva	Simva	OH-Simva	Simva	OH-Simva
Simva 10 mg (n=12)	2.36 (46)	0.57 (46)	6.82 (48)	5.10 (51)	3.52 (87)[a]	4.91 (41)[c]
Simva 10 mg + eze — mg (n=11)	2.94 (62)	0.90 (114)	8.07 (58)	9.10 (129)	3.76 (49)[b]	6.20 (77)[c]

Simva 10 mg + eze ~ ng (n=12)	2.38 (55)	0.63 (54)	7.82 (79)	5.64 (86)	2.78 (71)[a]	5.15 (36)[c]
Simva 10 mg + eze 10 mg (n=11)	2.65 (62)	0.62 (67)	8.42 (83)	5.55 (71)	3.46 (61)[b]	4.69 (35)[c]

[a]: n=11; [b]: n=10; [c]: n=8

Lovastatin: There was no significant drug interaction between ezetimibe and lovastatin. Study P00250 showed that the relative oral bioavailability of lovastatin and β-hydroxylovastatin after coadministration of lovastatin 20 mg with ezetimibe ~ 10, o ~ mg (once daily for 14 days) as compared to lovastatin 20 mg alone ranged from 53 to 78% based on log-transformed Cmax and AUC. In study P01382, the relative oral bioavailability of lovastatin after coadministration of lovastatin and ezetimibe (10 mg once daily for 7 days) compared to lovastatin alone was approximately 113% and 119% based on log-transformed Cmax and AUC values, respectively. The relative oral bioavailability of β-hydroxylovastatin after coadministration of lovastatin and ezetimibe compared to lovastatin alone was approximately 113% and 103% based on log-transformed Cmax and AUC values, respectively. The relative oral bioavailability of ezetimibe and total ezetimibe after coadministration of lovastatin (20 mg once daily for 7 days) and ezetimibe compared to ezetimibe alone was 129% and 103%, respectively, based on log-transformed Cmax, and 113% and 109%, respectively, based on log-transformed AUC values.

Pravastatin: There was no significant drug interaction between pravastatin (20 mg once daily for 14 days) and ezetimibe (10 mg once daily for 14 days) (P00447). The relative oral bioavailability of pravastatin after coadministration of pravastatin and ezetimibe compared to pravastatin alone was approximately 76% and 80% based on log-transformed Cmax and AUC values, respectively. The relative oral bioavailability of ezetimibe and total ezetimibe after coadministration of pravastatin and ezetimibe compared to ezetimibe alone was 115% and 123%, respectively, based on log-transformed Cmax, and 90% and 107%, respectively, based on log-transformed AUC values.

Atorvastatin: There was no significant drug interaction between ezetimibe (10 mg once daily for 14 days) and atorvastatin (10 mg once daily for 14 days) (P00460). The relative oral bioavailability of atorvastatin after coadministration of atorvastatin and ezetimibe compared to atorvastatin alone was approximately 107% and 96% based on log-transformed Cmax and AUC values, respectively. The relative oral bioavailability of ezetimibe and total ezetimibe after coadministration of atorvastatin and ezetimibe compared to ezetimibe alone was 131% and 112%, respectively, based on log-transformed Cmax, and 121% and 98%, respectively, based on log-transformed AUC values.

Cerivastatin: There was no significant drug interaction between ezetimibe (10 mg once daily for 14 days) and cerivastatin (0.3 mg once daily for 14 days) (P00754). The relative oral bioavailability of cerivastatin after coadministration of cerivastatin and ezetimibe compared to cerivastatin alone was approximately 133% and 124% based on log-transformed Cmax and AUC values, respectively. The relative oral bioavailability of ezetimibe and total ezetimibe after coadministration of cerivastatin and ezetimibe compared to ezetimibe alone was 70% and 100%, respectively, based on log-transformed Cmax, and 63% and 100%, respectively, based on log-transformed AUC values.

Fluvastatin: There was no significant drug interaction between ezetimibe (10 mg once daily for 14 days) and fluvastatin (20 mg once daily for 14 days) (P00755). The relative oral bioavailability of fluvastatin after coadministration of fluvastatin and ezetimibe compared to fluvastatin alone was approximately 73% and 61% based on log-transformed Cmax and AUC values, respectively. The relative oral bioavailability of ezetimibe and total ezetimibe after coadministration of fluvastatin and ezetimibe compared to ezetimibe alone was 114% and 107%, respectively, based on log-transformed Cmax, and 100% and 81%, respectively, based on log-transformed AUC values. It is agreed that the apparently large mean differences for Cmax and AUC values are

primarily due to the two pharmacokinetic outliers because fluvastatin is metabolized by CYP2C9 which exhibits polymorphism.

QD5. How does ezetimibe interact with other drugs?

Ezetimibe had no significant effect on the pharmacokinetics and pharmacodynamics of digoxin, warfarin, and glipizide. Cimetidine and antacid had no significant effect on oral bioavaiability of total ezetimibe and ezetimibe. Ezetimibe had no significant effect on pharmacokinetics of ethinyl estradiol anfd levonorgestrel.

Digoxin: There was no significant difference in the bioavailability of digoxin (0.5 mg) when it was coadministered with ezetimibe (10 mg once daily for 10 days) vs. digoxin alone ($p > 0.20$) (C98-114). The relative oral bioavailability of digoxin after coadministration of digoxin and ezetimibe compared to digoxin alone was approximately 93% and 102% based on log-transformed Cmax and AUC values, respectively. Since digoxin is a substrate of P-glycoprotein, the results of this study implied that ezetimibe had no effect on activities of P-glycoprotein. The coadministration of digoxin 0.5 mg plus ezetimibe 10 mg (Day 10) did not cause any clinically significant changes in the ECG parameters (HR, PR, QT and QTc intervals) compared to the changes caused by the administration of digoxin 0.5 mg alone (Day 1).

Warfarin: There was no significant difference in the bioavailability of warfarin (25 mg) when it was coadministered with ezetimibe (10 mg once daily for 7days) vs. warfarin alone (I98-106). There was no significant difference between the anticoagulant measures following warfarin administration with or without ezetimibe.

Oral Contraceptives: Ezetimibe (10 mg once daily for 7 days) had no significant effect on the pharmacokinetics of oral contraceptives (P00267). The relative bioavailability of ethinyl estradiol was 99.6% and 91.1% based on the mean AUC and Cmax values, respectively, with the coadministration of ezetimibe compared to oral contraceptive (OC) alone. The relative bioavailability of levonorgestrel was 100% and 95% based on the mean AUC and Cmax values, respectively, with the coadministration of ezetimibe compared to OC alone.

Cimetidine: Cimetidine (400 mg twice daily for 7 days) had no significant effect on the exposures to ezetimibe and total ezetimibe (P00746). The relative oral bioavailability of ezetimibe and total ezetimibe after coadministration of cimetidine and ezetimibe compared to ezetimibe alone was 120% and 122%, respectively, based on log-transformed Cmax, and 118% and 106%, respectively, based on log-transformed AUC values.

Antacid: Antacid (Supralox™ 20 mL) had no significant effect on the exposures to ezetimibe and total ezetimibe (P00748). The relative oral bioavailability of ezetimibe and total ezetimibe after coadministration of antacid and ezetimibe compared to ezetimibe alone was 110% and 70%, respectively, based on log-transformed Cmax, and 108% and 96%, respectively, based on log-transformed AUC values.

Glipizide: There was no significant interaction between ezetimibe (10 mg once daily for 8 days) and glipizide (10 mg single dose) (P00752). The relative oral bioavailability of glipizide after coadministration of glipizide and ezetimibe compared to glipizide alone was approximately 95% and 97% based on log-transformed Cmax and AUC values, respectively. The relative level of glucose after coadministration of glipizide and ezetimibe compared to glipizide alone was 98% based on log-transformed Cmax and AUC values. The relative oral bioavailability of ezetimibe and total ezetimibe after coadministration of glipizide and ezetimibe compared to ezetimibe alone was 126% and 92%, respectively, based on log-transformed Cmax, and 116% and 104%, respectively, based on log-transformed AUC values.

E. General Biopharmaceutics

QE1. Is the proposed to-be-marketed formulation used in the pivotal clinical trials?

The proposed to-be-marketed formulation was used in all Phase III clinical trials.

Initial clinical studies were done with a [redacted] All subsequent clinical studies used a tablet dosage form with a consistent qualitative and quantitative composition, manufactured using similar processes, with changes only to the tablet shape. All Phase III clinical safety and efficacy studies were conducted using the to-be-marketed tablet formula and shape, manufactured on equipment of similar design and operating principle as the proposed commercial manufacturing equipment including all possible minor variations in equipment design.

QE2. Is the in vitro dissolution method and specification adequately validated?

The dissolution method and specification was adequately validated.
The solubility of ezetimibe is extremely low in non-buffered media such as water, 0.1 N HCl and buffered media without surfactant. However, drug solubility is significantly improved in aqueous media containing an anionic surfactant such as [redacted] Since ezetimibe is not stable under acidic or basic conditions, a buffered dissolution medium at an intermediate pH [redacted] was selected. The effect of [redacted] concentration in the range of [redacted] was evaluated. The dissolution data indicated rapid and nearly superimposable dissolution profiles for all [redacted] concentrations [redacted] that exceeded the critical micelle concentration (CMC) of [redacted] which is approximately [redacted] Below the CMC of [redacted] concentrations of [redacted] incomplete dissolution was obtained. A dissolution medium of [redacted] was chosen.

The dissolution method was agreed upon during the March 14, 2000 teleconference. The dissolution method used [redacted] as the dissolution medium and USP Apparatus 2 (paddles) operated at 50 rpm. The dissolution profiles of tablets with different shapes produced by a slight different manufacturing processes appear to be similar.

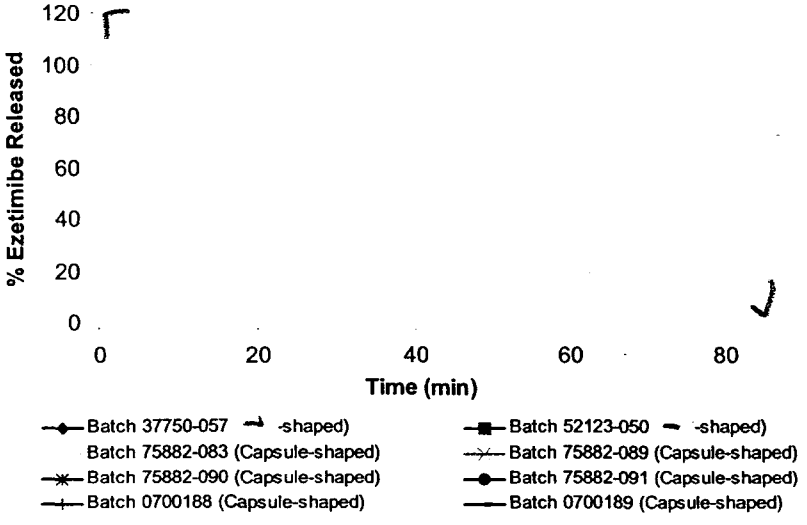

Figure 12. Dissolution Profiles of [redacted] -shaped and Capsule-shaped Ezetimibe Tablets

Table 24. Summary of Ezetimibe Capsule-Shaped Tablets Dissolution Profiles (% dissolved)

Time (min)	Batch 75882-083	Batch 75882-089	Batch 75882-090	Batch 75882-091	Batch 0700188	Batch 0700189
15						
30						
45						
60						

The sponsor proposed a specification of not less than Q= — dissolved in 30 minutes. Since all tested tablets dissolved more than — in 30 minutes, this dissolution specification is acceptable.

F. Analytical

QF1. Are analytical methods for ezetimibe adequately validated?

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VI. Labeling

(~~Strikeout text~~ should be removed from labeling; Double underlined text should be added to labeling.)

Under **CLINICAL PHARMACOLOGY** Section

Pharmacokinetics

Absorption

After oral administration, ezetimibe is absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). After a single 10-mg dose of ZETIA to fasted adults, mean ezetimibe peak plasma concentrations (C_{max}) of 3.4 to 5.5 ng/mL were attained within 4 to 12 hours (T_{max}). Ezetimibe-glucuronide mean C_{max} values of 45 to 71 ng/mL were achieved between 1 and 2 hours (T_{max}). There was no substantial deviation from dose proportionality between 5 and 20 mg. The absolute bioavailability of ezetimibe cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. Ezetimibe has variable bioavailability; the coefficient of variation, based on inter-subject variability, was 35 to 60% for AUC values.

Effect of Food on Oral Absorption

Concomitant food administration (high fat or non-fat meals) had no effect on the extent of absorption of ezetimibe when administered as ZETIA 10-mg tablets. The Cmax values of ezetimibe was increased by 38% with consumption of high fat meals. ZETIA can be administered with or without food.

Distribution

Ezetimibe and ezetimibe-glucuronide are bound to human plasma proteins

Metabolism and Excretion

Ezetimibe is primarily metabolized in the small intestine and liver via glucuronide conjugation (a phase II reaction) with subsequent biliary and renal excretion. Minimal oxidative metabolism (a phase I reaction) has been observed in all species evaluated.

In humans, ezetimibe is rapidly metabolized to ezetimibe-glucuronide. Ezetimibe and ezetimibe-glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10 to 20% and 80 to 90% of the total drug in plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with half-life of approximately 22 hours for both ezetimibe and ezetimibe-glucuronide. Plasma concentration-time profiles exhibit multiple peaks, suggesting enterohepatic recycling.

Following oral administration of ^{14}C-ezetimibe (20 mg) to human subjects, total ezetimibe (ezetimibe + ezetimibe-glucuronide) accounted for approximately 93% of the total radioactivity in plasma. After 48 hours, there were no detectable levels of radioactivity in the plasma.

Approximately 78% and 11% of the administered radioactivity were recovered in the feces and urine, respectively, over a 10-day collection period. Ezetimibe was the major component in feces and accounted

for 69% of the administered dose, while ezetimibe-glucuronide was the major component in urine and accounted for 9% of the administered dose.

Special Populations

Geriatric Patients

In a multiple dose study with ezetimibe given 10 mg once daily for 10 days, pPlasma concentrations for total ezetimibe are about 2-fold higher in the — (≥65 years) than in the

[ ]

Pediatric Patients

In a multiple dose study with ezetimibe given 10 mg once daily for 7 days, tThe absorption and metabolism of ezetimibe are similar in adolescents (10 to 18 years) and adults. Based on total ezetimibe, there are no pharmacokinetic differences between adolescents and adults. Pharmacokinetic data in the pediatric population <10 years of age are not available.

Gender

In a multiple dose study with ezetimibe given 10 mg once daily for 10 days, pPlasma concentrations for total ezetimibe are slightly higher (<20%) in women than in men.

[ ]

Race

Based on a meta-analysis — pharmacokinetic studies, there were no pharmacokinetic differences between Blacks and Caucasians.

Hepatic Insufficiency

After a single 10-mg dose of ezetimibe, the mean area under the curve (AUC) for total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic insufficiency (Child-Pugh score 5 to 6), compared to healthy subjects. The mean AUC values for total ezetimibe and ezetimibe was increased approximately 3-4 fold and 5-6 fold in patients with moderate (Child-Pugh score 7 to 9) or severe hepatic impairment (Child-Pugh score 10 to 15), respectively. In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic insufficiency, the mean AUC values for total ezetimibe and ezetimibe — were increased approximately 4-fold on Day 1 and Day 14 compared to healthy subjects. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, ZETIA is not recommended in these patients

Renal Insufficiency

After a single 10-mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl ≤30 mL/min/1.73 m^2), the mean AUC values for total ezetimibe, ezetimibe-glucuronide, and ezetimibe — were increased approximately 1.5-fold, compared to healthy subjects (n=9). —

[ ]

Drug Interactions (See also PRECAUTIONS, *Drug Interactions*)

[

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Warfarin: Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on bioavailability of warfarin and prothrombin time.

Digoxin: Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on the bioavailability of digoxin and the ECG parameters (HR, PR, QT, and QTc intervals).

Gemfibrozil: Concomitant administration of gemfibrozil (600 mg twice daily) significantly increased the oral bioavailability of total ezetimibe by a factor of 1.7. Ezetimibe (10 mg once daily) did not affect the bioavaiability of gemfibrozil.

Oral Contraceptives: Co-administration of ezetimibe (10 mg once daily) with oral contraceptives had no significant effect on the bioavailability of ethinyl estradiol or levonorgestrel.

Cimetidine: Multiple doses of cimetidine (400 mg twice daily) had no effect on the oral bioavailability of ezetimibe and total ezetimibe.

Antacid: A single dose of antacid (Supralox™ 20 mL) administration had no effect on the oral bioavailability of total ezetimibe, ezetimibe-glucuronide, or ezetimibe based on AUC values. The Cmax values of total ezetimibe was decreased by 30%.

Glipizide: Steady-state levels of ezetimibe (10 mg once daily) has no effect on the pharmacokinetics and pharmacodynamics of glipizide. A single dose of glipizide (10 mg) had no significant effect on the exposure to total ezetimibe or ezetimibe.

[

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Fenofibrate: Concomitant fenofibrate (200 mg once daily) administration increased the mean Cmax and AUC values of total ezetimibe approximately 64% and 48%, respectively. Pharmacokinetics of fenofibrate was not affected by ezetimibe (10 mg once daily).

Cholestyramine: Concomitant cholestyramine (4 g twice daily) administration decreased the mean AUC values of total ezetimibe and ezetimibe approximately 55% and 80%, respectively.

Under **PRECAUTIONS** Section

Drug Interactions (See also CLINICAL PHARMACOLOGY, *Drug Interactions)*

[

]

Cholestyramine: Concomitant cholestyramine administration decreased the mean AUC of total ezetimibe approximately 55%. The incremental LDL-C reduction due to adding ezetimibe to cholestyramine may be reduced by this interaction.

Fibrates: The safety and effectiveness of ezetimibe administered with fibrates have not been established.

Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile (see CLINICAL PHARMACOLOGY, *Animal Pharmacology*). coadministration of ZETIA with fibrates is not recommended until use in patients is studied.

Fenofibrate: In a pharmacokinetic study, concomitant fenofibrate administration increased total ezetimibe concentrations approximately 1.5-fold,

Gemfibrozil: In a pharmacokinetic study, concomitant gemfibrozil administration increased total ezetimibe concentrations approximately 1.7-fold,

HMG-CoA reductase inhibitors: No clinically significant pharmacokinetic interactions were seen when ezetimibe was co-administered with atorvastatin, simvastatin, pravastatin, lovastatin, or fluvastatin.

Cyclosporine: the patients who take both ezetimibe and cyclosporine should be carefully monitored.

VII. Appendix

A. proposed labeling

ZETIA™
(EZETIMIBE)
TABLETS

[

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Draft

Labeling

B. Individual Study Reviews

Title of the Study: SCH 58235: THE ABSORPTION, METABOLISM AND EXCRETION OF ^{14}C-SCH 58235 IN HEALTHY MALE VOLUNTEERS (Protocol C97-136)

Investigator(s): [redacted]

Publication(s): None

Studied Period: 13 Mar, 1998 – 23 Apr, 1998 | **Clinical Phase:** I

Objective(s): To characterize the absorption, metabolism and excretion of ^{14}C-SCH 58235 following a single oral 20-mg dose to healthy male subjects.

Methodology: This was a single-center, single-dose, open-label study. All subjects were confined to the study center during the study. Subjects received a single 20 mg ^{14}C-SCH 58235 [redacted] with 200 mL of non-carbonated water after a 10 hr fast. Blood samples (10 mL) for the determination of SCH 58235 (unconjugated, conjugated and total) and radioactivity concentrations in plasma and/or blood were collected at 0 hr (pre-dose) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216 and 240 hr post-dose. Additional 20-mL blood samples were obtained at 0.5, 5, 12 and 24 hr post-dose for metabolite profiling of plasma. Urine was collected just prior to drug administration and at block intervals of 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168, 168-192, 192-216 and 216-240 hr post-dose. Fecal samples were obtained prior to dose administration and then all bowel movements were collected up to 240-hr post-dose. Vital signs were obtained at pre-specified times for safety evaluation. Volunteers were continuously observed and questioned throughout the confinement periods for the possible occurrence of adverse events. Plasma SCH 58235 (unconjugated and total) was determined using a [redacted] assay with a lower limit of quantitation (LOQ) of [redacted] (unconjugated) and [redacted] (total). Plasma concentrations of conjugated SCH 58235 were calculated as the difference between unconjugated and total SCH 58235. Radioactivity concentrations were determined in blood (LOQ [redacted] and plasma (LOQ [redacted]) by [redacted] Metabolite profiles were determined in plasma, urine and feces by [redacted] In addition, the potential for [redacted] of SCH 58235 was investigated using [redacted]

Number of Subjects: Eight adult male volunteers were enrolled in and completed this study.

Diagnosis and Criteria for Inclusion: Adult, non-smoking, male volunteers between the ages of 18 and 40 years, in good health based upon medical history, physical exam, electrocardiogram, urine screen for drugs and laboratory safety tests.

Test Product, Dose, Mode of Administration, Batch No(s): ^{14}C-SCH 58235, 20 mg (100 µCi), oral, 38101-122

Reference Therapy, Dose, Mode of Administration, Batch No(s): None

Duration of Treatment: Single dose. Subjects were confined from 16 hr pre-dose to 240 hr post-dose.

Criteria for Evaluation: Pharmacokinetic parameters [Cmax, Tmax, AUC, Ae(day), Ae(total)], reported adverse events, chemistry panel, CBC, urinalysis and ECG.

Statistical Methods: Descriptive statistics (mean, standard deviation and % coefficient of variation)

SUMMARY-CONCLUSIONS:

RESULTS:

Pharmacokinetics: SCH 58235 was rapidly absorbed and conjugated following an oral dose. The mean (%CV) pharmacokinetic parameters for SCH 58235 (unconjugated, conjugated and total) in plasma and total radioactivity in plasma and blood following a single 20 mg oral dose of ^{14}C-SCH 58235 are listed in the table below:

Parameter	Unit	Plasma SCH 58235			Radioactivity		
		Unconjugated	Conjugated	Total	Unit	Plasma	Blood
Cmax	ng/mL	5.21 (52)	61.2 (51)	64.2 (51)	ng equiv/g	75.1 (47)	NC[a]
Tmax	hr	9.88 (114)	2.31 (66)	2.31 (66)	hr	2.63 (63)	NC
AUC(tf)	ng·hr/mL	86.4 (56)	636 (33)	726 (30)	ng equiv·hr/g	780 (42)	NC

a: NC = Not calculated

Title of the Study: SCH 58235: THE ABSORPTION, METABOLISM AND EXCRETION OF ^{14}C-SCH 58235 IN HEALTHY MALE VOLUNTEERS (Protocol C97-136)
Plasma concentration-time profiles of total and unconjugated drug had multiple peaks indicative of enterohepatic recycling. Due to these multiple peaks, a terminal elimination phase could not be defined and t½ estimates were not calculated. Radioactivity in blood was below the limit of quantitation [redacted] in the majority of samples; therefore pharmacokinetic parameters could not be calculated. Based on individual exposures (AUC), SCH 58235 accounted for about 10% of total SCH 58235, suggesting extensive conjugation; this was consistent with metabolite profiles. About 77.7% and 11.3% of the administered dose was excreted in feces and urine, respectively, by 240 hr post dose. Total recovery of radioactivity averaged 89% of the administered dose. The major metabolite was SCH 60663, a glucuronide conjugate of SCH 58235. Approximately 90, 86, 79 and 100% of the total radioactivity in plasma metabolite profiles at 0.5, 5, 12 and 24 hr post-dose was associated with SCH 60663, while only 4, 14, 22 and 0% of the radioactivity was associated with SCH 58235 at these time points. Similarly, the major metabolite in urine (0-72 hr composite) was SCH 60663 (about 9% of the administered dose). SCH 58235 was the major component in feces and accounted for about 69% of the administered dose. A minor (4.1% of the dose) metabolite, consistent with SCH 57871 (a SCH 58235-ketone) and/or its glucuronide conjugate, was detected in urine and feces. Trace amounts of the benzylic glucuronide of SCH 58235 (SCH 488128) were detected only in urine (0.9% of the dose). [redacted] of SCH 58235 was not observed. Greater than 99% of the total radioactivity excreted in urine (0-72 hr) and feces (0-96 hr) was characterized by [redacted] The presence of SCH 58235 in feces may be due to unabsorbed drug or to the hydrolysis of SCH 60663 to SCH 58235 during intestinal transit. There were no notable differences in metabolite profiles, excretion of radioactivity or pharmacokinetics between subjects.
Efficacy: Not evaluated.
Safety: There were no adverse events reported in this study. There were no clinically-significant abnormalities or changes in the routine clinical laboratory safety tests (complete blood count, blood chemistries and urinalysis). No clinically-significant changes were noted on physical examinations. There were no deaths or serious adverse events in this study.
CONCLUSIONS: • A single dose of 20 mg ^{14}C-SCH 58235 [redacted] ~100 µCi) was safe and well-tolerated following oral administration. • SCH 58235 was rapidly absorbed and extensively conjugated following oral administration. Drug-derived radioactivity was excreted in the feces (78%) and urine (11%). • The pharmacokinetics of SCH 58235 are consistent with extensive glucuronidation and enterohepatic recirculation. Exposure to SCH 58235 was only about 10% of total SCH 58235. • The major metabolite pathway for SCH 58235 consisted of glucuronidation of the 4-hydroxyphenyl group. Less than 1% of the dose was associated with a benzylic glucuronide of SCH 58235 (SCH 488128) in urine. Minor amounts of SCH 58235 were present in urine and/or plasma, while significant (69% of the dose) amounts of SCH 58235 were present in the feces, presumably as a result of hydrolysis of SCH 60663 and/or unabsorbed drug. • A minor (4.1% of the dose) metabolite, consistent with SCH 57871 and/or its glucuronide, was detected in urine and feces. • [redacted] of SCH 58235 was not observed.

Title of the Study: SCH 58235: Bioavailability of Single Oral Doses of Two Prototype Tablet Formulations and the Reference [redacted] Formulation of SCH 58235 In Normal Male Volunteers; a Four Way Crossover Study
Investigator(s): [redacted]
Publication(s): None
Studied Period: 21 October to 11 December 1997 — **Clinical Phase:** I
Objective(s): The primary objective of this study was to compare the bioavailability of two prototype tablets formulations of SCH 58235 relative to the current research [redacted] formulation. The secondary objective was to examine the dose-proportionality between 2 x [redacted] mg and 1 x 20 mg SCH 58235 research [redacted] formulations.
Methodology: Open-label, randomized, single-dose, four-period crossover design. Twelve volunteers were randomly assigned to receive one of the following four treatments during each period of the crossover. Treatment A: 1 x 10 mg SCH 58235 Prototype I tablet; Treatment B: 1 x 10 mg SCH 58235 Prototype II tablet; Treatment C: 2 x [redacted] mg SCH 58235 [redacted] (Reference); Treatment D: 1 x 20 mg SCH 58235 [redacted] All subjects received all treatments. Blood samples were collected at pre-specified times for safety and pharmacokinetic evaluations. Volunteers were continuously observed and questioned throughout the study for possible occurrence of adverse events. All plasma samples were assayed for unconjugated and total (unconjugated plus conjugated) SCH 58235 concentration using [redacted] methods.
Number of Subjects: 12
Diagnosis and Criteria for Inclusion: Normal adult healthy male volunteers between the ages of 18 and 40, in good health as determined by medical history and physical examination, laboratory safety tests, (blood chemistry, hematology, urinalysis) electrocardiogram and having weights (±15%) in accordance with current actuarial tables were empaneled for this study.
Test Product, Dose, Mode of Administration, Batch No(s): SCH 58235 10 mg tablets (Prototype I), oral, batch # 51510-110. SCH 58235 10 mg tablets (Prototype II), oral, batch # 51510-111. SCH 58235 20 mg [redacted] oral, batch # 37750-011.
Reference Therapy, Dose, Mode of Administration, Batch No(s): SCH 58235 2 x [redacted] mg [redacted] oral, batch # 37750-010.
Duration of Treatment: Single doses on four different occasions with seven days separating each treatment of the crossover.
Criteria for Evaluation: Physical Examinations, electrocardiograms, clinical laboratory tests were performed throughout the study and adverse events were recorded for safety evaluation. Blood samples were collected for 48 hours postdose for determination of SCH 58235 pharmacokinetic parameters (AUC, Cmax).
Statistical Methods: The pharmacokinetic parameters were analyzed using a crossover analysis of variance model. Data for the 20 mg [redacted] was dose normalized (to 10 mg) prior to analyses. The effects due to subject, period and treatment were extracted. The difference between bioavailability of each pair of formulations is based on analysis of the log-transformed AUC(tf) and Cmax data and is expressed as a ratio.
SUMMARY-CONCLUSIONS: **RESULTS:** The study was conducted as planned. **Safety:** A total of two (17%) subjects reported at least one adverse event. The adverse events reported were of a mild intensity and deemed by the Investigator to be unrelated to study treatment. Blood pressure, pulse rate, respiratory rate and oral body temperature evaluations showed no consistent changes of clinical relevance and remained within the range observed for healthy volunteers. The treatments were safe and well tolerated. **Clinical Pharmacology:** **Unconjugated SCH 58235** Point estimates of bioavailability [AUC(tf) and Cmax] for both prototypes were within 5% of the reference [redacted] The confidence intervals for AUC(tf) fell outside the [redacted] limits, however, the study was not designed to meet these criteria. Although the plasma unconjugated SCH 58235 concentration-time profiles for both prototype tablets were similar to that of the reference [redacted] the prototypes were not bioequivalent. The mean pharmacokinetic parameters of plasma unconjugated SCH 58235 are summarized as follows:

Title of the Study: SCH 58235: Bioavailability of Single Oral Doses of Two Prototype Tablet Formulations and the Reference — Formulation of SCH 58235 In Normal Male Volunteers; a Four Way Crossover Study

Parameter	Prototype I[a]		Prototype II[a]		Reference —	
	Mean	% CV	Mean	% CV	Mean	% CV
Cmax (ng/mL)	2.38	34	2.21	30	2.24	21
AUC(tf) (ng.hr/mL)	18.7	55	19.2	61	20.4	61
Tmax (hr)	10.5	54	13.3	85	9.58	31

a: Dose: 10 mg

Clinical Pharmacology (Cont'd):

Total (Unconjugated Plus Conjugated) SCH 58235

Point estimates of bioavailability of Prototype I and II tablets were within 12 and 20%, respectively, of the reference — None of the confidence intervals meet the — limits. The AUC(tf) confidence intervals fell just outside the — limits for Prototype I tablet (point estimate: 95%; CI: 79-114%). The mean pharmacokinetic parameters of plasma total SCH 58235 (unconjugated plus conjugated) are summarized as follows:

Parameter	Prototype I[a]		Prototype II[a]		Reference —	
	Mean	% CV	Mean	% CV	Mean	% CV
Cmax (ng/mL	48.6	37	36.9	50	45.1	48
AUC(tf)(ng.hr/mL)	363	76	337	73	412	83
Tmax (hr)	1.42	60	1.5	55	1.58	63

a: Dose: 10 mg

Dose Proportionality (2 x — ng — Versus 1 x 20 mg —

The mean pharmacokinetic parameters of both unconjugated SCH 58235 and total SCH 58235 are summarized as follows:

	Unconjugated SCH 58235				Total SCH 58235			
	— (2 x — mg)		— (1 x 20 mg)		— (2 x — ng)		— 1 x 20 mg)	
Parameter[a]	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV
AUC(tf)	20.4	61	70.1	39	412	83	794	60
Tmax	9.58	31	10.3	32	1.58	63	2.13	48
DN-Cmax	2.24	21	1.93	24	45.1	48	31.0	36
DN-AUC(tf)	20.4	61	35.1	39	412	83	397	60

a: Unit: Cmax-ng/mL; AUC-ng·hr/mL; Tmax-hr.

DN: Dose-normalized to 10 mg

The data indicate that plasma unconjugated and total SCH 58235 concentrations increased in a dose-related manner. A pairwise comparison on dose adjusted data indicate that plasma unconjugated SCH 58235 AUC(tf) and total SCH 58235 Cmax increased in a dose-related but not dose-proportional manner. A definitive statement about dose-proportionality for unconjugated Cmax and total AUC(tf) could not be made due to lack of statistical power.

CONCLUSIONS:

- Administration of SCH 58235 at a dose of 10 mg (2 x — mg) and 20 mg in — form, or a 10 mg dose of either tablet Prototypes I and II to normal volunteers was safe and well tolerated.
- Plasma unconjugated and total (unconjugated plus coniugated) SCH 58235 concentration-time profiles from the prototype tablet formulations and the reference — were similar.
- The prototype tablet formulations had similar bioavailability to the reference — Of the two prototype tablet formulations, Prototype I was most similar to the reference —
- There was a dose-related but not necessarily dose-proportional increase in Cmax and AUC(tf) of unconjugated and total SCH 58235.

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Title of the Study:	SCH 58235: DOSE-PROPORTIONALITY OF EZETIMIBE TABLETS: A THREE-WAY CROSSOVER STUDY (PROTOCOL P00750)
Investigator:	[redacted]
Publication(s):	None
Studied Period:	05 JUN 00 to 13 JUL 00 | Clinical Phase: I

Objective: The objective of this study is to evaluate the linearity and dose-proportionality of ezetimibe (SCH 58235) from the to-be-marketed ezetimibe tablet within a clinically relevant exposure dose range.

Methodology: This was a randomized, open-label, three-way crossover, single center study. Subjects were screened within 3 weeks prior to dosing, and those who met the entry criteria were confined to the study center on three consecutive occasions (approximately 1.5 days/period) separated by a minimum of 7 days between treatments. On the morning of Day 1 of each period, following a 10 hour fast, subjects received ezetimibe at a dose of either mg (Treatment A), 10 mg (Treatment B), or 20 mg (Treatment C). Vital signs, ECGs, and blood and urine samples were collected at specified times during the study for safety and pharmacokinetic evaluations. Blood samples for the determination of plasma unconjugated and total ezetimibe concentrations were collected prior to dosing and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hours post-dose. Plasma ezetimibe (unconjugated) and total ezetimibe (ezetimibe plus conjugated ezetimibe) concentrations were determined using [redacted] assays. The lower limits of quantitation (LOQ) for ezetimibe and total ezetimibe were [redacted] plasma, respectively; the linear ranges were [redacted] and [redacted], respectively. Plasma concentrations of conjugated ezetimibe, reported as ezetimibe equivalents, were calculated by subtracting the ezetimibe concentration from the corresponding total ezetimibe concentration for each sample. For safety evaluations physical examinations, vital signs, electrocardiograms, and clinical laboratory tests were conducted at Screening and at the conclusion of the study (24 hours after dosing). In addition, vital signs were also monitored before each treatment administration (0-hour) and at 24 hours after treatment administration during period 3..

Number of Subjects: Twenty-four adult male and female volunteers were enrolled and completed the study as planned.

Diagnosis and Criteria for Inclusion: Male and female subjects between the ages of 18 and 45 years inclusive. Subjects had to be free of any clinically significant disease based on results of a medical history, physical examination, electrocardiogram, and routine laboratory tests (blood chemistry, hematology, drug screen, HIV, hepatitis B/C, and urinalysis).

Test Product, Dose, Mode of Administration, Batch No(s): Ezetimibe (SCH 58235) tablets, ~ mg, oral, Batch No. 76466-067. Ezetimibe (SCH 58235) tablets, 10 mg, oral, Batch No. 75882-090.

Duration of Treatment: Each subject received a single oral dose of ezetimibe (SCH 58235 ~ mg, 10 mg or 20 mg on three separate occasions. Each dose was separated by a 7 day washout period.

Criteria for Evaluation: Physical examinations, electrocardiograms, vital signs, and clinical laboratory tests were performed throughout the study and adverse events were recorded for safety evaluation. For pharmacokinetic purposes, blood samples were collected over 24 hours post-dose for determination unconjugated and total ezetimibe pharmacokinetic parameters.

Statistical Methods: The dose-response relationship was based on AUC and Cmax. A regression model extracting, in sequential order, effects due to subject, linearity (LINEAR), and deviation from linearity (lack-of-fit, LOF) was fit using Type I Sums of Squares. This analysis, on the log of both the dose and response, was used to examine the appropriateness of the linear model. If the lack-of-fit (LOF) was not significant then the intercept and slope for the linear response was determined using a reduced model; subject and linearity were extracted. For log-transformed data, a slope of 1 indicated that a doubling of the dose results in a doubling of the response; this hypothesis was tested by comparing the slope with one.

In addition, the derived pharmacokinetic parameters were statistically analyzed using a crossover analysis of variance model. The effects due to subject, period and treatment were extracted. Dose adjusted original scale and log scale AUC and Cmax were evaluated; all other parameters were evaluated in the original scale. The power to detect a 20% difference between treatment means for an alpha level of 0.05 (two-tailed) was also computed. The pooled residual error and associated degrees of freedom from the analyses of variance were used in the calculation of power.

Preliminary analysis included examining the pharmacokinetic parameters for extreme values by reviewing the studentized ranges of deviations from the expected value derived from the analyses of variance to see if any value exceeded 3. The impact of any outliers on the results of the analyses were to be evaluated.

Ezetimibe pharmacokinetic parameters were summarized using descriptive statistics. Means, standard

deviations and coefficients of variation were provided for the concentration data at each time point and the pharmacokinetic parameters.

SUMMARY-CONCLUSIONS:
RESULTS:
Clinical Pharmacology:
Pharmacokinetics: Mean ezetimibe concentrations and derived pharmacokinetic parameters following a single oral dose of ezetimibe [redacted] mg, 10 mg or 20 mg healthy subjects (n=24) is shown in the following table:

Parameter	Units	Ezetimibe mg Mean	Ezetimibe mg % CV	Ezetimibe 10 mg Mean	Ezetimibe 10 mg % CV	Ezetimibe 20 mg Mean	Ezetimibe 20 mg % CV
Total Ezetimibe							
Cmax	ng/mL	50.1	38	73.6	43	119	40
Tmax[a]	hr	1.0	[redacted]	1.0	[redacted]	1.0	[redacted]
Tmax	hr	0.92	55	1.29	76	1.15	52
AUC(0-24 hr)	ng·hr/mL	240	41	440	35	819	39
Conjugated Ezetimibe							
Cmax	ng/mL	48.6	38	71.1	43	115	40
Tmax[a]	hr	1.0	[redacted]	1.0	[redacted]	1.0	[redacted]
Tmax	hr	0.92	55	1.29	76	1.10	52
AUC(0-24 hr)	ng·hr/mL	218	43	400	37	743	42
Ezetimibe							
Cmax	ng/mL	2.14	64	3.41	51	6.06	66
Tmax[a]	hr	1.75	[redacted]	6.0	[redacted]	7.0	[redacted]
Tmax	hr	3.82	94	8.17	86	7.27	73
AUC(0-24 hr)	ng·hr/mL	21.9	53	41.0	43	76.0	46

a: Median (range)

Statistical comparisons of the log-transformed AUC and Cmax values for evaluation of linearity and dose-proportionality for ezetimibe are presented in the following tables:

Statistical Evaluation of Linearity of the Dose-Response Relationship Based on the AUC(0-24 hr) Values Following a Single Oral Dose Administration of [redacted] 10 and 20 mg Ezetimibe to Healthy Subjects

Parameter	P-Value[a] Total Ezetimibe	Conjugated Ezetimibe	Ezetimibe
Lack of fit[b]	0.7623	0.7623	0.8224
Intercept[c]	0.000	0.000	0.000
Slope[d]	0.0002	0.0001	0.1337

a: Based on log-transformed data
b: Test for deviation from linearity
c: Test for intercept = 0
d: Test for slope = 1

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Title of the Study: SCH 58235: DOSE-PROPORTIONALITY OF EZETIMIBE TABLETS: A THREE-WAY CROSSOVER STUDY (PROTOCOL P00750)

Relative Bioavailability (Ratio) and the 90% Confidence Interval (CI) Based on Dose-Adjusted Cmax and AUC(0-24hr) in Ezetimibe Following a Single Oral Dose Administration of Ezetimibe 10 and 20mg to Healthy Subjects.

Treatment Comparison	Total Ezetimibe		Conjugated Ezetimibe		Ezetimibe	
	Ratio (%)	90% CI	Ratio (%)	90% CI	Ratio (%)	90% CI
	AUC(0-24hr)/D[a]					
Ezetimibe mg vs. 10 mg	107	100-114	107	100-114	104	94-115
Ezetimibe 20 mg vs. 10 mg	91.8	86-98	91.6	86-98	94.0	85-104
	Cmax/D[a]					
Ezetimibe mg vs. 10 mg	139	127-153	140	127-154	122	106-141
Ezetimibe 20 mg vs. 10 mg	82.3	75-90	82.2	75-90	87.1	76-100

a: Parameter normalized by a factor of 1, 2 or 4 according to administered dose of 10 or 20 mg, respectively.

The dose-response relationship based on the log-transformed dose and AUC values was linear (deviation from linearity, $p>0.7$) for all ezetimibe analytes and dose-proportional for ezetimibe (slope=1, $p=0.13$). The slopes for the log-transformed AUC-dose relationships for total and conjugated ezetimibe were significantly different from 1. The AUC values for total and conjugated ezetimibe were less than dose-proportional and increased in a 1:1.8:3.4 ratio when ezetimibe dose was increased in a ratio, however there was no substantial deviation from dose-proportionality between mg and 20 mg compared to 10 mg (clinical dose). The log-transformed Cmax-dose relationship for total ezetimibe, conjugated ezetimibe, as well as for ezetimibe was linear ($p>0.16$) but less than dose proportional (slope$\neq$1, $p\leq0.004$). The dose-adjusted data also support these conclusions.

Ezetimibe was rapidly absorbed and extensively conjugated following oral administration; the Tmax values for total and conjugated ezetimibe ranged from hr. The Tmax values for ezetimibe ranged from hr. Plasma total ezetimibe and ezetimibe concentrations exhibited multiple peaks, suggesting enterohepatic recycling. Ezetimibe exposure was 4-19% of the total ezetimibe based on the ratio of plasma AUC values.

Safety: Ezetimibe (SCH 58235) administered as a single dose of mg, 10 mg, or 20 mg was safe and well tolerated. Three subjects (13%) reported adverse events including headache and loose stools while receiving ezetimibe 20 mg. These adverse events were considered moderate in severity and possibly related to treatment with ezetimibe. There were no deaths or serious adverse events and there were no clinically significant abnormalities or changes in routine physical examinations, vital signs, ECGs or clinical laboratory tests.

CONCLUSIONS:

- Ezetimibe (SCH 58235) mg, 10 mg, or 20 mg single dose was safe and well tolerated in healthy volunteers.
- The dose-response relationship based on the log-transformed dose and AUC values was linear for all ezetimibe analytes and dose-proportional for ezetimibe.
- Log-transformed AUC values for total and conjugated ezetimibe were dose-related but less than dose-proportional, however there was no substantial deviation from dose-proportionality.
- The dose-response relationships based on the log-transformed dose and Cmax values of all ezetimibe analytes was linear but less than dose-proportional.

Title of the Study:	SCH 58235: Effect of Food on the Oral Bioavailability of Ezetimibe 10 mg Tablets: A Three Way Crossover Study (Protocol No. P00751)
Investigator:	[ ]
Study Center:	
Publication(s):	None
Studied Period:	10 MAY 00 to 05 JUN 00 — **Clinical Phase:** I

Objective: The objective of this study was to evaluate the effect of a high-fat and a nonfat meal, relative to a fasted state, on the oral bioavailability of ezetimibe from the to-be-marketed ezetimibe 10 mg tablet formulation.

Methodology: This was a randomized, open-label, three-way crossover, single dose study. Subjects were screened within 3 weeks prior to dosing, and those who met the entry criteria were confined to the study center on three consecutive occasions (approximately 2.5 days/period) separated by a minimum of 7 days between treatments. On the morning on Day 1 of each treatment period, following a 10 hour fast, subjects were randomized to receive ezetimibe 1 x 10 mg tablet orally and remain fasting (Treatment A), or to receive ezetimibe 1 x 10 mg tablet orally immediately following a standardized high-fat breakfast (Treatment B), or ezetimibe 1 x 10 mg tablet orally immediately following a standardized nonfat breakfast (Treatment C). Subjects randomized to receive the standardized breakfast (Treatment B or C) consumed the prescribed meal in a 20-minute period prior to drug administration and received the ezetimibe 10 mg tablet within 5 minutes after completing the breakfast. Each dose was administered with 200 mL of noncarbonated room temperature water. Subjects continued fasting (Treatment A) or did not eat again until the 4-hour study procedures were completed (Treatments B and C), at which time a standardized light lunch was served. Water was permitted throughout the fasting period. Volunteers remained awake and seated upright or were ambulatory for 4 hours postdose. Vital signs, ECGs, and blood and urine samples were collected at specified times during the study for safety and pharmacokinetic evaluations. Blood samples for the determination of plasma unconjugated and total ezetimibe concentrations were collected prior to dosing (zero hour) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, and 48 hours postdose. Plasma ezetimibe (unconjugated) and total ezetimibe (ezetimibe plus conjugated ezetimibe) concentrations were determined using [redacted] assays. The lower limits of quantitation (LOQ) for ezetimibe and total ezetimibe were [redacted] plasma, respectively; the linear ranges were [redacted] respectively. Plasma concentrations of conjugated ezetimibe, reported as ezetimibe equivalents, were calculated by subtracting the ezetimibe concentration from the corresponding total ezetimibe concentration for each sample. For safety evaluations physical examinations, vital signs, electrocardiograms, and clinical laboratory tests were conducted at Screening and at the conclusion of the study (48 hours after dosing). In addition, clinical laboratory tests and drug screens were repeated upon each confinement of the crossover prior to dosing (Day -1), and vital signs were also monitored at predose (0-hour) and at 24 and 48 hours after each treatment administration.

Number of Subjects: Eighteen male and female volunteers were enrolled and completed the study.

Diagnosis and Criteria for Inclusion: Male and female subjects between the ages of 18 and 45 years inclusive, having a Body Mass Index (BMI) between 19-27 (BMI=weight [kg]/height $[m]^2$). Subjects had to be free of any clinically significant disease based on results of a medical history, physical examination, electrocardiogram, and routine laboratory tests (blood chemistry, hematology, drug screen, HIV, hepatitis B/C, and urinalysis).

Test Product, Dose, Mode of Administration, Batch No(s): Ezetimibe (SCH 58235) tablets, 10 mg, oral, Batch No. 75882-090.

Duration of Treatment: Each subject received a single oral dose of ezetimibe (SCH 58235) 10 mg on three separate occasions, each dose separated by a 7 day wash out period.

Criteria for Evaluation: Physical examinations, electrocardiograms, vital signs, and clinical laboratory tests were performed throughout the study and adverse events were recorded for safety evaluation. For pharmacokinetic purposes, blood samples were collected over 48 hours postdose for determination of ezetimibe and total ezetimibe pharmacokinetic parameters.

Title of the Study: SCH 58235: Effect of Food on the Oral Bioavailability of Ezetimibe 10 mg Tablets: A Three Way Crossover Study (Protocol No. P00751)

Statistical Methods: Summary statistics were calculated for ezetimibe, total ezetimibe and conjugated ezetimibe concentration-time data at each time point and for the derived pharmacokinetic parameters. The parameters for ezetimibe (unconjugated), total ezetimibe and conjugated ezetimibe were statistically analyzed using a crossover analysis of variance model (ANOVA). The effects due to subject, period and treatment were extracted. The relative oral bioavailability of ezetimibe given in combination with food (Treatments B or C) compared to given under fasted conditions (Treatment A, reference) was expressed as the ratio of the two treatments for the log-transformed AUC and Cmax. Confidence intervals for these estimates of bioavailability and the power to detect a 20% difference in treatment means for an alpha level of 0.05 (two-tailed) were computed. If the ratio (expressed as a percent) of the treatment mean comparisons for log-transformed AUC and Cmax was outside the range of 50-200% (ie, more than a mean 50% decrease or 100% increase) for any of the analytes, then a potentially clinically significant food effect was indicated. Preliminary analysis included examining the pharmacokinetic parameters for extreme values by reviewing the studentized ranges of deviations from the expected values derived from the analyses of variance to see if any value exceeded 3. The impact of any outliers on the results of the analyses was evaluated.

SUMMARY-CONCLUSIONS:

RESULTS:

Clinical Pharmacology:

Pharmacokinetics:

Mean (%CV) total ezetimibe, ezetimibe and conjugated ezetimibe pharmacokinetic parameters and statistical comparisons of the log-transformed Cmax and AUC values are presented in the following table:

Parameter	Treatment[a]	Mean (%CV)	Point Estimate (%)[b]	Confidence Interval[c]
		Total Ezetimibe		
Cmax	A	70.6 (34)	--	--
	B	79.3 (55)	103	84-126
	C	74.7 (41)	103	84-127
AUC (tf)	A	722 (37)	--	--
	B	705 (32)	99	91-108
	C	654 (32)	92	85-100
		Ezetimibe		
Cmax	A	5.48 (66)	--	--
	B	7.91 (71)	138	112-170
	C	4.40 (60)	82	66-101
AUC (tf)	A	97.9 (55)	--	--
	B	95.2 (45)	100	92-109
	C	85.3 (48)	89	82-97
		Conjugated Ezetimibe		
Cmax	A	67.9 (34)	--	--
	B	72.3 (54)	98	80-119
	C	70.9 (40)	102	83-125
AUC (tf)	A	624 (37)	--	--
	B	610 (33)	99	91-108
	C	569 (32)	92	85-100

a: Treatment A = Fasted, Treatment B = High Fat, Treatment C = Nonfat

b: Expressed as a percent of Treatment B or C to Treatment A.

c: 90% confidence interval based on log-transformed data

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Title of the Study: SCH 58235: Effect of Food on the Oral Bioavailability of Ezetimibe 10 mg Tablets: A Three Way Crossover Study (Protocol No. P00751)

The coadministration of a high-fat or nonfat meal had no effect on the oral bioavailability of ezetimibe, total ezetimibe or conjugated ezetimibe based on AUC(tf), since the 90% confidence intervals (82-109%) fell within the bioequivalence limits of —— A difference in Cmax was observed for ezetimibe following administration of a high-fat meal vs. the fasted state. The relative oral bioavailability estimate, based on the comparison of log transformed Cmax values was 138%, and the corresponding 90% confidence interval ranged from 112-170%. This difference in Cmax values is not considered to be clinically significant as it is within the predefined 50-200% range. The relative oral bioavailability estimates, based on the comparison of log transformed Cmax values following a nonfat breakfast vs. fasted subjects, were 82%, 103% and 102% for ezetimibe, total and conjugated ezetimibe, respectively. Relative to the fasted state, there was a trend toward higher ezetimibe Cmax when ezetimibe was administered with a high-fat breakfast, and a trend toward a lower Cmax after a nonfat breakfast.

Safety: The results of this study show that ezetimibe 10 mg administered as a single dose was safe and well tolerated. Overall, 11 of the 18 subjects (61%) reported treatment-emergent adverse events, which included headache and dizziness of mild to moderate severity.

CONCLUSIONS:

- Ezetimibe (SCH 58235) 10 mg single dose was safe and well tolerated in healthy volunteers.
- The administration of ezetimibe with a high-fat meal significantly increased the Cmax but not the AUC(tf) of ezetimibe, without significantly affecting the Cmax or AUC(tf) of conjugated or total ezetimibe.
- The administration of ezetimibe with a nonfat meal decreased the Cmax and AUC(tf) of ezetimibe, without significantly affecting the Cmax or AUC(tf) of conjugated or total ezetimibe.
- Based on total ezetimibe concentrations, a food effect was not present. Food had no clinically significant effect on the relative oral bioavailability of ezetimibe or conjugated ezetimibe.

Title of the Study:	SCH 58235: Influence of Food on the Oral Bioavailability of SCH 58235 ——— Administered to Normal Male Volunteers: A Three-Way Crossover Study (Protocol C97-026)
Investigator(s):	———
Publication(s):	None
Studied Period:	30 JUNE 1997 to 17 SEPT 1997 — **Clinical Phase:** I
Objective:	To evaluate the effect of a high-fat and a non-fat meal, relative to a fasted condition on the oral bioavailability of SCH 58235 in healthy male volunteers.
Methodology:	Randomized, open-label, three-way crossover study. The study consisted of 3 treatments with each subject receiving each treatment consisting of SCH 58235, 20 mg p.o following an overnight fast (Treatment A), or within 5 minutes of completing a high-fat breakfast (Treatment B), or a non-fat breakfast (Treatment C). Blood and urine samples were collected at pre-specified times for safety and pharmacokinetic evaluations. Volunteers were continuously observed and questioned throughout the study for possible occurrence of adverse events. All plasma samples were assayed for unconjugated, and total (unconjugated plus conjugated) SCH 58235 concentrations using ——— methods.
Number of Subjects:	12 healthy male volunteers.
Diagnosis and Criteria for Inclusion:	Adult male volunteers between 18-40 years of age inclusive, in good health based on medical history, physical examination, electrocardiogram, and routine laboratory tests (blood chemistry, hematology, drug screen, HIV, Hepatitis B/C and urinalysis) and having weights in accordance with current actuarial tables (±15%) were empaneled for this study.
Test Product, Dose, Mode of Administration, Batch No(s):	SCH 58235 20 mg ——— oral, batch no. 37750-011, administered within 5 minutes of completion of a high-fat breakfast (Treatment B) or non-fat breakfast (Treatment C).
Reference Therapy, Dose, Mode of Administration, Batch No(s):	SCH 58235 20 mg ——— oral, batch no. 37750-011 administered after an overnight fast (Treatment A).
Duration of Treatment:	Single doses were administered in the morning for all three treatment periods at approximately 8 AM and subjects were followed for 48 hours postdose.
Criteria for Evaluation:	Physical examinations, electrocardiograms, vital signs and clinical laboratory tests were performed throughout the study and adverse events were recorded for safety evaluation. In addition, blood samples were collected over 48 hours in each period for determination of pharmacokinetics parameters (Cmax, Tmax, AUC, CL/F, t1/2).
Statistical Methods:	The individual plasma concentrations and derived pharmacokinetic parameters of SCH 58235 (unconjugated, conjugated and total [unconjugated plus conjugated]) for each time-point and treatment are listed for each volunteer. Summary statistics, including means and coefficients of variation are provided for each treatment. The derived pharmacokinetic parameters were statistically analyzed using a cross-over analysis of variance model extracting the effects due to subject, period and treatment. The bioavailability parameters Cmax and AUC(tf) were evaluated based on log-transformed data and were expressed as the ratio of high-fat to fasted, non-fat to fasted, and high-fat to non-fat treatments. Ninety percent (90%) confidence intervals for Cmax and AUC(tf) and the power to detect a 20% difference between treatment means for an alpha level of 0.05 (two-tailed) were computed.

Title of the Study: SCH 58235: Influence of Food on the Oral Bioavailability of SCH 58235 —— Administered to Normal Male Volunteers: A Three-Way Crossover Study (Protocol C97-026)

SUMMARY-CONCLUSIONS:
RESULTS:

Safety: Blood pressure, pulse rate, respiratory rate, oral body temperature evaluations showed no consistent changes of clinical relevance and remained within the range observed for healthy male volunteers. There were no deaths, serious or significant adverse events. With the exception of one subject described below, there were no clinically significant abnormalities or changes in routine or clinical laboratory safety tests from pre-treatment Baseline. Noteworthy changes were observed in SGPT levels for one subject who received SCH 58235 (primarily in the fasting state). This subject (No. 001) developed transient increases in SGPT (55-57 U/L; Reference range 7-46 U/L) starting at 48 hours post-dose when SCH 58235 was given with the non-fat and high-fat meals, with a maximum elevation of (73 U/L) occurring 48 hours post-dose when SCH 58235 was given in the fasted state. There were no clinically significant increases in SGOT or GGT. This abnormality returned to Baseline within 7 days after dosing (Period 3).

Five of the 12 subjects enrolled (42%) reported at least one adverse event following treatment administration. All adverse events were treatment-emergent and (regardless of association to the study drug) included skin nodule, headache, myalgia, neck/arm pain, dizziness and chest pain. Of the subjects who received SCH 58235 while fasting, 2 (17%) reported adverse events; with the non-fat meal, one subject (8%) reported an adverse event; with the high-fat meal, 3 (25%) reported adverse events. All adverse events were considered mild to moderate and each adverse event resolved spontaneously without sequelae. The only pharmacological intervention required was aspirin and ibuprofen for headache and arm pain, respectively. No serious adverse events or deaths were reported in this study. There was no apparent increase in the overall incidence of adverse events as associated with meal composition and SCH 58235. No subject discontinued participation in this study due to adverse events.

Clinical Pharmacology:
Consistent with observations in previous studies, SCH 58235 was rapidly and extensively conjugated (glucuronide conjugate), and plasma unconjugated SCH 58235 concentrations were low (~10%) compared to conjugated SCH 58235. Consequently, the unconjugated SCH 58235 concentrations (as also Cmax and AUC(tf)) were associated with higher variability.

Statistical analysis showed that, based on total SCH 58235, the presence of food, regardless of the fat content, increased the oral bioavailability of SCH 58235 to a moderate extent. Based on log-transformed data for total SCH 58235, the Cmax ratio for high-fat vs. fasted treatments for total SCH 58235 was 147% (90% CI, 118-182) and the ratio for non-fat vs. fasted treatments was 145% (90% CI, 118-179). For AUC(tf), the corresponding ratios were 131 and 124% with 90% CI's for the high-fat vs. fasted and non-fat vs. fasted treatments (90% CI, 117-146, 112-139, respectively). Based on the mean estimates of Cmax and AUC, a food effect is documented since these estimates are outside the upper confidence interval for Cmax ——) and AUC ——) suggested by recently proposed FDA guidelines.

CONCLUSIONS:

- SCH 58235 administered as a single oral dose of 20 mg with high-fat, non-fat meals and in the fasted state to young healthy male volunteers appears to be safe and well tolerated.
- All adverse events were mild to moderate and non-specific and there was no apparent difference in the pattern of adverse events among the meal types when administered with SCH 58235.
- Relative to the fasted state, food moderately (~30% based on AUC(tf) of total SCH 58235) increased the oral bioavailability of SCH 58235.
- The presence or absence of fat in the diet was not a significant factor in the bioavailability of SCH 58235.
- The current safety profile supports the continued investigation of SCH 58235 in human subjects.

Title of the Study: SCH 58235: The Effects of SCH 58235 On Drug Metabolizing Enzymes In Healthy Male Subjects (Protocol I97-137)	
Investigator:	
Publication(s): Zhu Y, Statkevich P, **Kosoglou T**, Zambas D, Patrick J, Cayen MN, Batra V. Effect of SCH 58235 on the activity of drug metabolizing enzymes in vivo. ***Clin Pharmacol Ther*** 2000;67(2):152 [abstract PIII-43].	
Studied Period: 11 MAY 1998 to 26 JUN 1998	**Clinical Phase: I**
Objective: To examine the effects of SCH 58235 on the activity of drug metabolizing enzymes in healthy male volunteers. The specific enzymes investigated were cytochrome P450 (CYP450) 1A2, 2C8/9, 2D6 and 3A4 and N-acetyltransferase.	
Methodology: Randomized, open-label, placebo-controlled, two-way crossover, single-center study. Twelve (12) volunteers were randomized to receive either Treatment A or Treatment B in conjunction with an oral CYP450 "cocktail" of dextromethorphan (30 mg), caffeine (200 mg), tolbutamide (500 mg) and dapsone (100 mg) and IV midazolam (0.05 mg/kg). Treatment A = SCH 58235, 2 x 10 mg tablets x 8 days. Treatment B = Placebo. Oral probe substrates, administered as a single "cocktail" 1 hour after SCH 58235 or placebo administration on Day 7. Midazolam administered via 30 minutes intravenous (IV) infusion 1 hour after the SCH 58235 or placebo dose on Day 8. Blood and urine samples were collected at pre-specified times for pharmacokinetic and safety evaluations. Blood samples for plasma unconjugated and total (unconjugated plus conjugated) SCH 58235 concentrations were collected only during the period in which a particular subject had received SCH 58235. Blood samples for determination of plasma caffeine, 1,7-paraxanthine, dapsone, monoacetyldapsone and serum midazolam concentrations, and urine samples for determination of tolbutamide, 4-hydroxytolbutamide, carboxytolbutamide, dextromethorphan, dextrorphan and 3-methoxymorphinan concentrations were collected during both treatment periods. Plasma unconjugated and total SCH 58235 concentrations were determined using assays with lower limits of quantitation (LOQ) of and with linear ranges of for unconjugated and total SCH 58235, respectively. Plasma conjugated SCH 58235 concentrations were calculated by subtracting the unconjugated SCH 58235 concentration from the corresponding total, expressed as SCH 58235 as SCH 58235 equivalents, SCH 58235 concentration for each sample. Plasma caffeine, dapsone and their respective metabolite concentrations were determined using assay methods. Serum midazolam concentrations were determined using a assay. Urine tolbutamide, dextromethorphan and their respective metabolite concentrations were determined using methods. Volunteers were continuously observed and questioned throughout the study for possible occurrence of adverse events.	
Number of Subjects: Twelve (12) healthy male volunteers.	
Diagnosis and Criteria for Inclusion: Adult male volunteers between 18-45 years of age inclusive, in good health based on medical history, physical examination, electrocardiogram, and routine laboratory tests (blood chemistry, hematology, urinalysis and drug screen) and having a BMI of 19-27 were empanelled for this study. Volunteers also underwent a CYP2D6 phenotyping to exclude those individuals who were poor CYP2D6 metabolizers (debrisoquine metabolic urinary ratio of >12.6).	
Test Product, Dose, Mode of Administration, Batch No(s): SCH 58235, 2 x 10 mg tablets, oral, Batch No. 52123-050.	
Reference Therapy, Dose, Mode of Administration, Batch No(s): Placebo tablets matching SCH 58235, 0 mg, oral, Batch No. 52123-048.	
Duration of Treatment: SCH 58235 20 mg was administered once daily in the morning for 8 consecutive days.	
Criteria for Evaluation: Physical examinations, electrocardiograms, clinical laboratory tests were performed throughout the study and adverse events were recorded for safety evaluation. In addition, blood and urine samples were collected on Days 7 and 8 after treatment administration for the determination of plasma/serum pharmacokinetic parameters or urinary excretion ratio of oral probe substrates.	
Statistical Methods: The measures of drug metabolizing enzyme activity for the two treatments were statistically analyzed using a cross-over analysis of variance model (ANOVA). The effects due to sequence, subject within sequence, phase and treatment were extracted. Ninety percent (90%) confidence intervals for the mean difference between the 2 treatments were calculated using the pooled residual error and associated degrees of freedom from the ANOVA. Summary statistics including means, standard deviations and coefficients of variation were provided for the derived parameters.	

Title of the Study: SCH 58235: The Effects of SCH 58235 On Drug Metabolizing Enzymes In Healthy Male Subjects (Protocol I97-137)

SCH 58235 pharmacokinetic parameters were summarized using descriptive statistics. Means, standard deviations and coefficients of variation were provided for the concentration data at each time point and the pharmacokinetic parameters.

SUMMARY-CONCLUSIONS:

RESULTS: The study was conducted as described in the protocol. However, due to the nature of the data and/or some technical difficulties, certain pharmacokinetic parameters could not be calculated and some analyses described in the protocol could not be done. Deviations from the planned analyses were not considered to have a significant effect on the conclusions derived from the experimental data.

Clinical Pharmacology:

Pharmacokinetics:

Mean parameters and statistical comparisons of the CYP450 enzyme markers following administration of probe substrates in combination with once-daily oral administration of SCH 58235 20 mg or placebo are shown in the table below:

Enzyme Activity	Matrix	Parameter	Treatment	Mean Parameter	%CV	p-Value	Point Estimate[a](%)	Confidence Interval[b]
CYP1A2	Plasma	AUC ratio[c]	SCH 58235 Placebo	0.79 0.69	64 48	0.517	114	77-151
CYP2C8/9	Urine	Urinary ratio[d]	SCH 58235 Placebo	865 823	33 26	0.228	105	98-112
CYP2D6	Urine	Urinary ratio[e]	SCH 58235 Placebo	$9.15x10^3$ $9.44x10^3$	87 132	0.878	97.0	64-130
CYP3A4 (total)	Urine	Urinary ratio[f]	SCH 58235 Placebo	5.17 5.47	47 52	0.513	94.7	80-109
CYP3A4 (hepatic)	Serum	AUC(tf)[g] (ng·hr/mL)	SCH 58235 Placebo	84.7 85.8	34 24	0.672	96.3	82-113
N-acetyl transferase	Plasma	AUC(0-24 hr)[h] (ng·hr/mL)	SCH 58235 Placebo	14694 15722	11 20	0.270	94.7	87-103

a: Expressed as a percent of Treatment A (SCH 58235 20 mg) to Treatment B (Placebo).

b: 90% confidence interval of mean differences, $\alpha = 0.1$.

c: AUC ratio of 1,7-paraxanthine to caffeine, n=12.

d: Urinary ratio of carboxytolbutamide plus 4-hydroxytolbutamide to tolbutamide, n=10.

e: Urinary ratio of dextromethorphan to dextrorphan, n=11.

f: Urinary ratio of dextromethorphan to 3-methoxymorphinan, n=10.

g: AUC of midazolam, n=12.

h: AUC(0-24 hr) of dapsone, n=12.

Comparison of concentrations of probe substrates and/or metabolites or parent/metabolite ratios, in both treatment periods showed no significant differences.

Safety:

All 12 subjects (100%) reported at least one adverse event during this study. The most commonly reported adverse events were somnolence and dizziness regardless of treatment. Blood pressure, pulse rate, respiratory rate, oral body temperature evaluations showed no consistent changes of clinical relevance and remained within the range observed for healthy male volunteers.

CONCLUSIONS:

- Multiple-dose administration of SCH 58235 20 mg given orally once-daily had no effect on the metabolic activity of CYP1A2, CYP2C8/9, CYP2D6, CYP3A4 or N-acetyltransferase enzymes in man.
- SCH 58235 has a low potential of causing clinically significant drug interactions when co-administered with commonly used drugs.

Title of the Study:	SCH 58235: Assessment of the Possible Pharmacokinetic and/or Pharmacodynamic Drug:Drug Interaction Between SCH 58235 and Warfarin (Protocol No. I98-106)
Investigator(s):	[redacted]
Publication(s):	Bauer KS, et al. Ezetimibe does not affect the pharmacokinetics or pharmacodynamics of warfarin (abstract PI-15). Clin Pharmacol Ther 2001;69(2):P5.
Studied Period:	11 MAR 1999 to 04 JUL 1999 — **Clinical Phase:** 1
Objective:	The objective of this study is to evaluate the potential pharmacokinetic and/or pharmacodynamic drug-drug interaction between ezetimibe (SCH 58235) and warfarin in healthy male volunteers.

Methodology: Open-label, single center, randomized, placebo controlled, two-way crossover, multiple dose study. After an overnight fast, adult male volunteers received ezetimibe (SCH 58235) 10 mg or placebo as outpatients on Days 1-6, 10-11 and as inpatients on Days 7-9. Subjects were confined to the study site on the afternoon of Day 6, approximately 12 hours prior to the Day 7 treatment. On Day 7, subjects received either one ezetimibe 10 mg or placebo tablet concurrently with warfarin 25 mg (5 x 5 mg tablets). Blood sampling for pharmacokinetic evaluation of ezetimibe (SCH 58235) were collected on Day 7 at predose (zero hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours after the Day 7 dose. In addition, predose (zero hour) blood samples were collected on Days 1, 6, 7, 8, and 9. Blood samples for pharmacokinetic evaluation of (R)- and (S)-warfarin were collected at predose (zero hour), and at 2, 4, 6, 8, 10, 12, 16, 24, 36, 48, 60, 72, 96, and 120 hours after the Day 7 warfarin administration. Prothrombin time (PT), was measured prior to (zero hour) and at 4, 8, 12, 24, 36, 48, 60, 72, 96, and 120 hours after the Day 7 warfarin administration. All plasma samples were assayed for unconjugated and total (conjugated plus unconjugated) ezetimibe concentrations using [redacted] methods with lower limits of quantitation (LOQ) of [redacted] plasma, respectivelv. The assay linear ranges for unconjugated and total ezetimibe were [redacted] respectively. Plasma concentrations of (R)-warfarin and (S)-warfarin were determined using [redacted] assays with lower limits of quantitation (LOQs) of [redacted] plasma. The assay linear ranges were [redacted] for both (R)- and (S)-warfarin. For safety evaluation, physical examinations, vital signs, electrocardiograms (ECGs) and clinical laboratory tests were conducted at screening and at the end of the study (Day 12). Vital signs and clinical laboratory tests were also assessed during the study. Subjects were continuously observed and questioned throughout the study for possible occurrence of adverse events.

Number of Subjects: Fifteen healthy male subjects were enrolled and 12 completed the study as planned. Three subjects (Subject Nos. 2, 7, and 8) discontinued from the study and were replaced. Subject No. 2 had completed Period 1 of the crossover, but he had an exaggerated PT response to warfarin and was dropped from the study at the discretion of the investigator. Subject No. 7 withdrew consent on Period 1 after receiving two doses of treatment. His discontinuation was not due to an adverse event. Subject No. 8 was discontinued predose on Day 1, Period 2 due to a positive drug screen.

Diagnosis and Criteria for Inclusion: Adult male subjects between 18-45 years of age inclusive, in good health based on medical history, physical examination, electrocardiogram, and routine laboratory tests (blood chemistry, hematology, drug screen, HIV, hepatitis B/C, and urinalysis) and having Body Mass Index (BMI) of 19-27 were empanelled for this study.

Test Product, Dose, Mode of Administration, Batch No(s): Ezetimibe (SCH 58235) tablets, 10 mg, oral, Batch No. 52123-050.

Reference Therapy, Dose, Mode of Administration, Batch No(s): Ezetimibe (SCH 58235) placebo, oral, Batch No. 52123-048. Warfarin (Marevan®, Unichem), 5 mg tablets, oral, Batch No. E2834A1, Expiration Date 2/2000.

Duration of Treatment: One ezetimibe 10 mg or placebo tablet was administered in the morning at approximately 8 AM every day for 11 consecutive days. Warfarin 25 mg was administered as a single dose (on Day 7) on two occasions.

Criteria for Evaluation: Physical examinations, electrocardiograms, vital signs, and clinical laboratory tests were performed throughout the study and adverse events were recorded for safety evaluation. All subjects who were enrolled and completed both periods of the crossover make up the population data set for the primary pharmacokinetic/pharmacodynamic comparisons. Summary statistics and adverse reaction tabulation are included for all treated subjects. Demographic and baseline variables are listed and

summarized using descriptive statistics.

Statistical Methods: Summary statistics were calculated for the plasma unconjugated, total, and conjugated ezetimibe and (R)- and (S)-warfarin concentration data at each time point and the derived pharmacokinetic parameters. The pharmacokinetic parameters for (R)- and (S)-warfarin were statistically analyzed using a crossover analysis of variance (ANOVA) model extracting the effects due to sequence, subject within sequence, period, and treatment. The AUC(tf), AUC(I) and Cmax parameters were evaluated based on log-transformed data. Ninety percent confidence intervals, the estimates of relative bioavailability, ie, mean difference in the log-transformed parameters expressed as a percent (%) Treatment B (warfarin plus ezetimibe) to Treatment A (warfarin plus placebo), and the power to detect a 20% difference between group means at an α level of 0.05 (two-tailed) were computed. The pharmacokinetic parameters AUC and Cmax were also analyzed in the original scale. Preliminary analyses included examining the pharmacokinetic parameters for extreme values by reviewing the studentized ranges of deviations from the expected value derived from the ANOVA to see if any value exceeded three.

Individual plasma PT, PT-ratio, INR, and INR-Ratio data were used for pharmacodynamic analysis. The PT-ratio and INR-ratio were calculated as the ratio of the PT or INR after warfarin dosing to the PT or INR measured just prior to dosing (zero hour of Day 7). The following derived pharmacodynamic parameters were also evaluated: area under the PT-time curve from Time 0-120 hours postdose ($AUC[0\text{-}120\ hr]_{PT}$), the area under the PT-ratio-time curve from Time 0-120 hours postdose ($AUC[0\text{-}120\ hr]_{PT\text{-}Ratio}$), the area under the INR-time curve from Time 0-120 hours postdose ($AUC[0\text{-}120\ hr]_{INR}$), and the area under the INR-ratio-time curve from Time 0-120 hours postdose ($AUC[0\text{-}120\ hr]_{INR\text{-}Ratio}$). These parameters were also statistically analyzed using a crossover ANOVA model extracting the effects due to sequence, subject within sequence, period, and treatment.

SUMMARY-CONCLUSIONS:

RESULTS:

Safety:

The multiple-dose administration of ezetimibe 10 mg or placebo with a single dose of warfarin 25 mg on Day 7 in healthy male volunteers was well tolerated. Six of fourteen subjects (43%) who received placebo plus warfarin and seven of fourteen subjects (50%) who received ezetimibe plus warfarin reported treatment emergent adverse events. The most common treatment-related adverse event was headache. One subject (Subject No. 2) had an exaggerated PT response to warfarin and was discontinued from the study at the discretion of the investigator. One subject (No. 8) experienced epistaxis Day 7, seven hours after receiving warfarin and ezetimibe. The epistaxis resolved spontaneously without sequelae. This subject was later discontinued for a positive drug screen predose on Day 1, Period 2.

Clinical Pharmacology:

Pharmacokinetics:

The key pharmacokinetic parameters for ezetimibe and warfarin are presented below:

		Ezetimibe Pharmacokinetics Day 7					
		Total Ezetimibe		Unconjugated Ezetimibe		Conjugated Ezetimibe	
Parameter	Units	Mean[a] (Range)	%CV	Mean[a] (Range)	%CV	Mean[a] (Range)	%CV
Cmax	ng/mL	97.2	39	8.46	53	92.0	40
Tmax	hr	1.11 (0.5-3.0)	62	4.29 (0.5-12)	100	1.11 (0.5-3.0)	62
AUC(0-24 hr)	ng·hr/mL	728	34	80.1	48	650	38
%AUC[b]	%	NA[c]	NC[d]	12.5	72	88.0	9

a: n=14, including Subject Nos. 2 and 8.

b: Calculated as $\frac{AUC(0-24\ hr)_{unconjugated\ SCH\ 58235}}{AUC(0-24\ hr)_{total\ SCH\ 58235}} \times 100\%$ and $\frac{AUC(0-24\ hr)_{conjugated\ SCH\ 58235}}{AUC(0-24\ hr)_{total\ SCH\ 58235}} \times 100\%$.

c: NA: not applicable.

d: NC: not calculated.

Title of the Study: SCH 58235: Assessment of the Possible Pharmacokinetic and/or Pharmacodynamic Drug:Drug Interaction Between SCH 58235 and Warfarin (Protocol No. I98-106)

The pharmacokinetics of total, unconjugated, and conjugated ezetimibe in this study were similar to those observed in a previous study following multiple-dose oral administration of ezetimibe 10 mg. Thus, a single oral dose of warfarin on Day 7 did not appear to alter the multiple-dose pharmacokinetics of ezetimibe.
Ezetimibe was rapidly absorbed and extensively glucuronidated following oral administration. Unconjugated ezetimibe exposure was approximately 12% of the total ezetimibe exposure. Plasma total and unconjugated ezetimibe concentrations exhibited multiple peaks, suggesting enterohepatic recycling.

Warfarin Pharmacokinetics

		Treatment A Warfarin with Placebo				Treatment B Warfarin with Ezetimibe			
		(R)-warfarin		(S)-warfarin		(R)-warfarin		(S)-warfarin	
Parameter	Units	Mean[a]	%CV	Mean[a]	%CV	Mean[a]	%CV	Mean[a]	%CV
Cmax	µg/mL	1.11	22	1.14	26	1.14	19	1.14	19
Tmax	hour	4.67	72	5.17	78	3.50	45	2.83	36
Tmax[b]	hour	4.00	[c]	4.00	[c]	2.00	[c]	2.00	[c]
AUC(tf)	µg·hr/mL	44.9	22	32.1	19	44.2	23	31.0	23

a: n=12 excluding Subject Nos. 2 and 8.

b: Median.

c: Range.

There were no significant differences in the exposure to either (R)- or (S)-warfarin between the two treatment groups based on AUC and Cmax.
A statistical comparison of the pharmacokinetic parameters of warfarin is listed below:

Analyte	Parameter	Relative Bioavailability(%)[b]	90% Confidence Interval[c]
(R)-Warfarin	Cmax[a]	103	97-110
	AUC(tf)[a]	98.1	91-105
(S)-Warfarin	Cmax[a]	101	93-110
	AUC(tf)[a]	95.8	90-102

a: Cmax - µg/mL, AUC(tf) - µg·hr/mL.

b: Percent ratio of the geometric mean value for Treatment B (warfarin plus ezetimibe) to Treatment A (warfarin plus placebo).

c: Ninety percent confidence interval based on log-transformed data, $\alpha = 0.05$, two-tailed.

The 90% confidence intervals for the ratios of log transformed Cmax and AUC(tf) for R- and S-warfarin fall within 80% to 125% guidelines for bioequivalence. Therefore, ezetimibe did not affect the pharmacokinetics of warfarin.

Pharmacodynamics:
The mean pharmacodynamic parameters are summarized below.

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Title of the Study: SCH 58235: Assessment of the Possible Pharmacokinetic and/or Pharmacodynamic Drug:Drug Interaction Between SCH 58235 and Warfarin (Protocol No. I98-106)

Parameter	Unit	Treatment A Warfarin With Placebo		Treatment B Warfarin With Ezetimibe		Difference (Treatment B-A)	95% CI
		Mean[a]	%CV	Mean[a]	%CV		
AUC(0-120 hr) $_{PT\text{-}Ratio}$	hr	147	8	148	9	1.06	-3.35–5.48
AUC(0-120 hr) $_{INR\text{-}Ratio}$	hr	158	11	158	12	0.51	-6.01–7.03
Plasma AUC(tf)$_{R\text{-}Warfarin}$	µg·hr/mL	44.9	22	44.2	23	-0.75	-4.48–2.99
Plasma AUC(tf)$_{S\text{-}Warfarin}$	µg·hr/mL	32.1	19	31.0	23	-1.07	-3.52–1.39
Plasma $AUC_{Total\ Warfarin}$[b]	µg·hr/mL	77.0	18	75.2	21	-1.81	-7.59–3.97
Normalized $AUC_{PT\text{-}Ratio}$[c]	hr/µg·hr/mL	1.99	26	2.09	33	0.10	-0.04–0.24
Normalized $AUC_{INR\text{-}Ratio}$[d]	hr/µg·hr/mL	2.14	29	2.24	36	0.10	-0.04–0.24

a: n=12.

b: Calculated as: plasma $AUC(tf)_{R-Warfarin}$ + plasma $AUC(tf)_{S-Warfarin}$.

c: Calculated as: $\frac{AUC(0-120\ hr)_{PT-Ratio}}{AUC_{Total\ Warfarin}}$.

d: Calculated as: $\frac{AUC(0-120\ hr)_{INR-Ratio}}{\text{plasma } AUC_{Total\ Warfarin}}$.

There was no significant difference between the anticoagulant measures ($AUC[0\text{-}120\ hr]_{PT\text{-}Ratio}$ or $AUC[0\text{-}120\ hr]_{INR\text{-}Ratio}$) following warfarin administration with or without ezetimibe. Therefore, ezetimibe did not affect the pharmacodynamics of warfarin.

CONCLUSIONS:

- Multiple-dose administration of ezetimibe (SCH 58235) 10 mg/day given with a single dose warfarin 25 mg was safe and well tolerated.
- Multiple-dose administration of ezetimibe 10 mg/day did not alter the single-dose pharmacokinetics of (R)- and (S)-warfarin.
- Ezetimibe was rapidly absorbed and extensively glucuronidated. The ezetimibe pharmacokinetics in this study were comparable to those previously reported following oral administration of ezetimibe 10 mg monotherapy.
- Single-dose warfarin 25 mg administration did not appear to alter the multiple-dose pharmacokinetics of ezetimibe.
- Multiple-dose administration of ezetimibe 10 mg/day did not affect the pharmacodynamics of a single dose of racemic warfarin 25 mg. Therefore, the coadministration of ezetimibe and warfarin is not expected to alter the anticoagulant response to warfarin.

Title of the Study:	SCH 58235: Pharmacokinetic/Pharmacodynamic Drug Interaction Study With Digoxin in Healthy Volunteers (Protocol No. C98-114)	
Investigator(s):	[redacted]	
Publication(s):	None	
Studied Period:	20 APR 1999 to 27 MAY 1999	**Clinical Phase:** I
Objective:	The primary objective of this study was to assess the potential for ezetimibe (SCH 58235) to affect the pharmacokinetics and/or pharmacodynamics of digoxin.	

Methodology: This was an open-label, single-center, multiple-dose study in healthy male volunteers. In the morning of each treatment day, after an overnight fast, each of the twelve male subjects received digoxin 0.5 mg orally on Days 1 and 10, and ezetimibe (SCH 58235) 10 mg orally once-daily for eight consecutive days (Days 3-10). On Days 1 and 3-10, the subjects continued fasting until two hours postdose, at which time regular standardized meals were served. Water was allowed during the fasting period. Blood samples were collected at prespecified times for safety and pharmacokinetic evaluations. Blood samples for determination of plasma digoxin concentrations were collected just prior to each dose of digoxin (0 hour) on Days 1 and 10 and at 0.5, 1, 1. 5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, and 48 hours after each dose of digoxin. Blood samples for determination of unconjugated and total plasma ezetimibe concentrations were collected just prior to the first dose of digoxin (0 hour) on Day 1, and just prior to the last dose of ezetimibe (0 hour) on Day 10 and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours after the last dose of ezetimibe (Day 10). All digoxin samples were assayed for digoxin concentrations using a [redacted] method with a lower limit of quantitation (LOQ) of [redacted] plasma. All ezetimibe (SCH 58235) plasma samples were assayed for unconjugated and total (conjugated plus unconjugated) ezetimibe concentrations using [redacted] methods with LOQs of [redacted] plasma for unconjugated and total ezetimibe, respectively.

For safety evaluation, physical examinations, vital signs, electrocardiograms (ECGs), and clinical laboratory tests were conducted at Screening and at the end of the study (Day 12). Additionally, ECGs and clinical laboratory tests were conducted on Days 1 and 10, and vital signs were conducted daily (Days 1-12). The Screening (Baseline) and Days 1 and 10 (two and six hours postdose) ECGs were used to evaluate the pharmacodynamic endpoints. Subjects were continuously observed and questioned throughout the study for possible occurrence of adverse events.

Number of Subjects: Twelve healthy male volunteers were enrolled and completed the study as planned.

Diagnosis and Criteria for Inclusion: Adult male subjects between 18-45 years of age inclusive, in good health based on medical history, physical examination, electrocardiogram, and routine laboratory tests (blood chemistry, hematology, and urinalysis) and having Body Mass Index (BMI) of 19-27 were empanelled for this study.

Test Product, Dose, Mode of Administration, Batch No(s): Ezetimibe (SCH 58235) tablets, 10 mg (1 x 10 mg), oral, Batch No. 52123-050.

Reference Therapy, Dose, Mode of Administration, Batch No(s): Digoxin tablets (Lanoxin®, Glaxo Wellcome, Inc.) 0.5 mg (2 x 0.25 mg) and Lot No. 8ZP1806, Expiration Date November 2001.

Duration of Treatment: One ezetimibe 10 mg tablet was administered to each subject in the morning at approximately 8 AM every day for eight consecutive days (Days 3-10).

Criteria for Evaluation: Physical examinations, electrocardiograms, vital signs, and clinical laboratory tests were performed throughout the study and adverse events were recorded for safety evaluation. All subjects who were enrolled completed treatment and make up the population data set for the pharmacokinetic, pharmacodynamic, and safety evaluations. Summary statistics and adverse reaction tabulation are included for all treated subjects. Demographic and Baseline variables are listed and summarized using descriptive statistics.

Statistical Methods: Summary statistics (means, standard deviations, and coefficients of variation) are provided for the concentration data at each time point and the derived pharmacokinetic parameters on Days 1 and 10. An analysis of variance (ANOVA) was performed on both original scale and log-transformed AUC and Cmax values to evaluate the effect of ezetimibe on the pharmacokinetics of digoxin.

The primary pharmacodynamic variables of interest for the determination of a pharmacodynamic drug interaction were changes from Baseline (Screening ECG) in the ventricular heart rate, PR, QT, and QTc intervals after digoxin alone (Day 1) vs. digoxin plus ezetimibe (Day 10) administration. Summary statistics (means, standard errors, 95% confidence intervals) were provided for each of the pharmacodynamic parameters from all of the ECGs performed in this study. The pharmacodynamic variables were also expressed as Day 1