

Title of the Study: SCH 58235: Pharmacokinetic/Pharmacodynamic Drug Interaction Study With Digoxin in Healthy Volunteers (Protocol No. C98-114)

and Day 10 changes from Baseline (expressed as a percent), as well as Day 10 changes from Day 1.

SUMMARY-CONCLUSIONS:

RESULTS:

Safety: Ezetimibe 10 mg/day administered in healthy adult male volunteers for eight days was safe and well tolerated. Reported adverse events were mild to moderate and consisted primarily of headache.

Clinical Pharmacology:

Pharmacokinetics:

The key pharmacokinetic parameters for digoxin and ezetimibe (SCH 58235) are presented below.

Mean (%CV) Pharmacokinetic Parameters of Digoxin After Oral Administration of Digoxin 0.5 mg, and Total, Unconjugated and Conjugated Ezetimibe (SCH 58235) After Oral Administration of ezetimibe 10 mg to Healthy Male Volunteers

Parameters (Units)	Digoxin ^a		Total SCH 58235 ^a	Unconjugated SCH 58235 ^a	Conjugated SCH 58235 ^a
	Day 1	Day 10	Day 10	Day 10	Day 10
C _{max} (ng/mL)	2.22 (32)	2.02 (25)	62.7 (26)	5.32 (36)	59.7 (26)
T _{max} (hour)	1.08 (27)	1.21 (21)	1.13 (43)	4.79 (71)	1.13 (43)
AUC(0-48 hr) (ng·hr/mL)	18.2 (19)	18.7 (24)	-	-	-
AUC(0-24 hr) (ng·hr/mL)	-	-	561 (18)	68.8 (18)	492 (20)

a: n=12.

NA=Not appropriate to calculate on Day 1.

There was no significant difference in the bioavailability of digoxin when it was coadministered with ezetimibe vs. digoxin alone ($p > 0.20$ for comparisons). The digoxin relative bioavailability estimate (90% confidence intervals) of Day 10 to Day 1 for C_{max} and AUC based on the log-transformed data were 92.7% (83-103) and 102% (95-108), respectively. The pharmacokinetics of ezetimibe were comparable to those observed in a previous study following multiple-dose oral administration of ezetimibe 10 mg.

Pharmacodynamics:

The coadministration of digoxin 0.5 mg plus ezetimibe 10 mg (Day 10 data) did not cause any clinically significant changes in the ECG parameters (ventricular heart rate, PR, QT and QTc intervals) compared to the changes caused by the administration of digoxin 0.5 mg alone (Day 1 data).

CONCLUSIONS:

- Ezetimibe (SCH 58235) administered at a daily dose of 10 mg for eight consecutive days as monotherapy or with a single dose of digoxin 0.5 mg to healthy adult male subjects was safe and well tolerated.
- Administration of ezetimibe 10 mg orally once daily for eight days did not affect the single dose pharmacokinetics of digoxin.
- There were no clinically significant changes in ECG parameters after the coadministration of ezetimibe with digoxin compared to digoxin alone.
- 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.
- Ezetimibe does not affect the pharmacokinetics or have any clinically significant effect on the pharmacodynamics of digoxin. Single dose digoxin does not appear to affect the pharmacokinetics of ezetimibe. The coadministration of ezetimibe and digoxin in patients is unlikely to cause a clinically significant drug interaction.

Title of the Study: SCH 58235: Assessment of a Multiple-Dose Drug Interaction Between SCH 58235 and Gemfibrozil in Healthy Volunteers (Protocol No. P00252)

Investigator(s): _____

Publication(s): None

Studied Period: 27 AUG 1999 to 08 OCT 1999

Clinical Phase: I

Objective: The objective of this study was to evaluate the potential for a pharmacokinetic interaction between ezetimibe (SCH 58235) and gemfibrozil.

Methodology: Randomized, open-label, three-way crossover study. The study consisted of an outpatient Screening phase of up to three weeks and an inpatient confinement to the study site of approximately 8.5 days during each treatment period. After an overnight fast, each subject received one of the following three treatments: **Treatment A:** Ezetimibe (SCH 58235) 10 mg orally once-daily (QD) for seven days; **Treatment B:** gemfibrozil 600 mg orally twice-daily (Q12h) for seven days and **Treatment C:** Ezetimibe 10 mg orally QD and gemfibrozil 600 mg orally Q12h, both for seven days. Subjects remained fasting until two hours postdose at which time a standardized breakfast was served followed by standardized meals at the appropriate times. A washout period of at least seven days separated the last and first dose of each subsequent period. Blood and urine samples were collected at prespecified times for safety and pharmacokinetic evaluations. Blood samples for the determination of plasma ezetimibe and gemfibrozil concentrations were collected prior to dosing (zero hour) on Day 1 in Period 1 and on Day 7 in each period and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, and 24 hours following dosing. Plasma concentrations of gemfibrozil were analyzed using a _____ method with the lower limit of quantitation (LOQ) of _____ plasma with linearity over the concentration range of _____. Plasma concentrations of unconjugated and total (conjugated and unconjugated) ezetimibe (SCH 58235) were determined using _____ assays with the LOQ of _____ plasma, respectively. The linear ranges were _____ for unconjugated and total ezetimibe, respectively. Plasma concentrations of conjugated ezetimibe, reported as ezetimibe equivalents, were calculated by subtracting the unconjugated ezetimibe concentration from the corresponding total ezetimibe concentration for each sample.

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 8 of Period 3). Additionally, clinical laboratory tests were conducted on Day -1 and vital signs were conducted daily during each treatment period, (Days 1-7). Volunteers were continuously observed and questioned throughout the study for possible occurrence of adverse events.

Number of Subjects: Twelve adult male volunteers were enrolled and completed the study.

Diagnosis and Criteria for Inclusion: Adult male and female volunteers between 18-45 years of age inclusive and having a Body Mass Index (BMI) between 19-27 were empanelled for this study. Patients 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. 52123-050.

Reference Therapy, Dose, Mode of Administration, Batch No(s): Gemfibrozil tablets (Lopid[®], Parke Davis Pharmaceuticals, Ltd., Div. of Warner-Lambert Co.), 600 mg, oral, Lot No. 15219V, Expiration Date 12/2000.

Duration of Treatment: Each subject received one ezetimibe (SCH 58235) 10 mg tablet once-daily for seven days on two separate occasions separated by at least seven days, for a total of 14 tablets. Each subject also received one gemfibrozil 600 mg tablet twice-daily (Q12h) for seven days on two separate occasions separated by at least seven days; for a total of 26 tablets (the Day 7 evening dose of gemfibrozil was not given as per protocol).

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 on Day 7 of each treatment period of the crossover for determination ezetimibe and gemfibrozil pharmacokinetic parameters. All subjects who were enrolled completed all three treatment periods and make up the population data set for the pharmacokinetic and safety evaluations. Summary statistics and adverse reaction tabulation are included for all subjects. Demographic and Baseline variables are listed and summarized using descriptive statistics.

Statistical Methods: Summary statistics including means, standard deviations and coefficients of variation were provided for the concentration data at each time point and the derived pharmacokinetic parameters. An analysis of variance (ANOVA) was performed on both original scale and log-transformed C_{max} and AUC

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values to evaluate the oral bioavailability of ezetimibe or gemfibrozil in combination relative to each drug administration alone. Ninety percent confidence intervals for these estimates and the power to detect a 20% difference between group means at 5% level of probability (two-tailed) were computed.

SUMMARY-CONCLUSIONS:

RESULTS:

Safety: Ezetimibe 10 mg QD and gemfibrozil 600 mg Q12h administered alone or concomitantly for seven days to healthy adult male volunteers were safe and well tolerated. Six of the 12 subjects (50%) reported adverse events during the course of the study, the most common being headache (3/12, 25%) and pharyngitis (2/12, 17%). All adverse events were mild in severity, except for one subject who complained of lower back pain of moderate severity (considered by the Investigator as unlikely related to treatment). Most adverse events resolved spontaneously; acetaminophen was administered to three subjects to relieve symptoms of sore throat, body aches, and lower back pain. There were no deaths or serious adverse events and there were no clinically significant abnormalities or changes in routine ECGs or clinical laboratory safety tests from pretreatment Baseline. No clinically relevant changes were noted on physical examinations. Entry and exit blood pressure, pulse rate, respiratory rate and oral body temperature remained in the range observed for subjects in this age group.

Clinical Pharmacology:

Pharmacokinetics:

The mean (%CV) Day 7 pharmacokinetic parameters for gemfibrozil and ezetimibe after oral administration of ezetimibe 10 mg once-daily (Treatment A), gemfibrozil 600 mg twice-daily (Treatment B) and the two drugs given concomitantly (Treatment C) are presented in the table below.

Parameters (Units)	Gemfibrozil ^a		Total Ezetimibe ^a		Conjugated Ezetimibe ^a		Unconjugated Ezetimibe ^a	
	Trt B	Trt C	Trt A	Trt C	Trt A	Trt C	Trt A	Trt C
C _{max} (µg/mL [gemfibrozil], ng/mL [ezetimibe])	26.4 (27)	23.7 (32)	75.4 (53)	135 (37)	70.2 (54)	128 (38)	7.12 (64)	9.68 (67)
T _{max} (hr) ^b	1	1.5	1	1.25	0.5	1	5	5
AUC(0-12 hr) (µg-hr/mL)	74.1 (26)	74.7 (29)	--	--	--	--	--	--
AUC(0-24 hr) (ng-hr/mL)	--	--	637 (44)	1071 (45)	552 ^c (52)	972 (47)	72.2 ^c (47)	111 (68)

a: n=12.

b: Median

c: n=10.

There were no significant differences in the exposure to gemfibrozil between the two treatments (Treatment B and Treatment C) based on the log transformed AUC(0-12 hr) and C_{max} data (p>0.05 for all comparisons). The point estimates based on the log-transformed C_{max} and AUC values for gemfibrozil were 89 and 99%, respectively, for Treatment C vs. Treatment B. The corresponding 90% confidence intervals for these point estimates were 78-101% and 92-107% based on the log-transformed C_{max} and AUC, respectively.

There was a statistically significant increase (p=0.001) in the plasma concentrations of total and conjugated ezetimibe after coadministration with gemfibrozil vs. ezetimibe given alone. The mean exposure to total and conjugated ezetimibe was 1.7-1.8-fold higher for Treatment C than Treatment A. The point estimates based on the log-transformed C_{max} and AUC values for total and conjugated ezetimibe were 191-196% and 164-169%, respectively, for Treatment C vs. Treatment A. The corresponding 90% confidence intervals for these point estimates were 149-253% and 142-201% based on the log-transformed C_{max} and AUC, respectively. There was an increase (<40%) in unconjugated ezetimibe concentrations after coadministration with gemfibrozil. This increase was statistically significant for C_{max} (p=0.017) but did not reach statistical significance for AUC (p=0.064); however, the statistical power to detect a difference was low (26%). The point estimates based on log-transformed C_{max} and AUC were 133% and 137%, respectively and the corresponding 90% confidence intervals were 111-160% and 109-173%, respectively.

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CONCLUSIONS:

- Ezetimibe (SCH 58235) 10 mg administered orally once-daily for seven days alone or in combination with gemfibrozil 600 mg twice-a-day to healthy male subjects was safe and well tolerated.
 - Ezetimibe did not alter the pharmacokinetics of gemfibrozil.
 - Gemfibrozil coadministration caused an increase in the plasma concentrations of ezetimibe. Exposure to total and conjugated ezetimibe was increased approximately 1.7-fold, while exposure to unconjugated ezetimibe was increased approximately 1.4-fold.
 - The coadministration of ezetimibe and gemfibrozil in patients is unlikely to cause a clinically significant drug interaction.
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**APPEARS THIS WAY
ON ORIGINAL**

Title of the Study: SCH 58235: Evaluation of a Possible Pharmacokinetic Interaction of Multiple-Dose SCH 58235 With Oral Contraceptives in Healthy Female Volunteers (Protocol No. P00267)

Investigator: _____

Publication(s): None

Studied Period: 24 MAR 00 to 09 MAY 00

Clinical Phase: I

Objective: The primary objective of this study was to assess the possible effects of ezetimibe (SCH 58235) on the pharmacokinetics of the active components of oral contraceptives in healthy premenopausal female volunteers. The secondary objective was to assess the safety and tolerability of oral contraceptives and ezetimibe in combination. The pharmacokinetics of ezetimibe in the presence of oral contraceptives was also determined.

Methodology: This was a randomized, double-blind, placebo-controlled, two-period crossover, single-center study. Subjects were established on a triphasic oral contraceptive for more than 3 months. The study took place over two oral contraceptive (OC) cycles. From Day 8 until Day 14 of each OC cycle, subjects were to take either ezetimibe 10 mg or matching placebo tablets. Subjects were confined to the study site from the evening of Day 13 until the morning of Day 15 of each period. 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 (SCH 58235) concentrations as well as plasma ethinyl estradiol and levonorgestrel concentrations were collected on Day 14 of each treatment period prior to dosing (0 hour) and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours postdose. Plasma unconjugated and total ezetimibe concentrations were determined using _____ assays. Plasma ethinyl estradiol and levonorgestrel concentrations were determined using _____ methods. For safety evaluation, physical examinations, vital signs, electrocardiograms, and clinical laboratory tests were conducted at Screening (Baseline) and at Day 15 of the second OC cycle (Follow-up). In addition, vital signs and routine laboratory tests were also monitored at intervals throughout the study.

Number of Subjects: Eighteen (18) premenopausal female subjects were enrolled and completed the study as planned.

Diagnosis and Criteria for Inclusion: Premenopausal female subjects between the ages of 18 and 45 years inclusive. Subjects must have been established on triphasic oral contraceptives for greater than 3 months and were to remain on them for the duration of the study. 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.

Reference Therapy, Dose, Mode of Administration, Batch No(s): Ezetimibe (SCH 58235) placebo tablets, oral, Batch No. 75882-062.

Duration of Treatment: Each subject received a single daily dose of ezetimibe 10 mg or matching placebo for 7 days (Day 8 through Day 14) during each of two OC cycles.

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 postdose for determination of unconjugated and total ezetimibe pharmacokinetic parameters as well as plasma ethinyl estradiol and levonorgestrel pharmacokinetic parameters.

Statistical Methods: Assessment of the effect of ezetimibe on the active components of the oral contraceptive (ethinyl estradiol and levonorgestrel) was made comparing the difference between the Day 14 OC log-transformed C_{max} and AUC(0-24 hour) for the ezetimibe treatment period (test) relative to the placebo period (reference). Confidence intervals for the differences between the two treatment periods and the power to detect a 20% difference between the treatment period 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 the confidence interval and power. Ezetimibe pharmacokinetic parameters were summarized using descriptive statistics. Means and standard deviations were provided for the concentration data at each time point for the pharmacokinetic parameters.

Title of the Study: SCH 58235: Evaluation of a Possible Pharmacokinetic Interaction of Multiple-Dose SCH 58235 With Oral Contraceptives in Healthy Female Volunteers (Protocol No. P00267)

SUMMARY-CONCLUSIONS:

RESULTS:

Clinical Pharmacology:

Pharmacokinetics: The mean pharmacokinetic parameters of ethinyl estradiol and levonorgestrel after coadministration of OC with either placebo or ezetimibe along with the statistical comparisons of relative bioavailability are summarized in the following tables.

Mean pharmacokinetic parameters and statistical comparison for ethinyl estradiol.

Parameter	Unit	Ethinyl Estradiol Plus Placebo		Ethinyl Estradiol Plus Ezetimibe		Relative Bioavailability (%) ^a	p-Value	90% Confidence Interval ^b	Power (%) ^c
		Mean	%CV	Mean	%CV				
Cmax	pg/mL	119	(36%)	109	(37%)	91.1	0.063	85-98	99
AUC(0-24 hr)	pg-hr/mL	1085	(29%)	1079	(26%)	99.6	0.885	92-107	98

a: Percent ratio of the mean value for ethinyl estradiol plus ezetimibe to ethinyl estradiol plus placebo.

b: 90% confidence interval based on log-transformed data, $\alpha = 0.05$, two-tailed.

c: Power to detect a 20% difference at the 5% level of probability.

Co-administration of ezetimibe with OC did not affect the pharmacokinetics of ethinyl estradiol. There were no significant differences between the oral bioavailability of ethinyl estradiol when OC was coadministered with placebo or ezetimibe, based on the log transformed AUC(0-24 hr) and Cmax data ($p > 0.06$). The relative oral bioavailability of ethinyl estradiol after coadministration of OC with ezetimibe compared to OC with placebo was 91.1% and 99.6% based on log transformed Cmax and AUC(0-24 hr) values, respectively. The 90% confidence intervals for the relative oral bioavailability were from 85-98% and 92-107% based on log transformed Cmax and AUC(0-24 hr) values, respectively.

Mean pharmacokinetic parameters and statistical comparison for levonorgestrel.

Parameter	Unit	Levonorgestrel Plus Placebo		Levonorgestrel Plus Ezetimibe		Relative Bioavailability (%) ^a	p-Value	90% Confidence Interval ^b	Power (%) ^c
		Mean	%CV	Mean	%CV				
Cmax	ng/mL	8.89	(29%)	8.45	(28%)	95.0	0.344	87-104	92
AUC(0-24 hr)	ng-hr/mL	113	(33%)	113	(32%)	100	0.968	94-108	99

a: Percent ratio of the mean value for levonorgestrel plus ezetimibe to levonorgestrel plus placebo.

b: 90% confidence interval based on log-transformed data, $\alpha = 0.05$, two-tailed.

c: Power to detect a 20% difference at the 5% level of probability.

Co-administration of ezetimibe with OC did not affect the pharmacokinetics of levonorgestrel. There were no significant differences between the oral bioavailability of levonorgestrel when OC was coadministered with placebo or ezetimibe based on the log transformed AUC(0-24 hr) and Cmax data ($p > 0.34$). The relative oral bioavailability of levonorgestrel after coadministration of OC with ezetimibe compared to OC with placebo was 95% and 100% based on log transformed Cmax and AUC(0-24 hr) values, respectively. The 90% confidence intervals for the relative oral bioavailability were 87-104% and 94-108%, based on log transformed Cmax and AUC(0-24 hr) values, respectively.

APPEARS THIS WAY
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Title of the Study: SCH 58235: Evaluation of a Possible Pharmacokinetic Interaction of Multiple-Dose SCH 58235 With Oral Contraceptives in Healthy Female Volunteers (Protocol No. P00267)

Safety:

Multiple doses of ezetimibe 10 mg coadministered with triphasic oral contraceptives were safe and well tolerated. Overall, 10 subjects (56%) reported at least one adverse event during the study. Ten subjects (56%) reported at least one adverse event while receiving ezetimibe (SCH 58235) plus OC, and 4 subjects (22%) reported at least one adverse event while receiving placebo plus OC. The most commonly reported adverse events were mild to moderate in severity and included headache, increased thirst and increased appetite. Concomitant medications including Tylenol® with codeine, Advil®, Excedrin®, naproxen, and Robaxacet® were used for the treatment of adverse events. There were no deaths or serious adverse events and there were no clinically significant abnormalities or changes in routine physical examinations, vital signs, or clinical laboratory tests. One subject had sinus bradycardia (heart rate of 47 bpm) at the follow-up ECG, which, although not considered a clinically significant finding by the investigator, it was considered a clinically significant change from Baseline (heart rate of 77 bpm on Screening ECG) and reported as an adverse event. A repeat follow-up ECG two days later (ie, 3 days after the last dose of study drug) revealed a normal sinus rhythm (heart rate of 68 bpm).

CONCLUSIONS:

- Multiple doses of ezetimibe (SCH 58235) 10 mg coadministered with triphasic oral contraceptives were safe and well tolerated.
 - Ezetimibe 10 mg coadministered with triphasic oral contraceptives did not effect the pharmacokinetics of ethinyl estradiol and levonorgestrel.
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APPEARS THIS WAY
ON ORIGINAL

Title of Study:	SCH 58235: Evaluation of the Effect of Cimetidine on the Pharmacokinetics of SCH 58235 in Healthy Subjects (Protocol No. P00746)	
Investigator(s):	[]	
Study Center(s):		
Publication(s):	None	
Studied Period:	29 Feb 2000 to 26 Apr 2000	Clinical Phase: I
Objective:	The primary objective of this study was to evaluate the potential for cimetidine to affect the pharmacokinetics of ezetimibe.	
Methodology:	This was a single-center, randomized, two-way crossover, open-label, multiple-dose, 23-day study in healthy subjects. After a Screening phase of up to 3 weeks, subjects were confined for approximately 16 days (8 days/period) with a 7 day washout between the last and first dose of each subsequent period. The morning of Day 1 following a 10-hour fast, each subject received one of the following treatments based on his/her assigned subject number and the study period, according to a randomization schedule provided by SPRI:	
	Treatment A:	Ezetimibe (SCH 58235) 10 mg p.o. QD (8 AM) x 7 days.
	Treatment B:	Ezetimibe (SCH 58235) 10 mg p.o. QD (8 AM) and cimetidine 400 mg p.o. Q12H (8 AM and 8 PM) ^a x 7 days.
	Each dose was administered with 200 mL of noncarbonated room temperature water. Subjects continued fasting for two hours postdose, at which time a standardized breakfast was served followed by standardized meals (ie, lunch, dinner and snacks) at appropriate intervals. Vital signs and blood samples were collected at protocol-specified times pre- and postdose during confinement for safety. Blood samples for the determination of plasma ezetimibe concentrations were collected prior to dosing (0 hour) on Day 1 in Period 1 and on Day 7 in each period, and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12 and 24 hours following dosing on Day 7 in each period. Physical examinations and electrocardiograms (ECGs) were conducted at Screening, and at the conclusion of the study (Period 2). Subjects were continuously observed and questioned throughout the study for possible occurrence of adverse events.	
Number of Subjects:	Thirteen healthy subjects were enrolled in this randomized, open-label, two-way crossover, single-center study. One subject discontinued due to an adverse event (rash) and was replaced. A total of 12 subjects completed the study as per protocol.	
Diagnosis and Criteria for Inclusion:	Adult male and female subjects between the ages of 18 and 45 years, inclusive, having a Body Mass Index (BMI) between 19-27 ($BMI = \text{weight [kg]} / \text{height [m]}^2$). To qualify for this study, subjects had to be in good health based on medical history, physical examination, electrocardiogram, and routine laboratory tests (blood chemistry, hematology and urinalysis).	
Test Product, Dose, Mode of Administration, Batch No(s):	Ezetimibe (SCH 58235) tablets, 10 mg, oral, Batch No. 75882-090.	
Reference Therapy, Dose, Mode of Administration, Batch No(s):	Cimetidine tablets (Tagamet [®] , SmithKline Beecham Laboratoires Pharmaceutiques, France), 400 mg, oral, Lot No. 418, Expiration Date January 2005.	
Duration of Treatment:	Each subject received one ezetimibe (SCH 58235) 10 mg tablet once-daily for 7 days on two separate occasions separated by 7 days, for a total of 14 tablets. Each subject also received one cimetidine 400 mg tablet twice-daily (Q12h) for 7 days on one occasion (concurrently with ezetimibe 10 mg); for a total of 13 tablets (the Day 7 evening dose of cimetidine was not given as per protocol).	
Criteria for Evaluation:	The effect of cimetidine on the pharmacokinetics of ezetimibe was assessed by comparing the pharmacokinetic parameters of unconjugated and total ezetimibe (SCH 58235) following multiple dose administration of ezetimibe (SCH 58235) alone and concomitantly with cimetidine for 7 days. Safety was assessed based on clinical laboratory test results (CBC, chemistry, urinalysis), vital signs, physical examinations, and electrocardiograms. Tolerability was assessed by the number/proportion of subjects reporting adverse events.	

Title of Study: SCH 58235: Evaluation of the Effect of Cimetidine on the Pharmacokinetics of SCH 58235 in Healthy Subjects (Protocol No. P00746)

Statistical Methods: Summary statistics, eg, means, standard deviations and coefficients of variation were provided for the pharmacokinetic parameters and the concentration data at each sample time. The derived pharmacokinetic parameters were statistically analyzed using a crossover analysis of variance model. The effects due to sequence, subject within sequence, period and treatment were extracted. The relative oral bioavailability of ezetimibe (SCH 58235) given in combination with cimetidine compared to ezetimibe given alone was expressed as the ratio of the two treatments for the log-transformed AUC and Cmax point estimate. 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) was also computed. The pooled residual error and associated degrees of freedom from the analyses of variance was used in the calculation of the confidence interval and power. A drug interaction was considered potentially clinically significant if the ratio 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. 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 exceeds 3. The impact of any outliers on the results of the analyses was evaluated. Demographic and baseline variables for all subjects were listed and summarized using descriptive statistics. Adverse events were listed and tabulated by body system organ class. Physical examinations and electrocardiograms were reviewed, with clinically significant changes noted. Clinical laboratory results and vital signs were listed and reviewed. Values outside laboratory reference ranges were flagged.

SUMMARY - CONCLUSIONS:

RESULTS:

Pharmacokinetics:

The mean (%CV) Cmax and AUC values and a statistical comparison of these log-transformed values for total, unconjugated and conjugated ezetimibe on Day 7 following once-daily oral administration of ezetimibe 10 mg alone or in combination with twice daily cimetidine 400 mg are summarized below:

Parameter	Ezetimibe		Ezetimibe Plus Cimetidine		Relative Bioavailability ^a (%)	Confidence Interval ^b
	Mean	%CV	Mean	%CV		
Total Ezetimibe						
Cmax	96.6	36	124	47	122	105-142
AUC(0-24 hr)	898	34	955	38	106	97-115
Unconjugated Ezetimibe						
Cmax	4.88	28	6.15	47	120	106-135
AUC(0-24 hr)	69.8	39	84.6	49	118	107-129
Conjugated Ezetimibe						
Cmax	92.9	37	118	48	121	104-140
AUC(0-24 hr)	828	36	870	41	104	95-114

a: Expressed as a percent ratio of ezetimibe plus cimetidine to ezetimibe.

b: Ninety percent confidence interval based on log-transformed data, $\alpha=0.1$.

Small mean increases of $\leq 22\%$ (based on log-transformed data; $<30\%$ based on nontransformed data) in ezetimibe Cmax and AUC were observed after coadministration of ezetimibe with cimetidine. The 90% confidence intervals for log-transformed AUC and Cmax were between 95-129% and 104-142%, respectively, for total, unconjugated and conjugated ezetimibe. The 90% confidence intervals for log-transformed AUC of 97-115% for total ezetimibe were within the bioequivalence acceptance criteria. A potentially clinically significant drug interaction was predefined if the ratio 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. Thus, no clinically significant treatment differences were found based on the mean ratio for AUC and Cmax for total, unconjugated and conjugated ezetimibe.

Title of Study: SCH 58235: Evaluation of the Effect of Cimetidine on the Pharmacokinetics of SCH 58235 in Healthy Subjects (Protocol No. P00746)

Safety: Three of the thirteen subjects enrolled (23%) reported treatment emergent adverse events. Two of the events occurred while the subjects were on ezetimibe alone. One subject experienced a mild headache, considered by the investigator not to be treatment related. The second subject experienced a moderate rash, considered by the investigator to be possibly treatment related and resulted in his discontinuation from the study. The third subject experienced a mild headache while on the combination of ezetimibe and cimetidine, considered by the investigator to be possibly related to treatment. The adverse events resolved in all three subjects with additional therapy. There were no deaths or serious adverse events and there were no clinically significant abnormalities or changes in routine ECGs or clinical laboratory safety tests from pretreatment Baseline. No clinically relevant changes were noted on physical examinations. Entry and exit blood pressure, pulse rate, and oral body temperature remained in the range observed for healthy subjects in these age groups.

CONCLUSIONS:

- Ezetimibe (SCH 58235) 10 mg administered orally once-daily at multiple doses alone and in combination with cimetidine was safe and well tolerated in healthy subjects.
 - Cimetidine coadministration with ezetimibe caused small (<30%) increases in ezetimibe C_{max} with no effect on the overall bioavailability of ezetimibe (based on total ezetimibe AUC).
 - The coadministration of cimetidine and ezetimibe do not pose a potential for a clinically significant pharmacokinetic drug interaction.
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APPEARS THIS WAY
ON ORIGINAL

Title of the Study: SCH 58235: Evaluation of the Effect of Antacid on the Pharmacokinetics of Ezetimibe in Healthy Subjects (Protocol No. P00748)

Investigator: _____

Study Center: _____

Publication(s): None

Studied Period: 6 APR 00 to 27 APR 00

Clinical Phase: 1

Objective: The primary objective of this study was to evaluate the potential for antacids to affect the pharmacokinetics of ezetimibe (SCH 58235).

Methodology: This was an open-label, single-dose, two-way crossover study conducted at a single center. After a Screening phase of up to 3 weeks, subjects were confined to the study center on two separate occasions for approximately 3 days (from Day-1 to Day 3) of each treatment period. On the morning of Day 1, after a 10 hour fast, each subject received either ezetimibe 10 mg alone (Treatment A), or Supralox[®] antacid 20 mL administered immediately prior to ezetimibe 10 mg (Treatment B), according to a randomization schedule provided by SPRI. Each dose of ezetimibe was administered with 200 mL of room temperature noncarbonated water. Subjects continued to fast until 2 hours postdose at which time a standardized breakfast was served. Blood and urine samples were collected at prespecified times for safety and pharmacokinetic evaluations. Blood samples for the determination of plasma ezetimibe and total ezetimibe concentrations were collected prior to dosing (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, and 48 hours postdose. Plasma ezetimibe and total ezetimibe concentrations were determined using _____ assays with the lower limit of quantitation (LOQ) of _____ plasma, respectively. The linear detection ranges were _____ for ezetimibe and total ezetimibe, 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 evaluation, physical examinations, vital signs, electrocardiograms, and clinical laboratory tests were conducted at Screening and at the conclusion of the study (48 hours postdose of Period 2). In addition, clinical laboratory tests were repeated upon each confinement at Day -1, and vital signs were measured at Day -1, and daily in the morning (predose or approximately 8 AM) during each confinement. A washout period of at least 7 days separated each treatment.

Number of Subjects: Twelve healthy adult male and female subjects 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, having a Body Mass Index (BMI) between 19-27 ($BMI = \text{weight [kg]} / \text{height [m]}^2$). 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, recertification date 02/2001.

Reference Therapy, Dose, Mode of Administration, Batch No(s): Antacid Suspension (Supralox[®] Suspension Buvable, _____ [manufacturer]/Theraplix [distributor], France), containing magnesium hydroxide _____ and aluminum hydroxide _____ oral, Lot No. 0182, Expiration Date 10/2002.

Duration of Treatment: Each subject received a single dose of ezetimibe 10 mg on two separate occasions separated by 7 days. Each subject also received a single dose of an antacid combination product (Supralox[®], containing magnesium and aluminum hydroxide salts) on one occasion (concurrently with ezetimibe 10 mg).

Criteria for Evaluation: The effect of antacid on the pharmacokinetics of ezetimibe was assessed by comparing the pharmacokinetic parameters of ezetimibe and total ezetimibe following single dose administration of ezetimibe alone and concomitantly with antacid. Safety was assessed based on clinical laboratory test results (CBC, chemistry, urinalysis), vital signs, physical examinations, and electrocardiograms. Tolerability was assessed by the number/proportion of subjects reporting adverse events.

Statistical Methods: Summary statistics including means, standard deviations and coefficients of variation were provided for the concentration data at each time point and the derived pharmacokinetic parameters. An analysis of variance (ANOVA) was performed on the log-transformed AUC and C_{max}

Title of the Study: SCH 58235: Evaluation of the Effect of Antacid on the Pharmacokinetics of Ezetimibe in Healthy Subjects (Protocol No. P00748)

values to evaluate the effect of antacid on the oral bioavailability of ezetimibe. Ninety percent (90%) confidence intervals and the point estimates for the mean difference in the log-transformed parameters (expressed as a ratio of the two treatments) and the power to detect a 20% difference between group means at an α level of 0.05 (two-tailed) were computed.

SUMMARY-CONCLUSIONS:

RESULTS:

Clinical Pharmacology:

Pharmacokinetics: The mean pharmacokinetic parameters and statistical comparisons of these log-transformed values following a single oral dose of ezetimibe 10 mg alone or in combination with antacid to healthy subjects are summarized in the following table.

Parameter	Units	Ezetimibe		Ezetimibe Plus Antacid		Point Estimate ^c (%)	Confidence Interval ^d
		Mean ^a	%CV	Mean ^a	%CV		
Total Ezetimibe							
Cmax	ng/mL	55.9	56	37.1	37	70	55-88
Tmax ^b	hr	1.00	NA	1.50	NA	NA	NA
AUC(tf)	ng-hr/mL	510	37	483	35	96	87-106
Ezetimibe							
Cmax	ng/mL	2.78	61	2.90	51	110	89-135
Tmax ^b	hr	1.50	NA	3.00	NA	NA	NA
AUC(tf)	ng-hr/mL	50.9	49	53.4	42	108	93-124
Conjugated Ezetimibe							
Cmax	ng/mL	54.2	57	34.9	40	67	53-85
Tmax ^b	hr	1.00	NA	1.50	NA	NA	NA
AUC(tf)	ng-hr/mL	459	41	429	40	94	86-104

a: n=12.

b: Median.

c: Expressed as a percent ratio of ezetimibe-plus antacid to ezetimibe.

d: 90% confidence interval based on log-transformed data, $\alpha=0.1$.

NA=Not applicable.

Antacid (Supralox[®]) administration with ezetimibe had no effect on the oral bioavailability of ezetimibe, total ezetimibe or conjugated ezetimibe based on AUC ($p>0.13$). The relative oral bioavailability estimates, based on log transformed AUC(tf) values following coadministration of ezetimibe with antacid compared to ezetimibe alone, were 108%, 96% and 94% for ezetimibe, total ezetimibe and conjugated ezetimibe, respectively. The corresponding 90% confidence intervals of ezetimibe, total ezetimibe and conjugated ezetimibe based on log-transformed data were within ———. When coadministered with antacid, the rate of ezetimibe absorption was slower, with the median time for ezetimibe to reach the maximum concentration, Tmax, increasing from 1.5 hours to 3 hours in the presence of antacid. The point estimates, based on log transformed Cmax values following coadministration of ezetimibe with antacid compared to ezetimibe alone, were 110%, 70% and 67% for ezetimibe, total ezetimibe and conjugated ezetimibe, respectively. These differences for total and conjugated ezetimibe Cmax values (mean <30%) were not considered to be clinically significant. Plasma ezetimibe and total ezetimibe concentrations exhibited multiple peaks, suggesting enterohepatic recycling. Ezetimibe was rapidly and extensively glucuronidated. Systemic exposure to ezetimibe was approximately 10% of that to total ezetimibe and was not affected by antacid coadministration.

Safety: Ezetimibe 10 mg administered as a single dose alone or in combination with antacid to healthy adult subjects was safe and well tolerated. There were no adverse events, or clinically significant abnormalities or changes in routine ECGs or clinical laboratory safety tests from Baseline. No clinically relevant changes were noted in vital signs or physical examinations.

Title of the Study: SCH 58235: Evaluation of the Effect of Antacid on the Pharmacokinetics of Ezetimibe in Healthy Subjects (Protocol No. P00748)

CONCLUSIONS:

- Ezetimibe (SCH 58235) 10 mg administered orally as a single dose to healthy subjects alone and in combination with antacid was safe and well tolerated.
 - Antacid (Supralox[®], containing a combination aluminum and magnesium hydroxide salts) coadministered with ezetimibe did not affect the relative oral bioavailability of all ezetimibe analytes based on AUC.
 - The concomitant administration of antacid and ezetimibe decreases the rate of absorption but does not alter the extent of ezetimibe bioavailability. The coadministration of antacids and ezetimibe does not cause a clinically significant interaction.
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APPEARS THIS WAY
ON ORIGINAL

Title of Study: SCH 58235: Assessment of a Multiple-Dose Drug Interaction Between Ezetimibe and Glipizide in Healthy Subjects (Protocol No. P00752)	
Investigator(s): _____	
Publication(s): Statkevich P, Reydermann L, Kosoglou T, Woloj M, Maxwell SE, Cutler DL, et al. Ezetimibe does not affect the pharmacokinetics and pharmacodynamics of glipizide [abstract PIII-12]. Clin Pharmacol Ther 2001;69(2):P67.	
Studied Period: 12 APR 00 to 29 APR 00	Clinical Phase: 1
Objective(s): The primary objective of this study was to evaluate the potential for ezetimibe (SCH 58235) to affect the pharmacokinetics and/or pharmacodynamics of glipizide. A secondary objective was to characterize the pharmacokinetics of ezetimibe and to evaluate the potential for glipizide to affect the pharmacokinetics of ezetimibe.	
Methodology: This was a single-center, open-label, single-dose/multiple-dose study. The study was to take place over an 11-day inpatient period. Subjects were confined to the study center for at least 12 hours prior to dosing (Day -1) until Day 10 (24 hours after the second dose of glipizide on Day 9). Subjects received glipizide 10 mg on Day 1 and Day 9, and ezetimibe 10 mg once-daily on Day 2 through Day 9. Vital signs, ECGs, and blood samples were collected at specified times during the study for safety, pharmacokinetic and pharmacodynamic evaluations. Blood samples for the determination of glipizide concentrations were collected prior to dosing (0-hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours postdose on Days 1 and 9. Blood samples for the determination of glucose concentrations were collected prior to dosing (0-hour) and at 0.5, 1, 2, 4, 8, 12, and 24 hours following each dose of glipizide (Days 1 and 9). Blood samples for the determination of plasma ezetimibe (unconjugated) and total ezetimibe concentrations were collected prior to dosing (0-hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours postdose on Days 8 and 9. Plasma concentrations of glipizide were determined using a _____ assay method with the lower limit of quantitation (LOQ) of _____ and linear range of _____. Plasma glucose concentrations were determined using a _____ method. Plasma ezetimibe (unconjugated) and total ezetimibe concentrations were determined using _____ assays with the LOQ of _____ plasma, respectively. The linear detection ranges were _____ for total ezetimibe and ezetimibe, 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. In addition, vital signs were also monitored at intervals following treatment administration.	
Number of Subjects: Twelve adult male 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, 10 mg, oral, Batch No. 75882-090.	
Reference Therapy, Dose, Mode of Administration, Batch No(s): Glipizide tablets (GLIBENESE [®] , Laboratoires Pfizer, France), 5 mg, oral, Lot No. 8007901, Expiration Date 03-2001.	
Duration of Treatment: Each subject received glipizide 10 mg on Day 1 and Day 9, and ezetimibe 10 mg once-daily for 8 days on Day 2 through Day 9.	
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 for determination of unconjugated and total ezetimibe and glipizide pharmacokinetic parameters, as well as plasma glucose concentrations for evaluation of glipizide pharmacodynamics.	
Statistical Methods: Summary statistics (means, standard deviations and coefficients of variation) for the pharmacokinetic and pharmacodynamic parameters and the concentration data at each time point were provided for all analytes. Additionally, 95% confidence intervals for the difference in pharmacodynamic parameters (ie, plasma glucose concentrations) between Day 1 (glipizide) and Day 9 (glipizide plus ezetimibe) were determined.	

Title of Study: SCH 58235: Assessment of a Multiple-Dose Drug Interaction Between Ezetimibe and Glipizide in Healthy Subjects (Protocol No. P00752)

An analysis of variance (ANOVA) was performed on both original scale and log-transformed C_{max} and AUC values to evaluate the relative oral bioavailability of glipizide given in combination with ezetimibe on Day 9 (after an 8-day pretreatment with ezetimibe) compared to glipizide given alone (Day 1). Similarly, the relative bioavailability of ezetimibe given in combination with glipizide on Day 9 compared to ezetimibe given alone (Day 8) was expressed as a ratio of the log-transformed AUC and C_{max} values. Ninety percent confidence intervals for these estimates and the power to detect a 20% difference between group means at 5% level of probability (two-tailed) were computed.

For glipizide, if the ratio (expressed as a percent) of the treatment mean comparisons for log-transformed AUC and C_{max} values was outside the range of 75-150% (ie, more than a mean 25% decrease or 50% increase), then this was considered as a potentially clinically significant drug interaction. For ezetimibe, if the ratio (expressed as a percent) of the treatment mean comparisons for log-transformed AUC and C_{max} values was outside the range of 50-200% (ie, more than a mean 50% decrease or 100% increase), then this was considered as a potentially clinically significant drug interaction.

Preliminary analyses included examining the pharmacokinetic parameters for outliers by reviewing the studentized residuals 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) plasma ezetimibe, glipizide and glucose pharmacokinetic parameters and statistical comparisons of the log-transformed C_{max} and AUC values following oral administration of glipizide 10 mg alone (Day 1), ezetimibe 10 mg alone (Day 8), or a combination of glipizide 10 mg plus ezetimibe 10 mg (Day 9) are presented in the following table:

**APPEARS THIS WAY
ON ORIGINAL**

Title of Study:	SCH 58235: Assessment of a Multiple-Dose Pharmacokinetic Drug Interaction Between SCH 58235 and Lovastatin in Healthy Subjects (Protocol No. P01382)	
Investigator(s):	[]	
Study Center:	[]	
Publication(s):	Reyderman L, Kosoglou T, Statkevich P et al. No pharmacokinetic drug interaction between ezetimibe and lovastatin. <i>Clin Pharmacol Ther</i> 2001;69:P66.	
Studied Period:	14 FEB 00 to 18 APR 00	Clinical Phase: I
Objective(s):	The primary objective of this study was to evaluate the potential for a pharmacokinetic interaction between ezetimibe (SCH 58235) and lovastatin.	
Methodology:	<p>This was a randomized, open-label, multiple-dose, three-way crossover, single-center study which took place over three treatment periods. Subjects were confined to the study center from at least 12 hours prior to each treatment period (Day -1) until Day 8 of each period. From Day 1 until Day 7 of each treatment period, subjects were randomized to take either ezetimibe 10 mg (Treatment A), or lovastatin 20 mg (Treatment B), or ezetimibe 10 mg plus lovastatin 20 mg (Treatment C). All doses were administered orally with 200 mL of non-carbonated, room-temperature water, once-daily in the morning. Subjects continued fasting until 2 hours postdose, at which time regular, standardized meals were served. Vital signs and blood samples were collected at specified times during the study for safety and pharmacokinetic evaluations. Blood samples for the determination of plasma ezetimibe and total ezetimibe concentrations, as well as lovastatin and β-hydroxylovastatin concentrations, were collected prior to dosing (0-hour) on Day 1 in Period 1 and on Day 7 in each period, and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 24 hours post-dose on Day 7 in each period. Plasma ezetimibe (unconjugated) and total ezetimibe (ezetimibe plus conjugated ezetimibe) concentrations as well as lovastatin and β-hydroxylovastatin concentrations were determined using _____ assays. Plasma ezetimibe and total ezetimibe assays had a lower limit of quantitation (LOQ) of _____ and _____ and the concentration ranges of _____, respectively. Plasma conjugated ezetimibe (ezetimibe-glucuronide) concentrations, reported as ezetimibe equivalents, were calculated by subtracting the ezetimibe concentration from the corresponding total ezetimibe concentration for each sample. The plasma lovastatin and β-hydroxylovastatin assay had an LOQ of _____ and a concentration range of _____ for both analytes. For safety evaluation, physical examinations, vital signs, electrocardiograms, and clinical laboratory tests were conducted at Screening (Baseline) and at Day 8 of Period 3. In addition, vital signs and routine laboratory tests were also monitored at intervals throughout the study. A washout period of at least 7 days separated each treatment.</p>	
Number of Subjects:	Nineteen male and female subjects enrolled in the study. Eighteen subjects completed the study as per protocol. Subject 2 discontinued the study for personal reasons, after completing Period 1 (Treatment C, ezetimibe 10 mg plus lovastatin 20 mg).	
Diagnosis and Criteria for Inclusion:	Healthy male and female subjects between the ages of 18 and 45 years inclusive, having a Body Mass Index (BMI) of 19-27. 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.	
Reference Therapy, Dose, Mode of Administration. Batch No(s):	Lovastatin (MEVINACOR [®]) manufactured by _____ 20 mg, tablets, Lot No. 0075780, Exp. Date August 2002.	
Duration of Treatment:	Each subject received a single daily dose of ezetimibe 10 mg, lovastatin 20 mg, or ezetimibe 10 mg plus lovastatin 20 mg for 7 days, during each of 3 treatment periods. A washout period of at least 7 days separated each treatment.	

Title of Study: SCH 58235: Assessment of a Multiple-Dose Pharmacokinetic Drug Interaction Between SCH 58235 and Lovastatin in Healthy Subjects (Protocol No. P01382)

Criteria for Evaluation: The potential for pharmacokinetic interaction between ezetimibe and lovastatin was assessed by evaluating the pharmacokinetic parameters of lovastatin, β -hydroxylovastatin, and ezetimibe and total ezetimibe following multiple-dose administration of ezetimibe alone, lovastatin alone, and both concomitantly for 7 days. Safety was assessed based on clinical laboratory test results (CBC, chemistry, urinalysis), vital signs, physical examinations, and electrocardiograms. Tolerability was assessed by the number/proportion of subjects reporting adverse events.

Statistical Methods: As this was a crossover study, the primary pharmacokinetic comparisons included those subjects with data for the two treatment periods being compared. Means, standard deviations and coefficients of variation, were provided for concentration data at each time point and for the derived pharmacokinetic parameters. The pharmacokinetic parameters for ezetimibe and lovastatin were statistically analyzed using a crossover analysis of variance (ANOVA) model. The effects due to subject, period and treatment were extracted. As subjects received each of the treatments (lovastatin and ezetimibe) in two of the three treatment periods, two periods were included in each of the analyses. The bioavailability of lovastatin and ezetimibe given in combination compared to lovastatin or ezetimibe given alone was expressed as the ratio of the two treatments for the log-transformed AUC and C_{max}. Confidence intervals for these estimates of bioavailability and 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 the confidence interval and power. If the ratio (expressed as a percent) of the treatment mean comparisons for log-transformed AUC and C_{max} was outside the range of 50-200% (i.e., more than a mean 50% decrease or 100% increase) for any of the analyses, then a clinically significant drug interaction may have been indicated. 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 three. 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 ezetimibe-glucuronide pharmacokinetic parameters and statistical comparisons of the log-transformed C_{max} and AUC values on Day 7 are presented in the following table:

Parameter	Unit	Ezetimibe	Ezetimibe + Lovastatin	Point Estimate(%) ^b	90% Confidence Interval ^c
		Mean ^a (%CV)	Mean ^a (%CV)		
Total Ezetimibe					
C _{max}	ng/mL	72.0 (34)	73.6 (27)	103	92-115
AUC(0-24 hr)	ng-hr/mL	621 (30)	687 (36)	109	97-122
Ezetimibe-Glucuronide					
C _{max}	ng/mL	68.9 (33)	68.8 (28)	100	89-113
AUC(0-24 hr)	ng-hr/mL	547 (31)	604 (39)	108	96-121
Ezetimibe					
C _{max}	ng/mL	5.23 (38)	7.03 (47)	129	108-154
AUC(0-24 hr)	ng-hr/mL	73.8 (43)	82.6 (37)	113	100-128

a: n=18.

b: Ratio of the mean value for Treatment C (Ezetimibe + Lovastatin) to Treatment A (Ezetimibe).

c: $\alpha=0.05$ (two tailed).

Title of Study: SCH 58235: Assessment of a Multiple-Dose Pharmacokinetic Drug Interaction Between SCH 58235 and Lovastatin in Healthy Subjects (Protocol No. P01382)

Co-administration of ezetimibe with lovastatin did not affect the pharmacokinetics of ezetimibe, based on total ezetimibe C_{max} and AUC. There were no significant differences (mean <15%) in the exposure [based on AUC(0-24 hr)] to total ezetimibe, ezetimibe-glucuronide and ezetimibe after co-administration with lovastatin vs. ezetimibe given alone. The point estimates based on the log-transformed C_{max} and AUC values for total ezetimibe, ezetimibe-glucuronide and ezetimibe were 100-129% and 108-113%, respectively, for the co-administration (Treatment C) vs. ezetimibe alone (Treatment A). The corresponding 90% confidence intervals for these point estimates were 89-154% and 96-128% based on the log-transformed C_{max} and AUC, respectively. The 90% confidence intervals for log-transformed C_{max} and AUC for total ezetimibe were within the bioequivalence acceptance criteria. For ezetimibe log-transformed AUC, the 90% confidence intervals were just outside (100-128%) the bioequivalence acceptance criteria.

Mean (%CV) lovastatin and β-hydroxylovastatin pharmacokinetic parameters and statistical comparisons of the log-transformed C_{max} and AUC values on Day 7 are presented in the following table:

Parameter	Unit	Lovastatin	Ezetimibe + Lovastatin	Point Estimate(%) ^b	90% Confidence Interval ^c
		Mean ^a (%CV)	Mean ^a (%CV)		
Lovastatin					
C _{max}	ng/mL	2.25 (43)	2.63 (43)	113	95-135
AUC(0-24 hr)	ng-hr/mL	18.3 (43)	21.3 (42)	119	93-151
β-Hydroxylovastatin					
C _{max}	ng/mL	1.99 (43)	2.32 (50)	113	95-134
AUC(0-24 hr)	ng-hr/mL	21.4 (44)	23.3 (52)	103	88-120

a: n=18.

b: Ratio of the mean value for Treatment C (Ezetimibe 10 mg + Lovastatin 20 mg) to Treatment B (Lovastatin 20 mg).

c: α=0.05 (two tailed).

Co-administration of ezetimibe with lovastatin had no significant affect on the pharmacokinetics of either lovastatin or β-hydroxylovastatin. There were no significant differences (mean <20%) in the exposure [based on AUC(0-24 hr)] to lovastatin and β-hydroxylovastatin after co-administration with ezetimibe vs. lovastatin given alone. The point estimates based on the log-transformed C_{max} and AUC values for lovastatin and β-hydroxylovastatin were 113% and 103-119%, respectively, for the co-administration (Treatment C) vs. lovastatin alone (Treatment B). The corresponding 90% confidence intervals for these point estimates were 95-135% and 88-151% based on the log-transformed C_{max} and AUC, respectively. The 90% confidence intervals for log-transformed AUC for the pharmacologically active β-hydroxylovastatin metabolite were within the 80-125% bioequivalence acceptance criteria.

Safety:

Multiple doses of ezetimibe 10 mg alone or in combination with lovastatin were safe and well tolerated. Overall, 5 subjects (26%) reported at least one adverse event during the study. Two subjects (11%) reported at least one adverse event while receiving ezetimibe 10 mg, three subjects (17%) reported at least one adverse event while receiving lovastatin 20 mg, and four subjects (21%) reported at least one adverse event while receiving ezetimibe 10 mg in combination with lovastatin 20 mg. Abdominal distention and pharyngitis were the only adverse events to be reported by more than one subject. All adverse events were mild to moderate in severity and required no additional treatment. Mild abdominal distention was the only treatment-related adverse event reported by more than one subject (one subject during treatment with ezetimibe alone and one subject during treatment with ezetimibe plus lovastatin). There were no deaths or serious adverse events and there were no clinically significant abnormalities or changes in routine physical examinations, vital signs, or clinical laboratory tests.

Title of Study: SCH 58235: Assessment of a Multiple-Dose Pharmacokinetic Drug Interaction
Between SCH 58235 and Lovastatin in Healthy Subjects (Protocol No. P01382)

CONCLUSIONS:

- Multiple doses of ezetimibe (SCH 58235) 10 mg alone or in combination with lovastatin 20 mg were safe and well tolerated.
 - Co-administration of ezetimibe with lovastatin did not significantly affect the pharmacokinetics of either ezetimibe, lovastatin or β -hydroxylovastatin.
 - Co-administration of ezetimibe and lovastatin is unlikely to cause a clinically significant pharmacokinetic drug interaction.
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APPEARS THIS WAY
ON ORIGINAL

Title of the Study: SCH 58235: THE EFFECT OF GENDER ON THE PHARMACOKINETIC PARAMETERS OF SCH 58235 (Protocol C98-107)	
Investigator(s): _____	
Publication(s): None	
Studied Period: 23 JUN 1998 to 07 AUG 1998	Clinical Phase: I
Objective: The primary objective of this study was to evaluate the effect of gender on the pharmacokinetic parameters of SCH 58235 after multiple dose administration to male and female volunteers. A secondary objective of this study was to evaluate the safety and tolerability of multiple doses of SCH 58235 in male vs. female volunteers.	
Methodology: Open-label, single-center, multiple-dose study. Twenty-four subjects, 12 males and 12 females, after an overnight fast received SCH 58235 20 mg (2 x 10 mg tablets) orally once-daily in the morning for 10 consecutive days. On Days 1 and 10, the subjects continued fasting until 4 hr post-dose. Water was allowed during the fasting period. Blood samples were collected at prespecified times for safety and pharmacokinetic evaluations. Blood samples for pharmacokinetic evaluation were collected predose (0 hr) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hr after the first (Day 1) and last (Day 10) doses of SCH 58235. In addition, pre-dose (0-hr) blood samples were collected on Days 7, 8 and 9. All plasma samples were assayed for unconjugated and total (conjugated plus unconjugated) SCH 58235 concentrations using _____ methods with lower limits of quantitation (LOQ) of _____ plasma for unconjugated and total SCH 58235, respectively. Subjects were continuously observed and questioned throughout the study for possible occurrence of adverse events.	
Number of Subjects: Twenty-four (24) healthy subjects (12 males and 12 females).	
Diagnosis and Criteria for Inclusion: Adult male and nonpregnant, nonlactating female 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 empaneled for this study.	
Test Product, Dose, Mode of Administration, Batch No(s): SCH 58235 tablets, 20 mg (2 x 10 mg), oral, Batch No. 52123-050.	
Reference Therapy, Dose, Mode of Administration, Batch No(s): None.	
Duration of Treatment: Two SCH 58235 10 mg tablets were administered in the morning at approximately 8 a.m. every day for 10 consecutive days.	
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 SCH 58235 treatment made up the population data set for the primary pharmacokinetic comparisons. Summary statistics and adverse reaction tabulation are included for all treated subjects. Demographic and Baseline variables are listed and summarized using descriptive statistics. These variables are also summarized for each gender group.	
Statistical Methods: Summary statistics (means, standard deviations and coefficients of variation) are provided for the concentration data at each sampling time and for the derived pharmacokinetic parameters for each gender group. Analyses of variance were used based on the original and log-transformed AUC and C _{max} to evaluate the effect of gender (treatment group).	
SUMMARY-CONCLUSIONS:	
RESULTS:	
Safety: SCH 58235 20 mg/day administered in healthy adult male and female volunteers for 10 days was safe and well tolerated. Reported adverse events were mild and consisted primarily of headache and gastrointestinal complaints.	

APPEARS THIS WAY
ON ORIGINAL

Title of the Study: SCH 58235: THE EFFECT OF GENDER ON THE PHARMACOKINETIC PARAMETERS OF SCH 58235 (Protocol C98-107)							
Clinical Pharmacology:							
The key pharmacokinetic parameters for SCH 58235 are presented below:							
Mean (%CV) pharmacokinetic parameters of Unconjugated, Conjugated, and Total SCH 58235 After Oral Administration of SCH 58235 20 mg to Healthy Male and Female Volunteers (Protocol C98-107)							
Parameters (Units)	Gender	Total ^a		Unconjugated ^a		Conjugated ^a	
		Day 1	Day 10	Day 1	Day 10	Day 1	Day 10
C _{max} (ng/mL)	Male	132 (44)	156 (34)	6.85 (43)	10.1 (34)	128 (45)	149 (36)
	Female	147 (69)	187 (53)	6.94 (32)	12.2 (39)	142 (70)	178 (53)
T _{max} (hr)	Male	1.58 (99)	1.04 (48)	6.58 (64)	7.88 (84)	1.58 (99)	1.08 (43)
	Female	1.33 (68)	1.08 (68)	7.38 (88)	7.04 (71)	1.33 (68)	1.08 (68)
AUC(0-24 hr) (ng-hr/mL)	Male	909 (44)	1523 (39)	79.5 (38)	149 (31)	830 (48)	1374 (42)
	Female	917 (38)	1740 (37)	82.1 (30)	185 (34)	835 (40)	1556 (39)
R	Male	NA	1.75 (29)	NA	2.04 (34)	NA	1.73 (29)
	Female	NA	1.97 (30)	NA	2.36 (37)	NA	1.94 (30)
a: n=12/gender group							
NA = Not appropriate to calculate on Day 1							
CONCLUSIONS:							
<ul style="list-style-type: none"> SCH 58235 administered at a daily dose of 20 mg for 10 consecutive days to healthy male and female subjects was safe and well tolerated. There were no differences in the overall incidence of adverse events between males and females, although apparently only females reported gastrointestinal adverse events. The pharmacokinetics of SCH 58235 were gender-independent. SCH 58235 was rapidly absorbed, extensively conjugated (glucuronide conjugate) and moderately accumulated (R 2.0) in plasma following multiple dose oral administration of 20 mg SCH 58235. This degree of accumulation is consistent with a drug having an elimination half-life of ~24 hours administered once-daily. 							

APPEARS THIS WAY
ON ORIGINAL

Title of the Study: SCH 58235: Effect of Age on the Pharmacokinetic Profile of SCH 58235 Following Multiple Oral Dose Administration in Healthy Male Volunteers (Protocol No. C98-115)

Investigator(s): _____

Publication(s): None

Studied Period: 13 MAY 1999 to 28 MAY 1999

Clinical Phase: I

Objective: The primary objective of this study was to evaluate the effect of age (young vs. elderly) on the pharmacokinetics of SCH 58235 after multiple-dose administration to male volunteers. A secondary objective of this study was to evaluate the safety and tolerability of multiple doses of SCH 58235 in young vs. elderly volunteers.

Methodology: Open-label, single-center, multiple-dose study. Twenty-four male subjects, 12 ages 18-45 years, 12 ages ≥ 65 years, after an overnight fast received SCH 58235 10 mg (1 x 10 mg tablet) orally once daily in the morning for 10 consecutive days. On Days 1 and 10, the subjects continued fasting until 4 hours postdose. Water was allowed during the fasting period. Blood samples were collected at prespecified times for safety and pharmacokinetic evaluations. Blood samples for pharmacokinetic evaluation were collected predose (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours after the first (Day 1) and last (Day 10) doses of SCH 58235. In addition, predose (0 hour) blood samples were collected on Days 7, 8, and 9. All plasma samples were assayed for unconjugated and total (conjugated plus unconjugated) SCH 58235 concentrations using _____ methods with lower limits of quantitation (LOQ) of _____ plasma for unconjugated and total SCH 58235, respectively. Subjects were continuously observed and questioned throughout the study for possible occurrence of adverse events.

Number of Subjects: Twenty-four healthy subjects (12 young and 12 elderly).

Diagnosis and Criteria for Inclusion: Adult male subjects between 18-45 years of age inclusive, and ≥ 65 years of age, 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 17-31 were empanelled for this study.

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

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

Duration of Treatment: One SCH 58235 10 mg tablet was administered to each subject in the morning at approximately 8 AM every day for 10 consecutive days.

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 SCH 58235 treatment made up the population data set for the primary pharmacokinetic 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 (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 for each age group. An analysis of variance (ANOVA) was performed on both original scale and log-transformed AUC and Cmax values to evaluate the effect of age (treatment group). The point estimate was expressed as the percent Cmax and AUC ratio of elderly to young based on the log-transformed data. Ninety percent confidence intervals for these point estimates and the power to detect and 80% difference between group means at 5% level of probability (two-tailed) were computed.

SUMMARY-CONCLUSIONS:

RESULTS:

Safety: Ezetimibe (SCH 58235) 10 mg/day administered to healthy adult young and elderly male volunteers for 10 days was safe and well tolerated. Reported adverse events were mild to moderate and consisted primarily of headache.

Clinical Pharmacology:

The key pharmacokinetic parameters for SCH 58235 are presented below.

Title of the Study: SCH 58235: Effect of Age on the Pharmacokinetic Profile of SCH 58235 Following Multiple Oral Dose Administration in Healthy Male Volunteers (Protocol No. C98-115)

Mean (%CV) Pharmacokinetic Parameters of Total, Unconjugated and Conjugated SCH 58235 After Oral Administration of SCH 58235 10 mg to Healthy Young and Elderly Male Volunteers.

Parameter (Unit)	Age Group	Total ^a		Unconjugated ^a		Conjugated ^a	
		Day 1	Day 10	Day 1	Day 10	Day 1	Day 10
C _{max} (ng/mL)	Young	66.6 (54)	76.2 (73)	3.35 (61)	4.87 (42)	65.6 (53)	74.1 (74)
	Elderly	113 (43)	139 (44)	4.21 (56)	5.73 (36)	111 (43)	135 (45)
T _{max} (hour)	Young	1.42 (58)	1.00 (80)	7.33 (29)	8.50 (20)	1.42 (58)	1.00 (80)
	Elderly	1.54 (54)	1.83 (112)	8.17 (30)	8.33 (52)	1.54 (54)	1.83 (112)
AUC(0-24 hr) (ng-hr/mL)	Young	503 (65)	646 (63)	36.3 (42)	57.4 (43)	467 (69)	589 (66)
	Elderly	905 (46)	1461 (52)	51.9 (58)	80.0 (36)	853 (46)	1380 (54)
R	Young	NA	1.33 (20)	NA	1.61 (27)	NA	1.31 (20)
	Elderly	NA	1.72 (40)	NA	1.83 (40)	NA	1.72 (41)
t _{1/2 eff} (hr)	Young	NA	12.8 ^b (40)	NA	19.2 ^b (33)	NA	13.8 ^d (25)
	Elderly	NA	20.7 ^c (53)	NA	24.4 ^b (43)	NA	20.6 ^c (54)

a: n=12/age group.

b: n=10.

c: n=11.

d: n=9.

NA=Not applicable for Day 1 data.

The plasma total and conjugated SCH 58235 concentrations were, on average, ~2-fold greater in elderly subjects than those in the young. There were statistically significant differences (p<0.01) in the C_{max} and AUC values between young and elderly subjects, although there was considerable overlap in the data. The plasma unconjugated SCH 58235 concentrations were, on average, ~1.3-fold greater in elderly subjects than those in the young but with considerable overlap in the data.

SCH 58235 accumulated in plasma following oral administration of 10 mg SCH 58235 once-daily. The accumulation indices (R) in the young and elderly ranged from _____ and _____ respectively, for unconjugated SCH 58235, and ranged from _____ and _____ respectively, for conjugated SCH 58235. The corresponding effective half-life (t_{1/2 eff}), indicating accumulation potential, in the young and elderly ranged from _____ hr and _____ hr, respectively, for unconjugated SCH 58235, and ranged from _____ hr and _____ hr, respectively, for conjugated SCH 58235. Although the mean R and t_{1/2 eff} values were slightly greater in the elderly vs. young, there were considerable overlap in the data between the young and elderly. These differences were deemed not clinically relevant.

CONCLUSIONS:

- Ezetimibe (SCH 58235) administered at a daily dose of 10 mg for 10 consecutive days to healthy young and elderly male subjects was safe and well tolerated. The overall incidence of adverse events was low (17%) and similar between elderly and young volunteers.
- Overall, systemic exposure (C_{max} and AUC) to total and conjugated SCH 58235 was significantly greater (~2-fold) in the elderly than that in the young, although there was considerable overlap in the data.
- Overall, systemic exposure (C_{max} and AUC) to unconjugated SCH 58235 was greater (~1.3-fold) in the elderly than that in the young, but with considerable overlap in the data.
- The observed pharmacokinetic differences in the young vs. elderly are unlikely to be clinically important. However, this conclusion will be confirmed in the Phase III clinical trials.

Title of the Study: SCH 58235: Evaluation of the Pharmacokinetics and Safety of Multiple-Dose SCH 58235 in Healthy Adolescent Volunteers (Protocol No. P00774)

Investigator(s): _____

Publication(s): None

Studied Period: 31 JAN 2000 to 11 FEB 2000

Clinical Phase: I

Objective: The objective of this study was to characterize the multiple-dose pharmacokinetic profile of ezetimibe (SCH 58235) in healthy adolescent children. A secondary objective was to evaluate the safety and tolerability of multiple-oral doses of ezetimibe 10 mg/day in healthy adolescent children.

Methodology: This was a single-center, multiple-dose, open-label, parallel-group study in healthy, adolescent male and female volunteers. The study consisted of an outpatient Screening phase of up to three weeks and an inpatient confinement period of eight consecutive days (beginning on Day -1). On Days 1-7, after an overnight fast, each subject received one ezetimibe (SCH 58235) 10 mg tablet, orally with 240 mL of noncarbonated, room-temperature water, once-daily in the morning at approximately 8 AM. On Days 1 and 7 subjects continued fasting for four hours postdose, at which time regular, standardized meals were served. On Days 2-6, subjects were allowed to have a light breakfast two hours after dosing, followed by standardized meals at the appropriate times. Blood samples were collected at prespecified time during the study for pharmacokinetic and safety evaluations. Blood samples for ezetimibe pharmacokinetics were collected on Days 1 and 7 immediately prior to drug administration (0 hour) and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours post dose. In addition, predose (0-hour) blood samples were collected on Days 5 and 6. Plasma concentrations of unconjugated and total ezetimibe were determined using _____

assays. The lower limits of quantitation (LOQ) for unconjugated and total ezetimibe were _____ plasma, respectively; the linear ranges were _____ respectively. Plasma concentrations of conjugated ezetimibe, reported as ezetimibe equivalents, were calculated by subtracting the unconjugated ezetimibe concentration from the corresponding total ezetimibe concentration for each sample. Blood and urine evaluation (CBC, blood chemistries, and urinalysis) were collected prior to the first dose (Day -1, Baseline) and at the conclusion of the study (Day 8, 24 hours after the last dose of study treatment). ECG's and vital signs were obtained at prespecified times for safety evaluation. Subjects were continuously observed and questioned throughout the study for possible occurrence of adverse events.

Number of Subjects: Eighteen subjects were enrolled and completed the study as planned.

Diagnosis and Criteria for Inclusion: Adolescent males and females between the ages of 10-18 years inclusive, having a Body Mass Index (BMI) of 19-27. To qualify for this study, subjects had to be in good health based on medical history, physical examination, electrocardiogram, and routine laboratory tests (blood chemistry, hematology, and urinalysis).

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

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

Duration of Treatment: Ezetimibe (SCH 58235) 10 mg tablets were administered alone in the morning at approximately 8 AM every day for seven consecutive days.

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. Summary statistics and adverse reaction tabulation are included for all treated subjects.

Statistical Methods: Summary statistics including means, standard deviations and coefficients of variation were provided for the pharmacokinetic and demographic data.

SUMMARY-CONCLUSIONS:

RESULTS: The study was conducted as described in the protocol. However, the final Day 8 (24 hours after last dose) laboratory analyses of ALT and inorganic phosphorus were inadvertently not done for any of the subjects. These protocol deviations were not considered to have a significant effect on the study assumptions, results, or conclusions derived from the experimental data.

Clinical Pharmacology:

Pharmacokinetics: The mean (%CV) pharmacokinetic parameters of total, unconjugated and conjugated ezetimibe on Days 1 and 7 following once-daily oral administration of ezetimibe 10 mg to adolescent children are summarized in the following table:

Title of the Study: SCH 58235: Evaluation of the Pharmacokinetics and Safety of Multiple-Dose SCH 58235 in Healthy Adolescent Volunteers (Protocol No. P00774)

Parameter (Unit)	Total Ezetimibe ^a		Unconjugated Ezetimibe ^a		Conjugated Ezetimibe ^a	
	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
C _{max} (ng/mL)	47.7 (34)	61.8 (39)	4.27 (31)	9.71 (51)	44.9 (36)	54.8 (40)
T _{max} (hr)	1.47 (90)	1.47 (118)	10.5 (70)	11.8 (58)	1.47 (90)	1.47 (118)
AUC(0-24 hr) (ng-hr/mL)	414 (40)	736 (43)	67.3 (34)	155 (49)	347 (44)	581 (46)
R	NA (NA)	1.82 (32)	NA (NA)	2.32 (37)	NA (NA)	1.72 (31)
t _{1/2eff} (hr)	NA (NA)	21.5 ^b (45)	NA (NA)	29.3 (50)	NA (NA)	19.8 ^b (45)

a: n=18.

b: n=17.

NA = Not applicable for Day 1 data.

Ezetimibe was rapidly absorbed and conjugated to the glucuronide-conjugate. The plasma total, unconjugated and conjugated ezetimibe concentrations exhibited multiple peaks, suggesting enterohepatic recycling. Ezetimibe accumulated in plasma following oral administration of ezetimibe 10 mg once-daily, with a mean accumulation index (R) of approximately two for total, unconjugated and conjugated ezetimibe, respectively. The corresponding mean effective half-life (t_{1/2eff}), was ~20-29 hours. The mean and range of individual C_{max} and AUC values of total and conjugated ezetimibe in these adolescent children, were similar to those observed in young and elderly adult subjects. However, the mean and individual unconjugated ezetimibe concentrations were higher (1.3- to 2.7-fold) in adolescent children than in adults. In this study, mean exposure to unconjugated ezetimibe concentrations (based on AUC) was ~20% of exposure to total ezetimibe, which is higher than the ~10% observed in previous studies in adult subjects.

Safety: Two out of the 18 subjects enrolled (11%) reported treatment emergent adverse events, including headache, nausea, and vomiting. One of the two subjects (Subject No. 15, a 17 yr old male), complained of headache characterized as moderate in intensity which required treatment with acetaminophen 1000 mg. There were no serious or significant adverse events or deaths reported in this study.

CONCLUSIONS:

- Ezetimibe (SCH 58235) administered at a daily dose 10 mg for seven consecutive days to healthy children aged 10 to 18 years was safe and well tolerated.
- Following oral administration in adolescent children, ezetimibe was rapidly absorbed, extensively glucuronidated, and the plasma concentration-time profiles exhibited multiple peaks suggesting enterohepatic recycling, similar to adult subjects.
- The mean accumulation ratio of ~2 following once-daily administration, and mean t_{1/2eff} values of 20-29 hours observed in adolescent children were similar to those observed in adults.

**APPEARS THIS WAY
ON ORIGINAL**

Title of the Study: SCH 58235: Assessment of the Possible Pharmacokinetic Profile of Ezetimibe in Volunteers With Normal Renal Function and Severe Chronic Renal Insufficiency (Protocol No. P00749)

Investigator(s): _____
Study Center(s): _____

Publication(s): None

Studied Period: 15 MAY 2000 to 16 OCT 2000 **Clinical Phase:** 1

Objective: The primary objective of this study was to characterize the single-dose pharmacokinetic profile of ezetimibe in male and female volunteers with severe chronic renal insufficiency. The secondary objective was to evaluate the safety and tolerability of ezetimibe when given to volunteers with normal renal function and severe, chronic renal insufficiency.

Methodology: Open-label, multiple-center, parallel-group, single-dose study. The study consisted of an outpatient screening phase of up to 3 weeks, and an inpatient confinement period of approximately 4 days, with subjects admitted at least 12 hours prior to dosing (Day -1) and followed for 72 hours postdose (discharged on Day 4). Subjects were stratified into two groups according to their creatinine clearance as shown in the table below:

Group	Creatinine Clearance	Subject Nos.
1	>80 mL/min/1.73m ²	1, 2, 3, 4, 5, 6, 7, 8, 17
2	10-29 mL/min/1.73m ² inclusive	9 ^a , 10, 11, 12, 14, 15, 16, 21, 22

a: CL_{Cr} = \geq mL/min/1.73m².

Subjects in the control group (Group 1) where possible, were matched in age, race, and gender to patients with chronic renal insufficiency (CRI). After an overnight fast, subjects received one ezetimibe (SCH 58235) 10 mg tablet orally with 200 mL of noncarbonated, room-temperature water, in the morning at approximately 8 AM. Subjects continued fasting for two hours postdose, at which time regular, standardized meals were served. Blood samples were collected at prespecified times during the study for pharmacokinetic and safety evaluations. Blood samples for ezetimibe pharmacokinetics were collected on Day 1 at predose (0-hr) and at 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours postdose. In addition, blood samples were collected at 1-hour postdose for determination of plasma protein binding.

Plasma concentrations of ezetimibe and total ezetimibe (ezetimibe plus conjugated ezetimibe) were determined using _____ assays with lower limits of quantitation (LOQs) of _____ plasma, respectively. Linear ranges were _____ for ezetimibe and total ezetimibe, respectively. Plasma concentrations of conjugated ezetimibe (ezetimibe-glucuronide), reported as ezetimibe equivalents, were calculated for each plasma sample by subtracting the ezetimibe concentration from the corresponding total ezetimibe concentration. Protein binding of total ezetimibe was determined by _____ using the _____ assay described above. Ezetimibe protein binding was not evaluated because plasma concentrations were too low to support analysis.

For safety evaluation, physical examinations, vital signs, electrocardiograms (ECGs), and clinical laboratory tests were conducted at screening, Day 1 and at the end of the study (Day 4). Vital signs were also assessed during the study. Subjects were continuously observed and questioned throughout the study for possible occurrence of adverse events.

Number of Subjects: Eighteen subjects (n=9 patients with chronic renal insufficiency, and n=9 healthy controls) were enrolled and completed the study.

Diagnosis and Criteria for Inclusion: Adult subjects between 18-65 years of age inclusive, and having Body Mass Index (BMI) between 17-31 were empanelled for this study. Subjects had to be in good health (Group 1, CL_{Cr} >80 mL/min/1.73m²), or have severe CRI (Group 2, CL_{Cr} \leq 29 mL/min/1.73m²) based on

Title of the Study: SCH 58235: Assessment of the Possible Pharmacokinetic Profile of Ezetimibe in Volunteers With Normal Renal Function and Severe Chronic Renal Insufficiency (Protocol No. P00749)

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.

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

Duration of Treatment: A single ezetimibe 10 mg tablet was administered in the morning of Day 1 at approximately 8 AM.

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. The effect of severe renal insufficiency on the plasma concentration data and derived pharmacokinetic parameters of ezetimibe, conjugated ezetimibe, and total ezetimibe was evaluated based on the ratio of the group means (patients with renal impairment/healthy subjects) for the primary pharmacokinetic parameters, AUC and C_{max}.

Statistical Methods: Summary statistics including means, standard deviations, and coefficients of variation were provided for the concentration data at each time point and the derived pharmacokinetic parameters. Analysis of variance (ANOVA) was used to extract the group effect (normal vs. severely impaired renal function) for the original scale and log-transformed AUC and C_{max} values and for the other PK parameters in the original scale. The power to detect a 100% increase in means between the two groups for an α level of 0.05 was calculated using pooled residual error and the associated degrees of freedom from the ANOVA. The 90% confidence intervals for the mean difference between the groups, expressed as a percent, was also calculated using the pooled residual error and associated degrees of freedom from the ANOVA. The relationship between renal function, ie, creatinine clearance and AUC, C_{max}, and clearance (CL/F) of ezetimibe were examined using graphical methods and regression analyses. Log-transformed data were used for AUC and C_{max} values, and original scale data for CL/F. A slope significantly different than zero would suggest a relationship between the renal function and PK parameters of ezetimibe. Preliminary analyses included examining the pharmacokinetic parameters for outliers by reviewing the studentized residuals to see if any value exceeded 3. The impact of any outliers on the results of the analyses was also evaluated.

SUMMARY-CONCLUSIONS:

RESULTS:

This study was planned to be conducted in 16 male and female volunteers with normal (n=8) and severe, chronic renal insufficiency (n=8). However, a total of 18 subjects participated in the study (n=9 per group), since the first patient enrolled (Subject 9) had a measured CL_{cr} slightly above the protocol-defined criterion (CL_{cr} of 10-29 mL/min/1.73m²). Thus, an additional patient with chronic renal insufficiency and a matching healthy control were enrolled to assure that at least 8 subjects met the protocol definition of severe, chronic renal insufficiency.

Safety: Overall, 4 of the 18 subjects enrolled (22%) reported treatment emergent adverse events, and included aggravated allergy symptoms, edema, dizziness, hemorrhoids, and somnolence. The incidence of adverse events was similar in the renal insufficiency group (3/9, 33%) and the healthy control group (1/9, 11%). 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 subjects (Group 1) and for patients with severe CRI (Group 2). There were no clinically significant changes or trends from Baseline noted in vital signs, ECGs, or clinical laboratory safety tests. No subject discontinued participation in this study due to adverse events or any other reason. Of note, one patient who was screened for the study (assigned Subject No. 13) was hospitalized for pneumonia and congestive heart failure. Since, this event occurred several days prior to the Baseline (Day -1) evaluation, this patient did not fulfill the protocol criteria for enrollment and therefore was not enrolled and was not dosed with the study drug.

Clinical Pharmacology:

Pharmacokinetics: The pharmacokinetic parameters for total and conjugated ezetimibe for Subject No. 16 with renal insufficiency were significantly greater than those for the rest of the subjects with renal insufficiency. The exposure (AUC[*I*]) to total and conjugated ezetimibe was 6-10 times greater and exposure to ezetimibe was 1.4-7.5 times greater for Subject No.16 compared to exposure in other subjects in this group, possibly due to concomitant cyclosporin administration. Based on the statistical criteria, this subject was determined to be a pharmacokinetic outlier for total and conjugated ezetimibe and his data were

Title of the Study: SCH 58235: Assessment of the Possible Pharmacokinetic Profile of Ezetimibe in Volunteers With Normal Renal Function and Severe Chronic Renal Insufficiency (Protocol No. P00749)

excluded from the primary pharmacokinetic and statistical analyses and data interpretation. Pharmacokinetic results and statistical analyses with Subject No. 16 included appear in the statistical report (Appendix 6).

The mean (%CV) pharmacokinetic parameters and statistical comparison of the log-transformed C_{max} and AUC values for ezetimibe, conjugated ezetimibe, and total ezetimibe following a single oral administration of ezetimibe 10 mg to subjects with normal renal function and severe chronic renal insufficiency (excluding subject No. 16) are summarized below:

Parameter	Units	Healthy Subjects		Severe Chronic Renal Insufficiency		Point Estimate ^c (%)	90% Confidence Interval
		Mean ^a	%CV	Mean ^b	%CV		
Total Ezetimibe							
C _{max}	ng/mL	109	39	117	35	108	79 - 147
T _{max} ^d	hr	1.0	—	1.0	—	—	—
t _{1/2}	hr	22.1	46	30.1 ^e	44	—	—
AUC(tf)	ng-hr/mL	894	33	1317	28	150	117 - 190
Conjugated Ezetimibe							
C _{max}	ng/mL	106	40	113	35	108	78 - 148
T _{max} ^d	hr	1.0	—	1.0	—	—	—
t _{1/2}	hr	22.8	44	30.4 ^e	43	—	—
AUC(tf)	ng-hr/mL	805	36	1181	30	149	113 - 197
Ezetimibe							
C _{max}	ng/mL	5.12	44	6.65	56	124	80 - 191
T _{max} ^d	hr	6.0	—	4.5	—	—	—
t _{1/2}	hr	22.4 ^b	52	28.9 ^e	59	—	—
AUC(tf)	ng-hr/mL	86.5	56	137	60	155	97 - 248

a: n=9.

b: n=8.

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

d: Median (range).

e: n=7.

Exposure (AUC(tf)) to total and conjugated ezetimibe was, on average, 47% higher (based on non-transformed data) in subjects with renal insufficiency, however, there was considerable overlap of the data. The point estimate (90% confidence interval) for log-transformed AUC values for total ezetimibe was 150% (117-190%). The mean ezetimibe terminal phase half-life (t_{1/2}) was approximately 22 hours in healthy subjects and approximately 30 hours in patients with severe renal insufficiency. Ezetimibe exposure was 5-27% of the total ezetimibe exposure based on the ratio of plasma AUC values, and was similar between healthy subjects and patients with severe chronic renal disease.

The relationship between the pharmacokinetic parameters AUC, C_{max}, and CL/F and creatinine clearance (CL_{cr}) was evaluated. The slopes of the linear regression of CL_{cr} and AUC was significantly different from zero for total and conjugated ezetimibe, indicating a negative correlation with the renal function. A weak but significant relationship was also observed between CL_{cr} and CL/F for ezetimibe.

Title of the Study: SCH 58235: Assessment of the Possible Pharmacokinetic Profile of Ezetimibe in Volunteers With Normal Renal Function and Severe Chronic Renal Insufficiency (Protocol No. P00749)

The mean (%CV) protein binding data for total ezetimibe is presented in the table below:

Total Ezetimibe Conc. (ng/mL plasma)		
Plasma	Ultrafiltrate (unbound)	% Protein Binding ^a
Patients With Severe Renal Insufficiency (n=9)		
81.0 (46)	5.26 (47)	93.4 (1)
Healthy Subjects (n=9)		
105 (49)	5.80 (57)	94.5 (1)

a: %Protein Binding = $\frac{\text{Plasma Concentration} - \text{Ultrafiltrate Concentration}}{\text{Plasma Concentration}} \times 100.$

Severe chronic renal insufficiency did not affect the protein binding of total ezetimibe. Mean protein binding for total ezetimibe were 94.5% and 93.4% in healthy subjects and subjects with chronic renal insufficiency, respectively.

CONCLUSIONS:

- Single-dose administration of ezetimibe 10 mg to healthy subjects and patients with severe chronic renal insufficiency was safe and well tolerated.
- Patients with severe chronic renal insufficiency had approximately 50% higher exposure to ezetimibe and total ezetimibe compared to matched healthy controls.
- Creatinine clearance was inversely related to total and conjugated ezetimibe exposure.
- Creatinine clearance did not appear to be correlated with C_{max} and AUC values for ezetimibe.
- Severe chronic renal insufficiency did not affect the protein binding of total ezetimibe.
- The increased exposure to total ezetimibe in patients with chronic renal insufficiency treated with ezetimibe is not considered to be of clinical significance.
- No dose adjustment of ezetimibe is required in patients with chronic renal insufficiency.

**APPEARS THIS WAY
ON ORIGINAL**

Title of the Study: SCH 58235: Assessment of the Possible Pharmacokinetic Profile of Ezetimibe in Volunteers With Normal Renal Function and Severe Chronic Renal Insufficiency (Protocol No. P00749)

The mean (%CV) protein binding data for total ezetimibe is presented in the table below:

Total Ezetimibe Conc. (ng/mL plasma)		
Plasma	Ultrafiltrate (unbound)	% Protein Binding ^a
Patients With Severe Renal Insufficiency (n=9)		
81.0 (46)	5.26 (47)	93.4 (1)
Healthy Subjects (n=9)		
105 (49)	5.80 (57)	94.5 (1)

a: %Protein Binding = $\frac{\text{Plasma Concentration} - \text{Ultrafiltrate Concentration}}{\text{Plasma Concentration}} \times 100.$

Severe chronic renal insufficiency did not affect the protein binding of total ezetimibe. Mean protein binding for total ezetimibe were 94.5% and 93.4% in healthy subjects and subjects with chronic renal insufficiency, respectively.

CONCLUSIONS:

- Single-dose administration of ezetimibe 10 mg to healthy subjects and patients with severe chronic renal insufficiency was safe and well tolerated.
- Patients with severe chronic renal insufficiency had approximately 50% higher exposure to ezetimibe and total ezetimibe compared to matched healthy controls.
- Creatinine clearance was inversely related to total and conjugated ezetimibe exposure.
- Creatinine clearance did not appear to be correlated with C_{max} and AUC values for ezetimibe.
- Severe chronic renal insufficiency did not affect the protein binding of total ezetimibe.
- The increased exposure to total ezetimibe in patients with chronic renal insufficiency treated with ezetimibe is not considered to be of clinical significance.
- No dose adjustment of ezetimibe is required in patients with chronic renal insufficiency.

**APPEARS THIS WAY
ON ORIGINAL**

Title of the Study: SCH 58235: Single-Dose Pharmacokinetics in Subjects With Various Degrees of Chronic Liver Disease (Protocol No. P00251)

Investigator(s): _____

Publication(s): None

Studied Period: 15 JUL 1999-19 SEP 1999

Clinical Phase: I

Objectives: The primary objective of this study was to compare in the pharmacokinetics of ezetimibe (SCH 58235) in subjects with normal liver function to subjects with various degrees of stable chronic liver disease. The secondary objective was to evaluate the safety and tolerability of single-dose ezetimibe in patients with chronic liver disease.

Methodology: This was an open-label, single-dose, parallel-group study conducted in a single center. The study consisted of an outpatient Screening phase of up to three weeks and an inpatient treatment period of approximately 2.5 days. A total of 20 male and female volunteers were stratified into four groups: subjects with hepatic impairment were assigned to one of three liver function groups according to their score by Pugh's Modification of Child's Classification of Severity of Liver Disease determined at the time of Screening, and one group of eight healthy subjects served as controls. The four groups were as follows:

- 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).

After an overnight fast, each subject received a single dose of ezetimibe 10 mg orally with 200 mL of room temperature, noncarbonated water. Subjects continued fasting until four hours postdose, at which time regular standardized meals were served. Water was allowed during the fasting period. Blood and urine samples were collected at prespecified times for safety and pharmacokinetic evaluations. Blood samples for the determination of plasma ezetimibe concentrations were collected prior to dosing (zero hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, and 72 hours following dosing. Plasma concentrations of unconjugated and total (conjugated and unconjugated) ezetimibe (SCH 58235) were determined using _____ assays with the lower limit of quantitation (LOQ) of _____ plasma, respectively. The linear ranges were _____ for unconjugated and total ezetimibe, respectively. Plasma concentrations of conjugated ezetimibe, reported as ezetimibe equivalents, were calculated by subtracting the unconjugated ezetimibe concentration from the corresponding total ezetimibe concentration for each sample.

For safety evaluation, physical examinations, vital signs, electrocardiograms (ECGs) and clinical laboratory tests were conducted at Screening, upon confinement (Day -2/-1), and at the end of the study (Day 4, 72 hours postdose). Additional vital signs measurements were conducted on Day 1 at predose, 2, 12, 24, and 48 hours postdose. Volunteers were continuously observed and questioned throughout the study for possible occurrence of adverse events.

Number of Subjects: Twenty adult male (n=18) and female (n=2) volunteers were enrolled and completed the study as planned.

Diagnosis and Criteria for Inclusion: Adult male and female volunteers between 18-65 years of age inclusive were empanelled for this study. Subjects in Groups 1-3 had to have documented chronic liver disease for greater than one year. Subjects in Group 4 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. 52123-050.

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

Duration of Treatment: Each subject received a single dose of ezetimibe (SCH 58235) 10 mg tablet administered orally in the morning at approximately 8 AM.

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 72 hours postdose for determination of unconjugated and total (unconjugated plus conjugated) ezetimibe concentrations.

Title of the Study: SCH 58235: Single-Dose Pharmacokinetics in Subjects With Various Degrees of Chronic Liver Disease (Protocol No. P00251)

Statistical Methods: Summary statistics including means, standard deviations and coefficients of variation were provided for the concentration data at each time point and the derived pharmacokinetic parameters. An analysis of variance (ANOVA) was performed on the original scale and log-transformed AUC and C_{max} values to evaluate the effect of liver disease on the pharmacokinetics of ezetimibe. Ninety percent confidence intervals and the point estimates for the mean difference in the log-transformed parameters (expressed as a percent of the extent of liver disease to healthy state) and the power to detect a 20% difference between group means at an α level of 0.05 (two-tailed) were computed. Additionally, an ANOVA was performed on the ratio of the unconjugated to total ezetimibe AUC(I) values to determine the effect of liver disease on the extent of ezetimibe conjugation.

SUMMARY-CONCLUSIONS:

RESULTS:

Safety: Ezetimibe 10 mg administered as a single dose to healthy adult subjects and patients with various degrees of hepatic dysfunction was safe and well tolerated. Seven of the 20 subjects (35%) reported adverse events during the study, the most common being headache (4/20, 20%). All adverse events were mild in severity. All adverse events were considered unlikely related to drug except for one episode of headache and one episode of nausea. There were no deaths or serious adverse events and there were no clinically significant abnormalities or changes in routine ECGs or clinical laboratory safety tests from pretreatment Baseline. No clinically relevant changes were noted on physical examinations. Entry and exit blood pressure, pulse rate, respiratory rate, and oral body temperature remained in the range observed for patients and healthy subjects in these age groups.

Clinical Pharmacology:

Pharmacokinetics:

The mean pharmacokinetic parameters of ezetimibe 10 mg following a single oral dose to healthy volunteers and patients with various degrees of stable chronic liver disease are summarized in the following table.

Parameter	Group 1 Mild Liver Disease		Group 2 Mod. Liver Disease		Group 3 Sev. Liver Disease		Group 4 Healthy Subjects	
	Mean ^{a,d}	CV%	Mean ^{a,d}	CV%	Mean ^{a,e}	CV%	Mean ^{c,f}	CV%
Total Ezetimibe								
C _{max} (ng/mL)	141	32	181	22	189	27	98.2	50
T _{max} ^b (hr)	1.25		1.75		4		1	
AUC(tf) (ng-hr/mL)	1543	16	3001	17	3682	36	916	43
Conjugated Ezetimibe								
C _{max} (ng/mL)	138	32	171	24	178	31	95.3	50
T _{max} ^b (hr)	1.25		1.75		3		1	
AUC(tf) (ng-hr/mL)	1468	14	2685	16	3418	41	864	45
Unconjugated Ezetimibe								
C _{max} (ng/mL)	4.10	37	13.07	41	16.2	43	3.86	118
T _{max} ^b (hr)	6		10		7		6	
AUC(tf) (ng-hr/mL)	75.8	54	316	51	265	57	54.6	36

a: n=4.

b: Median.

c: n=8.

d: Three males/one female.

e: Four males.

f: Eight males.

Title of the Study: SCH 58235: Single-Dose Pharmacokinetics in Subjects With Various Degrees of Chronic Liver Disease (Protocol No. P00251)

Plasma ezetimibe concentrations were higher in subjects with liver disease compared to those in healthy volunteers. The mean exposure (AUC[*t*]) to total and conjugated ezetimibe increased with the severity of hepatic impairment 1.7-4 times compared to that in healthy volunteers ($p=0.001-0.01$). These differences were also observed for unconjugated ezetimibe in patients with moderate and severe hepatic impairment ($p=0.01$). However, the exposure to unconjugated ezetimibe in patients with mild liver impairment was comparable to that in healthy volunteers. Although the $t_{1/2}$ values were lower in patients with severe hepatic impairment compared to those in healthy volunteers, there was no apparent trend in the $t_{1/2}$ values with the increase in the hepatic dysfunction. Ezetimibe was rapidly and extensively glucuronidated; the exposure (based on AUC) to unconjugated ezetimibe represented 4-14% of that to total ezetimibe. Neither the presence, nor the severity of liver disease affected the extent of ezetimibe conjugation, the primary clearance mechanism of ezetimibe. Overall, the increased plasma ezetimibe concentrations observed with increasing liver impairment are more consistent with increased bioavailability rather than a decreased clearance or elimination. Based on the results of this single dose study, it appears that multiple-dose administration in patients with hepatic impairment will not lead to an increased extent of drug accumulation.

CONCLUSIONS:

- Ezetimibe (SCH 58235) 10 mg administered orally as a single dose to healthy subjects and patients with various degrees of stable chronic liver disease was safe and well tolerated.
 - With the exception of the exposure to unconjugated ezetimibe in patients with mild hepatic impairment, compared to that in healthy volunteers, liver impairment increased the exposure to ezetimibe 1.7-4-fold.
 - The increase in exposure to total, conjugated and unconjugated ezetimibe appeared to correlate with the severity of liver disease; patients with severe liver impairment showed the highest exposure to ezetimibe.
 - The apparent extent of ezetimibe conjugation (based on the exposure of unconjugated to total ezetimibe) was not affected by the presence or severity of liver disease.
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Title of the Study: SCH 58235: Multiple-Dose Pharmacokinetic and Safety Evaluation in Subjects with Moderate Chronic Liver Disease (Protocol No. P01912)	
Investigators:	}
Study Centers:	
Publication(s):	None
Studied Period:	25 AUG 2000 to 23 JAN 2001
Clinical Phase:	I
Objective:	The objective of this study was to characterize the multiple-dose pharmacokinetics and accumulation potential of ezetimibe in subjects with moderate hepatic impairment relative to healthy subjects. A secondary objective was to evaluate the safety and tolerability of multiple-oral doses of ezetimibe 10 mg/day in patients with moderate, chronic liver disease.
Methodology:	<p>This was a two center, multiple-dose, open-label, parallel-group study in patients with moderate, chronic liver disease. A control group of healthy subjects was also included. The study consisted of an outpatient screening phase of up to three weeks and an inpatient confinement period of 15 consecutive days (beginning on Day -1). On Days 1 to 14, after an overnight fast, each subject received one ezetimibe (SCH 58235) 10 mg tablet, orally with 200 mL of noncarbonated, room-temperature water, once-daily in the morning at approximately 8 AM. Subjects continued fasting for two hours postdose, at which time regular, standardized meals were served.</p> <p>Blood samples were collected at prespecified times during the study for pharmacokinetic and safety evaluations. Blood samples for ezetimibe pharmacokinetics were collected on Days 1 and 14 immediately prior to drug administration (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hours postdose. In addition, predose (0-hour) blood samples were collected on Days 10, 11, 12, and 13. Pooled plasma samples were prepared for each of the 22 subjects by combining samples from Day 14 at sampling times of 1.5 hours, 2 hours, and 3 hours (1 mL from each of the 3 time points) for the determination of protein binding.</p> <p>Plasma concentrations of ezetimibe and total ezetimibe were determined using _____ assays. The lower limits of quantitation (LOQ) for ezetimibe and total ezetimibe were _____ plasma, respectively; the linear ranges were _____, 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. Protein binding of total ezetimibe was determined using _____. Plasma _____ samples were then analyzed using the _____ assay developed for the determination of total ezetimibe in human plasma, and cross-validated for _____. The LOQ for this method was _____ for a 200-μL sample, and the linear concentration range was _____.</p> <p>For safety evaluation, physical examinations, vital signs, electrocardiograms (ECGs), and clinical laboratory tests (CBC, blood chemistries, and urinalysis) were conducted at screening and at the end of the study (Day 15). Blood and urine samples for safety evaluation were also collected prior to the first dose (Day -1, baseline). In addition, blood samples were collected for safety evaluations (SGPT, SGOT, GGT, CPK, Alk. Phos.) predose on Days 3, 7, and 10. Subjects were continuously observed and questioned throughout the study for possible occurrence of adverse events.</p>
Number of Subjects:	A total of 22 subjects were enrolled and completed the study. Of these, 11 subjects had moderate chronic liver disease, and 11 had normal liver function and served as controls.
Diagnosis and Criteria for Inclusion:	Adult male or female subjects with moderate hepatic impairment and healthy controls between the ages of 18-70 years inclusive. To qualify for this study, subjects in the hepatic dysfunction group (Group 1) had to have moderate chronic liver disease for greater than 1 year with extent of the disease defined by Pugh's Modification of Child's Classification of Severity of Liver Disease (Score 7-9). They also had to be free of significant medical conditions unrelated to their hepatic disorder, which would significantly interfere with participation in the study. Subjects in the control group (Group 2) had to be in good health based on medical history, physical examination, electrocardiogram, and routine laboratory tests (blood chemistry, hematology, and urinalysis).
Test Product, Dose, Mode of Administration, Batch No(s):	Ezetimibe (SCH 58235) tablets, 10 mg, oral,

Title of the Study: SCH 58235: Multiple-Dose Pharmacokinetic and Safety Evaluation in Subjects with Moderate Chronic Liver Disease (Protocol No. P01912)

Batch No. 75882-090.

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

Duration of Treatment: Ezetimibe (SCH 58235) 1x 10 mg tablet was administered in the morning at approximately 8 AM every day for 14 consecutive days.

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. The effect of liver disease on the plasma concentration data and derived pharmacokinetic parameters of ezetimibe, conjugated ezetimibe, and total ezetimibe was evaluated based on the ratio of the group means (patients with hepatic impairment/healthy subjects) for the primary pharmacokinetic parameters, AUC, and Cmax.

Statistical Methods: Summary statistics including means, standard deviations, and coefficients of variation were provided for the pharmacokinetic and demographic data. The effect of liver disease was based on the primary pharmacokinetic parameters, AUC, and Cmax, and were expressed as the ratio of the group means (patients with hepatic impairment/healthy subjects). Analysis of variance (ANOVA) was used to evaluate the effect based on log-transformed AUC and Cmax. Ninety percent confidence intervals for the ratio and the power to detect a 20% difference between group means for an α level of 0.05 (two-tailed) were also computed. The pooled residual error and associated degrees of freedom from the ANOVA were used in the calculation of the confidence interval and power. Preliminary analyses included examining the pharmacokinetic parameters for outliers by reviewing the Studentized residuals to see if any value exceeded 3. The impact of any outliers on the results of the analyses was evaluated.

SUMMARY-CONCLUSIONS:

RESULTS: The study was conducted as described in the protocol.

Safety: Three of the 22 subjects enrolled (14%) reported treatment emergent adverse events, including headache, leg pain and dyspepsia. Subject No. 2 complained of leg pain and a urinary tract infection, both adverse events of moderate severity, and were treated with cyclobenzaprine and ciprofloxacin, respectively. Subject No. 19 complained of mild dyspepsia which was treated with antacid tablets. Subject No. 20 complained of a mild headache which resolved without treatment. All adverse events were either mild or moderate in intensity. No subject discontinued participation in this study due to adverse events or any other reason.

There were no clinically significant changes or trends from baseline noted in vital signs, ECGs, or clinical laboratory safety tests, including those tests assessing muscle and liver function. There was a trend towards a decrease in serum total-cholesterol and LDL-cholesterol (LDL-C) in both hepatically impaired patients and healthy controls, with an average decrease in LDL-C from pretreatment baseline of -18.5% and -13.7%, respectively.

Clinical Pharmacology:

Pharmacokinetics:

The mean (%CV) pharmacokinetic parameters of ezetimibe, conjugated ezetimibe, and total ezetimibe on Days 1 and 14 and statistical comparison based on Day 14 log-transformed Cmax and AUC values are shown in the table below:

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Title of the Study: SCH 58235: Multiple-Dose Pharmacokinetic and Safety Evaluation in Subjects with Moderate Chronic Liver Disease (Protocol No. P01912)

Parameter	Unit	Day 1		Day 14		Day 14	
		Healthy Subjects (n=11)	Subjects with Liver Disease (n=11)	Healthy Subjects (n=11)	Subjects with Liver Disease (n=11)	Relative Bioavailability (%) ^a	90% Confidence Interval
Total Ezetimibe							
C _{max}	ng/mL	84.2 (64)	248 (48)	100 (47)	276 (32)	296	213 - 411
T _{max} ^b	hr	1.0	2.0	1.0	3.0	—	—
AUC(0-24 hr)	ng·hr/mL	529 (39)	2287 (33)	853 (47)	3089 (37)	380	259 - 558
Conjugated Ezetimibe							
C _{max}	ng/mL	82.7 (65)	239 (49)	95.4 (48)	257 (33)	290	207 - 405
T _{max} ^b	hr	1.0	2.0	1.0	3.0	—	—
AUC(0-24 hr)	ng·hr/mL	489 (41)	2118 (35)	760 (49)	2749 (36)	383	260 - 564
Ezetimibe							
C _{max}	ng/mL	3.50 (36)	16.0 (41)	7.20 (57)	22.3 (57)	326	212 - 500
T _{max} ^b	hr	6.0	5.0	8.0	5.0	—	—
AUC(0-24 hr)	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 (range).

Plasma concentrations for all ezetimibe analytes were higher in subjects with moderate chronic liver disease compared those in healthy subjects. The mean exposure (based on AUC) to all ezetimibe analytes in subjects with moderate chronic liver disease was approximately 4 times that of healthy subjects. The accumulation of total and conjugated ezetimibe on multiple dose administration was minimal and comparable between healthy subjects (mean R=1.60, 1.67) and subjects with moderate chronic liver disease (mean R=1.37, 1.42), respectively. Mean accumulation ratio (R) of ezetimibe was 2.31 and 1.94 in healthy subjects and subjects with moderate chronic liver disease, respectively.

Ezetimibe was rapidly absorbed and conjugated to the phenolic glucuronide following oral ezetimibe administration to healthy subjects and subjects with moderate chronic liver disease; the T_{max} values for total and conjugated ezetimibe ranged from — hours. The T_{max} values for ezetimibe ranged from — hours. Plasma total ezetimibe and ezetimibe concentrations exhibited multiple peaks, suggesting enterohepatic recycling. Based on the ratio of plasma AUC values, ezetimibe exposure was 2-22% of the total ezetimibe exposure in healthy subjects and subjects with moderate chronic liver disease, with no apparent differences between the two study populations.

The mean (%CV) protein binding data for total ezetimibe is presented in the table below:

Total Ezetimibe Conc. (ng/mL plasma)		
Plasma	(unbound)	% Protein Binding ^a
Patients With Moderate Hepatic Impairment (n=11)		
239 (42)	16 (46)	93.3 (2)
Healthy Subjects (n=11)		
66 (50)	4 (51)	93.9 (1)

$$a: \% \text{ Protein Binding} = \frac{\text{Plasma Concentration} - \text{Concentration}}{\text{Plasma Concentration}} \times 100.$$

Title of the Study: SCH 58235: Multiple-Dose Pharmacokinetic and Safety Evaluation in Subjects with Moderate Chronic Liver Disease (Protocol No. P01912)

Moderate chronic liver disease did not affect the protein binding of total ezetimibe. Mean protein binding were 93.9% and 93.3% in healthy subjects and subjects with moderate chronic liver disease, respectively.

CONCLUSIONS:

- Ezetimibe (SCH 58235) 10 mg administered once-daily for 14 days to healthy subjects and patients with moderate chronic liver disease was safe and well tolerated.
 - Patients with moderate chronic liver disease had approximately 4-fold higher exposure to ezetimibe and total ezetimibe compared to matched healthy controls, based on log-transformed data.
 - The mean accumulation ratio of all ezetimibe analytes ranged for 1.4 to 2.3 and was not affected by hepatic dysfunction. Furthermore, the extent of ezetimibe glucuronidation was apparently not affected by moderate chronic liver disease.
 - Moderate chronic liver disease did not affect the protein binding of total ezetimibe.
 - Serum LDL-C concentrations decreased during the 14-day treatment period with ezetimibe 10 mg/day, with an average decrease from pretreatment baseline of -18.5% and -13.7% for patients with moderate chronic liver disease and healthy controls, respectively.
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NAME OF COMPANY: Schering-Plough Research Institute NAME OF FINISHED PRODUCT: TBD NAME OF ACTIVE INGREDIENT(S): SCH 58235	INDIVIDUAL STUDY SYNOPSIS Page 1 of 3
Title of the Study: RISING, SINGLE-DOSE SAFETY AND TOLERANCE STUDY IN HEALTHY MALE VOLUNTEERS (PROTOCOL I96-088)	
Investigator(s): _____	
Publication(s): None	
Studied Period: 13 JUNE 1996 to 28 JULY 1996	Clinical Phase: I
Objectives: 1) To evaluate the safety and tolerability of SCH 58235 when administered orally at single doses of — 10, — mg to healthy male volunteers; 2) To determine the single-dose pharmacokinetic profile of SCH 58235 in healthy male volunteers.	
Methodology: Randomized, double-blind, placebo-controlled, rising single-dose parallel group safety and tolerance study. Nine volunteers in each dose group were assigned to receive either SCH 58235 (n=6) or placebo (n=3) according to a random code. 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 both unchanged and total (unchanged plus conjugated) SCH 58235 concentration using _____ methods.	
Number of Subjects: 45 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, and urinalysis) and having weights in accordance with current actuarial tables (\pm 15%) were empaneled for this study.	
Test Product, Dose, Mode of Administration, Batch No(s): SCH 58235 — mg and 10 mg — , oral, batch no. 36809-032 and 36809-031, respectively.	
Reference Therapy, Dose, Mode of Administration, Batch No(s): SCH 58235 Placebo — mg and 10 mg — oral, batch no. 36809-017 and 36809-018, respectively.	
Duration of Treatment: Single doses were administered in the morning for all treatment groups at approximately 8 AM and subjects were followed for 72 hours postdose.	
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 samples were collected over 72 hours for determination of pharmacokinetics parameters (C _{max} , T _{max} , AUC, CL/F, t _{1/2}). Urine samples were not assayed due to stability issues.	
Statistical Methods: The pharmacokinetic parameters for each dose were summarized using means, standard deviations and coefficients of variation. In addition, an analysis of variance was done extracting effects due to treatment (dose). The analysis was done on log-transformed dose-adjusted as well as unadjusted AUC(tf) and C _{max} values.	

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<p>NAME OF COMPANY: Schering-Plough Research Institute</p> <p>NAME OF FINISHED PRODUCT: TBD</p> <p>NAME OF ACTIVE INGREDIENT(S): SCH 58235</p>	<p align="center">INDIVIDUAL STUDY SYNOPSIS</p> <p align="center">Page 2 of 3</p>
<p>Title of the Study: RISING, SINGLE-DOSE SAFETY AND TOLERANCE STUDY IN HEALTHY MALE VOLUNTEERS (PROTOCOL I96-088)</p>	
<p>SUMMARY - CONCLUSIONS</p> <p>RESULTS: The study was conducted as planned. Urine SCH 58235 excretion data are not reported from this study due to sample stability problems.</p> <p>Safety: Ten of the 45 subjects enrolled (22%) reported at least one adverse event. Adverse events (regardless of association to the study drug or placebo) included headache, hot flushes, diarrhea and pharyngitis. Of the 30 subjects who received SCH 58235, 6 (20%) reported adverse events, which is similar to the incidence rate (4/15; 27%) observed for the subjects receiving placebo. All adverse events were considered mild. No pharmacological intervention was required and each adverse event resolved spontaneously without sequelae. No serious adverse events or deaths were reported in this study.</p> <p>There was no apparent increase in the overall incidence of adverse events as the dose of SCH 58235 increased from _____ mg. In general, there was no apparent difference in the pattern of adverse events among the doses of SCH 58235 or between SCH 58235 and placebo. No subject discontinued participation in this study due to adverse events.</p> <p>With the exception of one subject described below, there were no clinically significant abnormalities or changes in routine or special clinical laboratory safety tests from pretreatment baseline. Noteworthy changes were observed in liver function tests for one subject who received SCH 58235 _____ mg. This subject had a mildly elevated concentration of alkaline phosphatase at baseline, and mild (<3-fold increase from the upper reference limit) increases in SGPT and to a lesser extent SGOT, without increase in GGT, that were greatest 6 days after dosing. The values returned toward baseline within 3 weeks after dosing.</p> <p>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.</p> <p>Clinical Pharmacology: The appearance of unchanged SCH 58235 in plasma was slow, with dose-related mean times to maximum concentration (T_{max}) ranging from approximately _____ hours; mean T_{max} for total (i.e., unchanged plus conjugated) drug, however, was independent of dose and was consistently between 1 and 2 hours, suggesting good absorption and rapid conjugation. Exposure to unchanged drug alone, based on mean values for maximum plasma concentration (C_{max}) and area under the curve of plasma concentration versus time (AUC), was only about ~10% of exposure to total drug, suggesting that conjugation was extensive, as well as rapid.</p> <p>Unchanged and total SCH 58235 plasma concentrations increased in a dose-related manner with total SCH 58235 concentrations significantly greater than unchanged SCH 58235. At the lowest dose (_____ mg) all samples from all subjects were below the assay LOQ: _____ for unchanged SCH 58235, but total SCH 58235 concentrations were quantifiable in 5 out of 6 subjects (except subject 2) up to approximately 3 hr post-dose. In general plasma SCH 58235 concentrations (total and unchanged) at individual time-points showed larger variability at the lower (_____ mg) doses than at the higher doses.</p> <p>The multiple peaks observed during the elimination phase of the plasma concentration versus time curves suggest significant input of drug over time, most likely due to enterohepatic recycling. The mean C_{max} of unchanged SCH 58235 ranged from 2 to 12 ng/mL for doses between _____ mg, total SCH 58235 ranging from 10 to 170 ng/mL for doses between _____ mg.</p>	

<p>NAME OF COMPANY: Schering-Plough Research Institute</p> <p>NAME OF FINISHED PRODUCT: TBD</p> <p>NAME OF ACTIVE INGREDIENT(S): SCH 58235</p>	<p align="center">INDIVIDUAL STUDY SYNOPSIS Page 3 of 3</p>
<p>Title of the Study: RISING, SINGLE-DOSE SAFETY AND TOLERANCE STUDY IN HEALTHY MALE VOLUNTEERS (PROTOCOL I96-088)</p>	
<p>Because of either insufficient data in the terminal phase or due to the multiple peaks (or both), the terminal phase half-life could not be estimated for unchanged or conjugated SCH 58235 using routine methods (i.e., regression analysis). However, an accumulation half life ($t_{1/2_{accum}}$) could be estimated at some doses using equations 1 and 2.</p> $k_{accum} = -\frac{1}{\tau} \cdot \ln [1 - AUC(0-24h) + AUC(I)] \quad \text{eq. 1}$ $t_{1/2_{accum}} = \frac{0.693}{k_{accum}} \quad \text{eq. 2}$ <p>where τ is the dosing interval (24 hr). In eq. 1, AUC(tf) was used instead of AUC(I) because the terminal phase rate constant could not be estimated at most doses. The approximation is appropriate because sampling was performed for a sufficiently long period of time (72 hours) after dosing.</p> <p>The mean $t_{1/2_{accum}}$ of unchanged SCH 58235 at the _____ mg doses were 19 and 31 hours, respectively; the mean $t_{1/2_{accum}}$ of total SCH 58235 at the 10, _____ mg doses ranged from 16 to 24 hours. These estimates suggest a 2-fold accumulation potential for SCH 58235 following once-daily administration.</p> <p>AUC(tf) and Cmax values of unchanged and total SCH 58235 appeared to be linear, and generally proportional to dose. For both unchanged and total SCH 58235, statistical analysis showed no significant differences between the dose-adjusted AUC(tf) and Cmax values at the three highest doses (10, _____ mg). The statistical power achieved to detect a 20% difference between doses was extremely low (generally <10%).</p>	
<p>CONCLUSIONS:</p> <ul style="list-style-type: none"> • SCH 58235 administered as single oral doses of _____, _____ mg to young healthy male volunteers appears to be safe and well tolerated. • There were no dose-related increases in adverse events, and no SCH 58235-related toxicity was identified. All adverse events were mild and non-specific and there was no apparent difference in the pattern of adverse events among the doses of SCH 58235 or between SCH 58235 and placebo. • Following oral administration, SCH 58235 was rapidly absorbed, and slowly eliminated with an accumulation half-life ranging from 16 to 31 hours. The plasma concentration-time profiles (both unchanged and total SCH 58235) exhibited multiple peaks suggesting enterohepatic recycling and a 2-fold accumulation potential for SCH 58235 following once-daily administration. • The current safety profile supports the continued investigation of SCH 58235 in human subjects. 	

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NAME OF COMPANY: Schering-Plough Research Institute NAME OF FINISHED PRODUCT: TBD NAME OF ACTIVE INGREDIENT(S): SCH 58235	INDIVIDUAL STUDY SYNOPSIS Page 1 of 3
Title of the Study: SCH 58235: RISING, MULTIPLE-DOSE SAFETY AND TOLERANCE STUDY IN HEALTHY MALE VOLUNTEERS (PROTOCOL NO. I96-139)	
Investigator(s): _____	
Publication(s): None	
Studied Period: 01 OCTOBER 1996 to 09 JANUARY 1997	Clinical Phase: I
Objectives: 1) To evaluate the safety and tolerability of SCH 58235 when administered orally at multiple doses of 10, _____ mg to healthy male volunteers; 2) To determine the multiple-dose pharmacokinetic profile of SCH 58235 in healthy male volunteers.	
Methodology: Randomized, double-blind, placebo-controlled, rising multiple-dose, parallel-group, safety and tolerance study. Twelve volunteers in each dose group were randomly assigned to receive either SCH 58235 (n=9) or placebo (n=3). 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 unchanged and total (unchanged plus conjugated) SCH 58235 concentration using _____ methods.	
Number of Subjects: 36 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, and urinalysis) and having weights in accordance with current actuarial tables (\pm 15%) were empaneled for this study.	
Test Product, Dose, Mode of Administration, Batch No(s): SCH 58235 10 mg _____ oral, batch no. 36809-031. SCH 58235 10, _____ mg/day x 14 days.	
Reference Therapy, Dose, Mode of Administration, Batch No(s): SCH 58235 Placebo _____ oral, batch no. 36809-018.	
Duration of Treatment: A single daily dose was administered orally in the morning for 14 consecutive days.	
Criteria for Evaluation: Physical examinations, electrocardiograms, clinical laboratory tests and adverse events were recorded for safety evaluation. Pharmacokinetic parameters (C _{max} , T _{max} , AUC, CL/F, t _{1/2}).	
Statistical Methods: The pharmacokinetic parameters for each dose were summarized using means, standard deviations and coefficients of variation. Analysis of variance was performed on log-transformed, dose-adjusted AUC and C _{max} values.	

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ON ORIGINAL

<p>NAME OF COMPANY: Schering-Plough Research Institute</p> <p>NAME OF FINISHED PRODUCT: TBD</p> <p>NAME OF ACTIVE INGREDIENT(S): SCH 58235</p>	<p align="center">INDIVIDUAL STUDY SYNOPSIS</p> <p align="center">Page 2 of 3</p>
<p>Title of the Study: SCH 58235: RISING, MULTIPLE-DOSE SAFETY AND TOLERANCE STUDY IN HEALTHY MALE VOLUNTEERS (PROTOCOL NO. I96-139)</p>	
<p>SUMMARY - CONCLUSIONS</p> <p>Results: The study was conducted as planned.</p> <p>Safety: Sixteen of the 36 subjects enrolled (44%) reported at least one adverse event. The most common adverse event (regardless of association to the study drug or placebo) was headache. Of the 27 subjects who received SCH 58235, 11 (41%) reported adverse events, which is similar to the incidence rate (5/9; 56%) observed for the subjects receiving placebo. The majority of the adverse events were mild, with 5 of the 16 subjects' adverse events reported as moderate in intensity. There were no serious adverse events or deaths reported in this study.</p> <p>There was no apparent increase in the overall incidence of adverse events as the dose of SCH 58235 increased from 10 mg to 30 mg. In general, there was no apparent difference in the pattern of adverse events among the doses of SCH 58235 or between SCH 58235 and placebo. Ten of the 36 subjects enrolled (8 active, 2 placebo) had noteworthy elevations in liver function tests. One subject (No. 26; 30 mg dose) discontinued treatment when his SGPT values reached 3x the upper reference limit. With the exception of these liver function test elevations, there were no other clinically significant abnormalities or changes in vital signs, ECGs, routine or special clinical laboratory tests from pretreatment baseline.</p> <p>Clinical Pharmacology:</p> <p>The appearance of unchanged SCH 58235 in plasma was slow, with dose-related mean times to maximum concentration (T_{max}) ranging from approximately 6 to 9 hours; mean T_{max} for total drug, however, was independent of dose and was consistently between 2 and 3 hours, suggesting good absorption and rapid conjugation. Exposure to unchanged drug alone, based on mean values for maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve from time 0 to 24 hours on Day 14, AUC(0-24hr)_{ss}, was only about 10% of exposure to total drug, suggesting that conjugation was extensive. Mean C_{max} and AUC(0-24hr)_{ss} of SCH 58235 were dose-related from 10 to 30 mg but did not appear dose-proportional.</p> <p>Due to multiple peaks, possibly due to enterohepatic recirculation, a terminal-phase half-life could not be estimated for SCH 58235 using routine methods; results from an alternate method based on drug accumulation suggest an effective half-life of approximately 24 hours.</p> <p>Total cholesterol and LDL-cholesterol appeared to decrease after treatment with SCH 58235 compared to pretreatment baseline or placebo. However, HDL-cholesterol appeared to decrease and triglycerides appeared to increase during the 14-day study period for both SCH 58235- and placebo-treated subjects.</p>	

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<p>NAME OF COMPANY: Schering-Plough Research Institute</p> <p>NAME OF FINISHED PRODUCT: TBD</p> <p>NAME OF ACTIVE INGREDIENT(S): SCH 58235</p>	<p align="center">INDIVIDUAL STUDY SYNOPSIS</p> <p align="center">Page 3 of 3</p>
<p>Title of the Study: SCH 58235: RISING, MULTIPLE-DOSE SAFETY AND TOLERANCE STUDY IN HEALTHY MALE VOLUNTEERS (PROTOCOL NO. I96-139)</p>	
<p>Conclusions:</p> <ul style="list-style-type: none"> ● SCH 58235 administered as multiple oral doses of 10, — mg to young healthy male volunteers appears to be safe and well tolerated. Most adverse events were mild and non-specific and there was no apparent difference in the pattern of adverse events among the doses of SCH 58235 or between SCH 58235 and placebo. ● There were no dose-related increases in adverse events and, with the possible exception of liver function test abnormalities, no SCH 58235-related toxicity was identified. ● Following oral administration, SCH 58235 was rapidly absorbed and conjugated, and slowly eliminated. The profiles for both unchanged and total SCH 58235 concentrations exhibited multiple peaks suggesting enterohepatic recycling. The degree of accumulation was moderate (approximately 2-fold), suggesting an accumulation half-life of approximately 24 hours. ● SCH 58235 was extensively conjugated to the glucuronide; unchanged plasma SCH 58235 concentrations were only approximately 10% of total SCH 58235 concentrations. ● Steady-state was attained by Day 10, as expected for a drug with an accumulation half-life of 24 hours and dosed once daily. ● AUC(0-24 hr)_{ss} and C_{max} values of unchanged SCH 58235 and total SCH 58235 were dose-related between 10 and — mg, but did not appear to be dose-proportional. ● The current potential benefit/risk profile supports the continued investigation of SCH 58235 in human subjects. 	

**APPEARS THIS WAY
ON ORIGINAL**

Title of the Study: SCH 58235: Assessment of a Multiple-Dose Pharmacokinetic Drug Interaction Between SCH 58235 and Simvastatin in Healthy Volunteers (Protocol I98-311)	
Investigator(s): _____	
Publication(s): None	
Studied Period: 26 NOV 1998 to 06 MAY 1999	Clinical Phase: I
Objective: The primary objective of this study was to evaluate the potential for a pharmacokinetic drug interaction of SCH 58235 on simvastatin. Secondary objectives were to evaluate the safety, tolerance and pharmacodynamic effects of the coadministration of SCH 58235 and simvastatin in healthy subjects.	
Methodology: This was a single-center, randomized, evaluator-blind, placebo-controlled, multiple-dose parallel-groups study in healthy, hypercholesterolemic volunteers. The study consisted of an outpatient screening phase of up to 4 weeks, an outpatient NCEP Step I Diet stabilization period of at least 7 days (during Week -1), and an inpatient confinement period of 16 days (beginning on Day -2), during which compliance with the NCEP Step I Diet was maintained. On Day 1, after an overnight fast, each subject received one of the following five treatments (n=12/treatment): Treatment A: Simvastatin 10 mg + SCH 58235 _____ mg; Treatment B: Simvastatin 10 mg + SCH 58235 _____ mg; Treatment C: Simvastatin 10 mg + SCH 58235 placebo; Treatment D: SCH 58235 placebo; and Treatment E: Simvastatin 10 mg + SCH 58235 10 mg (Treatment E was added as a protocol amendment after evaluating the safety from the first panel of volunteers who completed the study). All doses were administered orally with 200 mL of non-carbonated, room-temperature water, once-daily in the morning for 14 consecutive days. Subjects continued fasting until 2 hours postdose, at which time regular, standardized meals were served. Blood and urine samples were collected at prespecified times during the study for pharmacokinetic, pharmacodynamic and safety evaluations. Blood samples for simvastatin and hydroxysimvastatin pharmacokinetic evaluation were collected prior to the first dose (0 hour on Day 1) and just prior to the last dose (0 hour on Day 14) and at 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 hours after the last dose of study treatment. In addition, a blood sample was collected at 1 hour (mean T _{max} for total SCH 58235) after the last dose (Day 14) for determination of plasma SCH 58235 concentration. Plasma simvastatin and hydroxysimvastatin concentrations were determined using a _____ with a lower limit of quantitation (LOQ) of _____ and a linear range of _____ for both simvastatin and hydroxysimvastatin. Plasma unconjugated and total (unconjugated plus conjugated) SCH 58235 concentrations were determined using _____ assays with LOQs of _____ and the linear ranges of _____ for the unconjugated and total SCH 58235, respectively. Subjects were continuously observed and questioned throughout the study for possible occurrence of adverse events.	
Number of Subjects: Sixty (60) volunteers were planned, however 58 were randomized and 57 subjects completed the study as planned. One subject (No. 115) was dropped from the study due to an adverse event (pain and swelling of wrist).	
Diagnosis and Criteria for Inclusion: Adult males and females of nonchildbearing potential between the ages of 18 and 50 years inclusive, having a Body Mass Index (BMI) of 19-27. To qualify for this study, subjects had to be in good health based on medical history, physical examination, electrocardiogram, and routine laboratory tests (blood chemistry, hematology and urinalysis), and have a screening serum LDL-cholesterol (LDL-C) concentration of ≥ 130 mg/dL.	
Test Product, Dose, Mode of Administration, Batch No(s): SCH 58235 tablets, _____ mg, oral, Batch No. 37750-063; SCH 58235 tablets _____ mg, oral, Batch No. 37750-055; SCH 58235 tablets, 10 mg, oral, Batch No. 52123-050.	
Reference Therapy, Dose, Mode of Administration, Batch No(s): Placebo tablets matching SCH 58235, oral, Batch No. 37750-053; Simvastatin (ZOCOR [®] 10, MSD) 10 mg, tablets, Lot No. 983929, Exp. Date July 2001.	
Duration of Treatment: SCH 58235 _____ 10 mg tablets were coadministered with simvastatin 10 mg in the morning at approximately 8 AM every day for 14 consecutive days.	
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 SCH 58235 treatment made up the population data set for the primary pharmacokinetic comparisons. Summary statistics and adverse reaction tabulation are included for all treated subjects. Demographic and Baseline variables are listed and summarized using descriptive statistics. These variables are also summarized for each treatment group.	

Title of the Study: SCH 58235: Assessment of a Multiple-Dose Pharmacokinetic Drug Interaction Between SCH 58235 and Simvastatin in Healthy Volunteers (Protocol I98-311)

Statistical Methods: Summary statistics including means, standard deviations and coefficients of variation were provided for the concentration data at each time point and the derived pharmacokinetic parameters. An analysis of variance (ANOVA) with one factor (treatment) was performed on the original scale and log-transformed C_{max} and AUC values to evaluate the effect of treatment on the pharmacokinetics of simvastatin and hydroxysimvastatin. The relative oral bioavailability of simvastatin and hydroxysimvastatin following Treatments A, B or E (simvastatin + SCH 58235) as compared to Treatment C (simvastatin alone) was expressed as the C_{max} and AUC ratio from each treatment based on log-transformed data. Ninety percent (90%) confidence intervals for these estimates of relative bioavailability and the power to detect a 20% difference between treatment means for an α level of 0.05 (two-tailed) were computed.

Analysis of Variance models extracting treatment effect were performed to compare the 5 treatment groups at Baseline, Day 7, Day 14, endpoint (the last observed LDL-C after Day 1 and up to Day 14) and Day 15. Actual values, changes from Baseline and percent changes from Baseline for lipid parameters LDL-C, total cholesterol, HDL-C and triglycerides were evaluated. Pairwise comparisons of each treatment group vs. placebo and each of the three combinations of SCH 58235/simvastatin arms vs. simvastatin alone were tested using the least square mean procedures. In addition, percent changes in LDL-C were categorized as follows: <10%, 10 to 25%, 25 to <35%, 35 to <50% and \geq 50%, and the distribution of subjects in each category were tabulated.

SUMMARY-CONCLUSIONS:

RESULTS:

Clinical Pharmacology:

Safety:

Overall, 24 out of the 58 subjects enrolled (41%) reported treatment emergent adverse events, the most common consisting of headache (7/58; 12%), and flatulence (5/58; 9%). The incidence of adverse events was similar between treatments, with no evidence of dose-related increases. The incidence of adverse events during coadministration of simvastatin and SCH 58235 was similar to placebo. Most adverse events were characterized as mild to moderate in intensity, and all except one resolved spontaneously; one subject required treatment with acetaminophen to control his influenza-like symptoms. One subject (No. 115) was dropped from the study after receiving 10 days of treatment because of an adverse event (pain and swelling of wrist), considered as possibly related to treatment by the investigator. All adverse events resolved without sequelae.

Pharmacokinetics:

The key mean (%CV) pharmacokinetic parameters for simvastatin (Simva) and hydroxysimvastatin (OH-simva) are presented in the table below:

Parameters (Units)	C _{max} (ng/mL)		T _{max} (hr) ^a		AUC(0-24h) (ng-hr/mL)		t _{1/2} (hr)	
	Simva	OH-simva	Simva	OH-simva	Simva	OH-simva	Simva	OH-simva
Simvastatin 10mg (n=12)	2.36 (46)	0.57 (46)	1	4	6.82 (48)	5.10 (51)	3.52 (87) ^b	4.91 (41) ^d
Simvastatin 10 mg + SCH 58235 ~mg (n=11)	2.94 (62)	0.90 (114)	1	3	8.07 (58)	9.10 (129)	3.76 (49) ^c	6.20 (77) ^d
Simvastatin 10 mg + SCH 58235 ~ng (n=12)	2.38 (55)	0.63 (54)	1	3.5	7.82 (79)	5.64 (86)	2.78 (71) ^b	5.15 (36) ^d
Simvastatin 10 mg + SCH 58235 10 mg (n=11)	2.65 (62)	0.62 (67)	1	3	8.42 (83)	5.55 (71)	3.46 (61) ^c	4.69 (35) ^d

a: Median (range)
b: n=11
c: n=10
d: n=8

Title of the Study: SCH 58235: Assessment of a Multiple-Dose Pharmacokinetic Drug Interaction Between SCH 58235 and Simvastatin in Healthy Volunteers (Protocol I98-311)

As illustrated in the above table the mean AUC and Cmax values for simvastatin and hydroxysimvastatin were similar amongst all treatment groups. The results indicate that SCH 58235 has no apparent effect on the pharmacokinetics of simvastatin or its active hydroxy acid metabolite (hydroxysimvastatin). The relative bioavailability of simvastatin and hydroxysimvastatin after oral administration of 10 mg simvastatin in combination with either 1 or 10 mg SCH 58235 as compared to 10 mg simvastatin alone based on both log-transformed Cmax and AUC values ranged from 96-138%.

The increases in plasma total, unconjugated and conjugated SCH 58235 concentrations at 1-hour post-dose were dose-related.

Pharmacodynamics:

The mean (S.E.) percent change from Baseline in serum lipid concentrations following once-daily oral administration of simvastatin 10 mg alone or in combination with SCH 58235 1 or 10 mg, or placebo administered for 14 days to healthy hypercholesterolemic volunteers is shown in the following table.

Parameters		LDL-C	Total-C	HDL-C	Triglycerides
Treatment	Day				
Placebo (n=11)	7	-3.2 (3.1)	-3.8 (3.6)	-15.9 (3.2)	8.1 (11.6)
	14	-3.2 (5.1)	-4.1 (5.3)	-20.0 (4.6)	34.5 (17.5)
Simvastatin 10mg (n=12)	7	-27.4 (2.9)	-19.5 (2.6)	-8.5 (2.1)	-14.1 (5.1)
	14	-34.9 (3.2)	-28.4 (2.4)	-8.1 (3.3)	-19.2 (5.8)
Simvastatin 10 mg + SCH 58235 1 mg (n=11)	7	-30.6 (3.4)	-25.0 (2.6)	-10.9 (2.9)	-0.4 (11.6)
	14	-37.5 (4.6)	-30.8 (3.0)	-9.5 (3.6)	1.1 (8.1)
Simvastatin 10 mg + SCH 58235 10 mg (n=12)	7	-34.7 (2.6)	-28.1 (2.0)	-11.3 (2.1)	-10.3 (5.9)
	14	-40.1 (3.1)	-32.2 (2.3)	-9.4 (2.5)	-14.1 (5.9)
Simvastatin 10 mg + SCH 58235 10 mg (n=12)	7	-41.4 (3.1)	-34.6 (2.6)	-15.3 (2.3)	-4.4 (6.7)
	14 ^a	-51.9 (2.6)	-36.6 (3.3)	-12.6 (4.1)	-6.2 (10.4)

a: n=11

The coadministration of SCH 58235 and simvastatin 10 mg caused a dose-dependent reduction in LDL- and total-cholesterol, with no apparent effect on HDL-cholesterol or triglycerides. All active treatments caused statistically significant (p<0.01) decreases in percent change from Baseline in LDL-cholesterol vs. placebo. The coadministration of simvastatin 10 mg plus SCH 58235 10 mg caused a statistically (p<0.01) greater mean percent reduction in LDL-cholesterol than simvastatin 10 mg alone.

CONCLUSIONS:

- SCH 58235 administered at a daily dose of 1 or 10 mg concurrently with simvastatin 10 mg for 14 consecutive days to healthy male subjects was safe and well tolerated.
- SCH 58235 had no effect on the pharmacokinetics of simvastatin and hydroxysimvastatin.
- Plasma SCH 58235 concentrations at 1 hour post-dose were dose-related.
- The coadministration of SCH 58235 with simvastatin caused a dose-dependent percent reduction in serum LDL- and total-cholesterol, without significantly affecting serum HDL-cholesterol or triglycerides.
- The coadministration of SCH 58235 and HMGCo-A reductase inhibitor simvastatin did not increase the incidence of liver transaminases or CPK abnormalities.

Title of the Study: SCH 58235: Assessment of a Multiple-Dose Drug Interaction Between SCH 58235 and Lovastatin in Healthy Volunteers (Protocol No. P00250)

Investigator(s):

Study Center:

Publication(s): Kosoglou T, Meyer I, Cutler DL et al. Pharmacodynamic interaction between the selective cholesterol absorption inhibitor ezetimibe and lovastatin (abstract 390). Proceedings of the 3rd International Congress on Coronary Artery Disease From Prevention to Intervention; 2000 Oct 2-5; Lyon, France. International Congress on Coronary Artery Disease Abstract Book 2000;3(1):101.

Studied Period: 02 JUN 1999 to 23 AUG 1999

Clinical Phase: 1

Objective: The primary objectives of this study were to evaluate the safety, tolerance and pharmacodynamic effects of the coadministration of ezetimibe (SCH 58235) and lovastatin in healthy subjects at clinically relevant doses. A secondary objective was to evaluate the potential for a pharmacokinetic drug interaction of ezetimibe on lovastatin.

Methodology: This was a single-center, randomized, investigator/evaluator-blind, placebo-controlled, multiple-dose parallel-group study in healthy, hypercholesterolemic volunteers. The study consisted of an outpatient screening phase of up to four weeks, an outpatient NCEP Step 1 Diet stabilization period of at least seven days (during Week -1), and an inpatient confinement period of 16 days (beginning on Day -2), during which compliance with the NCEP Step 1 Diet was maintained. On Day 1, after an overnight fast, each subject received one of the following six treatments (n=8/treatment): **Treatment A:** Lovastatin 20 mg; **Treatment B:** Lovastatin 20 mg plus ezetimibe 10 mg; **Treatment C:** Lovastatin 20 mg plus ezetimibe 10 mg; **Treatment D:** Lovastatin 20 mg plus ezetimibe 20 mg; **Treatment E:** Lovastatin 40 mg plus ezetimibe 10 mg; or **Treatment F:** placebo. All doses were administered orally with 200 mL of noncarbonated, room-temperature water, once-daily in the morning, in a fasted state, for 14 consecutive days. Subjects continued fasting until two hours postdose, at which time regular, standardized meals were served. Blood and urine samples were collected at prespecified times during the study for pharmacodynamic, pharmacokinetic, and safety evaluations.

Blood samples for pharmacodynamic evaluation (LDL-C, total-C, HDL-C, triglycerides) were collected at Screening and on Days -1, 1 (Baseline), 7, 14, and 15 (24 hours after the last dose of study treatment). Subjects fasted for at least eight hours prior to the blood sample collection for pharmacodynamic evaluation. Lipid concentrations were determined using commercially available direct quantitative assay methods

For safety evaluation, physical examinations, vital signs, electrocardiograms (ECGs), and clinical laboratory tests (CBC, blood chemistries, and urinalysis) were conducted at Screening and at the end of the study (Day 15). Blood and urine samples for safety evaluation were also collected prior to the first dose (Day -1, Baseline). In addition, blood samples were collected for safety evaluations (SGPT, SGOT, GGT, CPK, and Alk. Phos.) predose on Days 3, 7, and 10. Subjects were continuously observed and questioned throughout the study for possible occurrence of adverse events.

Blood samples for lovastatin and β -hydroxylovastatin pharmacokinetic evaluation were collected prior to the first dose (zero hour on Day 1) and just prior to the last dose (zero hour on Day 14) and at 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours after the last dose of study treatment. In addition, a blood sample was collected at one hour (mean T_{max} for total ezetimibe) after the last dose (Day 14) for determination of plasma ezetimibe and total ezetimibe concentrations. Plasma lovastatin and β -hydroxylovastatin concentrations were determined using a

assay with a lower limit of quantitation (LOQ) of and a linear range of for both lovastatin and β -hydroxylovastatin. Plasma ezetimibe (unconjugated) and total ezetimibe (ezetimibe plus conjugated ezetimibe) concentrations were determined using assays with LOQs of and the linear ranges of and for ezetimibe and total ezetimibe, respectively. Plasma conjugated ezetimibe (ezetimibe-glucuronide) concentrations, reported as ezetimibe equivalents, were calculated by subtracting the ezetimibe concentration from the corresponding total ezetimibe concentration for each sample.

Title of the Study: SCH 58235: Assessment of a Multiple-Dose Drug Interaction Between SCH 58235 and Lovastatin in Healthy Volunteers (Protocol No. P00250)

Number of Subjects: Forty-eight subjects were enrolled and 47 completed the study as planned. One subject (Subject No. 014, [lovastatin 40 mg plus ezetimibe 10 mg treatment]) discontinued the study on Day 8 due to an adverse event. This subject reported myalgia of moderate severity, however he did not have elevations in CPK or transaminases.

Diagnosis and Criteria for Inclusion: Adult males and females of nonchildbearing potential between the ages of 18 and 50 years inclusive, having a Body Mass Index (BMI) of 19-31. To qualify for this study, subjects had to be in good health based on medical history, physical examination, electrocardiogram, and routine laboratory tests (blood chemistry, hematology, and urinalysis), and have a Screening serum LDL-cholesterol (LDL-C) concentration of ≥ 130 mg/dL. Subjects had to be willing to maintain a NCEP Step 1 diet from one week prior to and throughout the study period.

Test Product, Dose, Mode of Administration, Batch No(s): Ezetimibe (SCH 58235) tablets - mg, oral, Batch No. 37750-056. Ezetimibe tablets, 10 mg, oral, Batch No. 37750-057.

Reference Therapy, Dose, Mode of Administration, Batch No(s): Placebo tablets matching ezetimibe, oral, Batch No. 37750-053. Lovastatin (MEVINACOR[®] manufactured by _____) tablets, 20 mg, oral, Lot No. 0050620, expiration date December 2001.

Duration of Treatment: Ezetimibe - 10, or 20 mg tablets with lovastatin 20 mg tablet, ezetimibe 10 mg tablet with lovastatin 40 mg tablet, lovastatin 20 mg tablet, or placebo tablets were administered in the morning at approximately 8 AM every day for 14 consecutive days.

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. The key pharmacodynamic endpoints were fasted (for at least 8 hours prior to the blood sample collection) serum lipids (LDL-C, total-C, HDL-C, triglycerides) collected pre-dose on Days 1 (Baseline), 7, 14, and 15 (24 hours after the last dose of study treatment). The primary pharmacodynamic variable to assess treatment effect and the potential for a therapeutic benefit of the co-administration of ezetimibe and lovastatin was LDL-C. The potential for a pharmacokinetic interaction of ezetimibe on lovastatin was assessed by evaluating the pharmacokinetic parameters (C_{max} and AUC) of lovastatin and β -hydroxylovastatin on Day 14 of treatment.

Statistical Methods: Summary statistics including means, standard deviations or standard errors were provided for the demographic and pharmacodynamic data. Actual values, changes from baseline and percent changes from baseline for lipid parameters LDL-C, total cholesterol, HDL-C and triglycerides were evaluated. Analysis of variance (ANOVA) models extracting treatment effect were performed to compare the six treatment groups at baseline (Day 1), Day 7, Day 14, endpoint (the last observed LDL-C after Day 1 and up to Day 14), and Day 15. Pairwise comparisons were performed using the least square mean procedures. In addition, percent changes in LDL-C were categorized as follows: <10%, 10 to <25%, 25 to <35%, 35 to <50% and $\geq 50\%$, and the distribution of subjects in each category were tabulated.

Summary statistics including means, standard deviations, and coefficients of variation were provided for the concentration data at each time point and the derived pharmacokinetic parameters. ANOVA was performed on the original scale and log-transformed percent C_{max} and AUC values to evaluate the effect of ezetimibe on the pharmacokinetics of lovastatin and β -hydroxylovastatin. The relative oral bioavailability of lovastatin and β -hydroxylovastatin following administration of lovastatin given in combination with ezetimibe compared to lovastatin given alone was expressed as the C_{max} and AUC ratio of the treatments based on log-transformed data. Ninety percent (90%) confidence intervals for these estimates of relative bioavailability and the power to detect a 20% difference between treatment means for an α level of 0.05 (two-tailed) were computed.

SUMMARY-CONCLUSIONS:

RESULTS:

Title of the Study: SCH 58235: Assessment of a Multiple-Dose Drug Interaction Between SCH 58235 and Lovastatin in Healthy Volunteers (Protocol No. P00250)

Safety: Overall 22 subjects (46%) reported treatment emergent adverse events, the most common being headache (11/48; 23%), flatulence (6/48; 13%), myalgia (4/48; 8%), furunculosis (2/48; 4%) and loose stools (2/48; 4%). The incidence of adverse events was similar among the six treatments, with no evidence of increased AEs during coadministration of lovastatin and ezetimibe compared to lovastatin alone or placebo. Most adverse events were characterized as mild in severity and resolved spontaneously. Four subjects reported adverse events characterized as moderate in severity (two reported headache and two myalgia). The two subjects with moderate headache required a single dose of acetaminophen 500 mg to treat their headache. The one subject with myalgia was discontinued from the study on Day 8, while the second subject with myalgia continued in the study with spontaneous diminution of the severity of his symptoms with continued treatment and eventual resolution of his symptoms within two days of study completion. One subject was treated with iodine ointment for treatment of folliculitis. There were no serious adverse events or deaths reported in this study. There were no clinically significant changes or trends from Baseline noted in vital signs, ECGs or clinical laboratory tests, including those tests assessing muscle and liver function.

Clinical Pharmacology:

Pharmacodynamics:

The mean (SE) percent change from baseline in serum lipid concentrations following once-daily oral administration of lovastatin 20 mg alone, or lovastatin 20 mg or 40 mg in combination with ezetimibe administered for 14 days to healthy hypercholesterolemic volunteers is shown in the following table.

Treatment	Day	LDL-C	Total-C	HDL-C	Triglycerides
Lovastatin 20 mg (n=8)	7	-27.4 (4.3) ^b	-17.0 (5.6)	-17.8 (3.6)	-15.3 (6.0)
	14	-33.2 (2.4) ^b	-29.0 (4.6)	-11.2 (6.5)	-16.2 (10.6)
Lovastatin 20 mg + Ezetimibe –mg (n=8)	7	-36.6 (3.1)	-26.7 (3.2)	-12.9 (3.2)	-19.2 (3.8)
	14	-51.4 (3.4) ^d	-39.3 (2.7)	-13.5 (4.8)	-27.9 (7.0)
Lovastatin 20 mg + Ezetimibe 10 mg (n=8)	7	-39.6 (4.5) ^c	-27.8 (6.5)	-13.3 (3.4)	-32.3 (9.2)
	14	-51.0 (4.3) ^d	-38.3 (5.4)	-13.4 (2.4)	-31.3 (9.1)
Lovastatin 20 mg + Ezetimibe 20 mg (n=8)	7	-38.2 (4.8)	-23.5 (5.7)	-12.0 (5.4)	-29.8 (7.7)
	14	-49.0 (3.9) ^d	-35.3 (4.5)	-13.8 (5.9)	-33.4 (10.5)
Lovastatin 40 mg + Ezetimibe 10 mg (n=8)	7	-45.7 (4.3)	-29.9 (4.6)	-18.9 (5.0)	-30.3 (3.6)
	14 ^a	-56.0 (2.7)	-42.6 (3.7)	-18.0 (8.1)	-26.2 (12.3)
Placebo (n=8)	7	-11.5 (3.4)	-5.0 (3.4)	-18.2 (2.7)	-6.6 (9.1)
	14	-17.3 (4.5)	-16.7 (4.9)	-22.9 (3.5)	-7.6 (13.8)

a: n=7.

b: $p \leq 0.01$ vs. placebo.

c: $p < 0.05$ vs. lovastatin 20 mg.

d: $p < 0.01$ vs. lovastatin 20 mg.

The administration of lovastatin 20 mg caused a significantly ($p < 0.01$) greater mean percent reduction in LDL-C vs. placebo. There were no statistically significant changes in HDL-C or triglycerides for lovastatin 20 mg vs. placebo. Lovastatin 20 mg decreased total-cholesterol, however, this did not reach statistical significance on Day 14 ($p = 0.06$ vs. placebo). The coadministration of lovastatin 20 mg plus ezetimibe – 10, or 20 mg caused a statistically ($p < 0.01$) greater mean percent reduction in LDL-C than lovastatin 20 mg alone, with a mean Day 14 reduction of ~16-18% more for the combination vs. lovastatin 20 mg alone. Furthermore, 6 of the 8 subjects in the lovastatin 20 mg plus ezetimibe 10 mg treatment group achieved $\geq 50\%$ reduction in LDL-C on Day 14, compared to 0/8 treated with lovastatin 20 mg alone.

Pharmacokinetics:

The mean (%CV) pharmacokinetic parameters for lovastatin and β -hydroxylovastatin on Day 14 are presented in the table below: