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

| Parameter | Unit | Lovastatin 20 mg[a] | Lova 20 mg + Eze – mg[a] | Lova 20 mg + Eze 10 mg[a] | Lova 20 mg + Eze 20 mg[a] | Lova 40 mg + Eze 10 mg[b] |
|---|---|---|---|---|---|---|
| | | Lovastatin | | | | |
| Cmax | ng/mL | 3.48 (72) | 2.16 (38) | 2.37 (72) | 2.81 (58) | 4.33 (105) |
| Cmax[c] | ng/mL | 2.86 (NA) | 2.03 (NA) | 1.99 (NA) | 2.55 (NA) | 3.05 (NA) |
| Tmax[d] | hr | 3 — | 1.5 — | 2 — | 1.5 — | 1 — |
| AUC(0-24 hr) | ng·hr/mL | 34.0 (55) | 20.5 (51) | 18.1 (76) | 25.5 (37) | 32.7 (58) |
| AUC (0-24 hr)[c] | ng·hr/mL | 28.6 (NA) | 18.5 (NA) | 15.1 (NA) | 24.0 (NA) | 28.8 (NA) |
| | | β-Hydroxylovastatin | | | | |
| Cmax | ng/mL | 2.75 (33) | 2.24 (64) | 2.26 (43) | 1.91 (30) | 3.67 (41) |
| Cmax[c] | ng/mL | 2.64 (NA) | 1.90 (NA) | 2.05 (NA) | 1.83 (NA) | 3.45 (NA) |
| Tmax[d] | hr | 3 — | 3 — | 3 — | 2 — | 2 — |
| AUC(0-24 hr) | ng·hr/mL | 30.2 (44) | 20.4 (54) | 22.2 (52) | 20.2 (29) | 32.5 (49) |
| AUC (0-24 hr)[c] | ng·hr/mL | 27.5 (NA) | 17.9 (NA) | 19.1 (NA) | 19.5 (NA) | 29.2 (NA) |

a: n=8.

b: n=7.

c: Geometric mean.

d: Median (range).

The results show that coadministration of ezetimibe and lovastatin does not increase the plasma concentrations/exposures to lovastatin and β-hydroxylovastatin. In fact, the coadministration treatments had lower plasma concentrations/exposure to lovastatin and β-hydroxylovastatin vs. lovastatin alone. The distributions of individual plasma concentrations, Cmax and AUC values for lovastatin or β-hydroxylovastatin encompassed the same range amongst all treatment groups regardless of the dose of ezetimibe.

Statistical comparison of the log-transformed Cmax and AUC values for lovastatin and β-hydroxylovastatin is shown in the table below.

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

| Parameter | Treatment Comparison[a] | Point Estimate[b] (%) | Confidence Interval[c] |
|---|---|---|---|
| | Lovastatin | | |
| Cmax | B/A | 71.1 | 43-117 |
| | C/A | 69.8 | 42-115 |
| | D/A | 89.4 | 54-148 |
| AUC(0-24 hr) | B/A | 64.7 | 41-102 |
| | C/A | 52.7 | 34-83 |
| | D/A | 84.0 | 53-132 |
| | β-Hydroxylovastatin | | |
| Cmax | B/A | 72.1 | 50-104 |
| | C/A | 77.8 | 54-112 |
| | D/A | 69.5 | 48-100 |
| AUC(0-24 hr) | B/A | 65.0 | 43-99 |
| | C/A | 69.5 | 45-106 |
| | D/A | 70.7 | 46-108 |

a: A = Lovastatin 20 mg alone;
B = Lovastatin 20 mg plus Ezetimibe – mg;
C = Lovastatin 20 mg plus Ezetimibe 10 mg;
D = Lovastatin 20 mg plus Ezetimibe 20 mg.

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

c: Ninety percent confidence interval based on log-transformed data, α=0.05 (2-tailed).

The relative oral bioavailability of lovastatin and β-hydroxylovastatin after coadministration of lovastatin 20 mg with ezetimibe – 10, or 20 mg as compared to lovastatin 20 mg alone ranged from 53-89% based on log-transformed Cmax and AUC. The 90% confidence intervals for the relative oral bioavailability based on log-transformed Cmax and AUC ranged from 42-148% and 34-132% for lovastatin, respectively, and 48-112% and 43-108% for β-hydroxylovastatin, respectively.
The mean (%CV) plasma ezetimibe, conjugated ezetimibe, and total ezetimibe concentrations at one hour postdose on Day 14 are summarized in the table below:

| | Plasma Concentration (ng/mL) | | | |
|---|---|---|---|---|
| Analyte | Treatment B[a] 20 mg + – mg[c] | Treatment C[a] 20 mg + 10 mg[c] | Treatment D[a] 20 mg + 20 mg[c] | Treatment E[b] 40 mg + 10 mg[c] |
| Total Ezetimibe | 44.6 (41) | 83.5 (25) | 133 (21) | 89.7 (19) |
| Ezetimibe | 1.60 (29) | 2.77 (68) | 5.89 (37) | 2.92 (29) |
| Conjugated Ezetimibe | 43.0 (42) | 80.7 (26) | 128 (21) | 86.7 (20) |

a: n=8.

b: n=7.

c: Lovastatin dose plus ezetimibe dose.

For unexplained reasons plasma concentrations for ezetimibe and total ezetimbe were determinable in one and two subjects, respectively, following Treatment A (lovastatin alone plus placebo), and in one and three subjects, respectively, following Treatment F (placebo). The increases in plasma ezetimibe, conjugated ezetimibe and total ezetimibe concentrations at one hour postdose were dose-related following oral administration of ezetimibe – 10, or 20 mg in combination with lovastatin 20 mg. The plasma ezetimibe or total ezetimibe concentrations following coadministration of ezetimibe 10 mg with lovastatin 20 mg were similar to those following ezetimibe 10 mg with lovastatin 40 mg, which suggests a lack of an effect of lovastatin on ezetimibe one-hour concentrations.

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

**CONCLUSIONS:**

- Ezetimibe (SCH 58235) administered at a daily dose of ~ 10, or 20 mg concurrently with lovastatin 20 mg, or ezetimibe 10 mg with lovastatin 40 mg for 14 consecutive days to healthy male subjects with hypercholesterolemia was safe and well tolerated.

- The coadministration of ezetimibe and the HMGCo-A reductase inhibitor lovastatin did not increase liver transaminases or CPK levels.

- Lovastatin 20 mg caused a significantly ($p<0.01$) greater percent reduction in LDL-C than placebo, without significantly affecting serum HDL-C or triglycerides. Lovastatin 20 mg decreased total-cholesterol, however this did not reach statistical significance ($p=0.06$ vs. placebo).

- The coadministration of ezetimibe ~ 10, or 20 mg and lovastatin 20 mg once-daily caused a significantly ($p<0.01$) greater percent reduction in serum LDL-C than lovastatin 20 mg alone, with a mean reduction of ~16-18% more for the combination treatment.

- Ezetimibe administered with lovastatin did not increase the exposure to lovastatin and β-hydroxylovastatin. Plasma ezetimibe concentrations at one-hour postdose were dose-related.

- The coadministration of ezetimibe and lovastatin is not expected to cause a clinically significant pharmacokinetic drug interaction.

| | |
|---|---|
| **Title of the Study:** | SCH 58235: Assessment of a Multiple-Dose Drug Interaction Between SCH 58235 and Pravastatin in Healthy Volunteers (Protocol No. P00447) |
| **Investigators:** | [redacted] |
| **Study Centers:** | |
| **Publication(s):** | None. |
| **Studied Period:** | 20 JUL 1999 to 22 OCT 1999 — **Clinical Phase:** 1 |

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

**Methodology:** This was a randomized, evaluator blind, placebo-controlled, multiple-dose parallel-group study in healthy, hypercholesterolemic subjects (Screenin LDL-C ≥130 mg/dL). The study consisted of an outpatient Screening phase of up to 4 weeks, an outpatient NCEP Step 1 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 1 Diet was maintained. On Day 1, after an overnight fast, each subject received one of the following four treatments (n=8/treatment): **Treatment A**: Pravastatin 20 mg + ezetimibe 10 mg; **Treatment B**: Pravastatin 20 mg; **Treatment C**: Ezetimibe 10 mg; or **Treatment D**: placebo. All doses were administered orally with 200 mL of noncarbonated, 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 pharmacodynamic, pharmacokinetic, and safety evaluations.

Blood samples for pharmacodynamic evaluation (LDL-C, total-C, HDL-C, triglycerides) were collected at Screening, on Days -1, 1 (Baseline), 7, 14 and Day 15 (24 hours after the last dose of study treatment). Subjects fasted for at least 8 hours prior to the blood sample collection. Lipid concentrations were determined using commercially available direct quantitative assay methods [redacted]

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 pravastatin 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 Tmax for total ezetimibe) after the last dose (Day 14) for determination of plasma ezetimibe and total ezetimibe concentrations. Plasma pravastatin concentrations were determined using a [redacted] with a lower limit of quantitation (LOQ) of [redacted] and a linear range of [redacted] Plasma ezetimibe (unconjugated) and total ezetimibe (ezetimibe plus conjugated ezetimibe) concentrations were determined using [redacted] assays with LOQ of [redacted] and the linear ranges of [redacted] 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.

**Number of Subjects:** Thirty-three subjects were enrolled and completed the study.

**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.

**Title of the Study:** SCH 58235: Assessment of a Multiple-Dose Drug Interaction Between SCH 58235 and Pravastatin in Healthy Volunteers (Protocol No. P00447)

**Test Product, Dose, Mode of Administration, Batch No(s):** Ezetimibe (SCH 58235) 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. Pravastatin (PRAVASIN® manufactured by Bristol-Myers Squibb, München, Germany) tablets, 20 mg, oral, Batch Nos. 111A (Site 1) and 113A (Site 2); expiration date April 2001 (both batches).

**Duration of Treatment:** Ezetimibe 10 mg tablet with pravastatin 20 mg tablet, pravastatin 20 mg tablet, ezetimibe 10 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 predose 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 coadministration of ezetimibe and pravastatin was LDL-C. The potential for a pharmacokinetic interaction of ezetimibe on pravastatin was assessed by evaluating the pharmacokinetic parameters (Cmax and AUC) of pravastatin 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 4 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 ≥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 Cmax and AUC values to evaluate the effect of ezetimibe on the pharmacokinetics of pravastatin. The relative oral bioavailability of ezetimibe or pravastatin administered in combination relative to each drug administered alone was expressed as the Cmax 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 $\alpha$ level of 0.05 (two-tailed) were computed.

**SUMMARY-CONCLUSIONS:**

**RESULTS:** This was originally planned as a single-center study in 32 healthy hypercholesterolemic subjects. Due to difficulties in completing enrollment in a timely manner at the primary site, a second center was recruited to complete the study. The primary site contributed 25 subjects, and the second site was requested by the sponsor to enroll 8 subjects (rather than 7 subjects) in order to have balanced treatments (ie, 2 subjects/treatment). Furthermore, the study was originally intended to evaluate the effect of ezetimibe on the pharmacokinetics of pravastatin. Because there was sufficient plasma after the completion of the pravastatin assays, in addition to the first set of 33 plasma samples (one sample/subject), as described in the protocol, it was decided to assay all pharmacokinetic samples for ezetimibe and total ezetimibe concentrations so that the effect of pravastatin on ezetimibe pharmacokinetics could also be evaluated. The decision to assay the plasma samples for complete ezetimibe pharmacokinetic evaluation was made prior to database lock and unblinding of the study.

**Safety:** Overall 21 subjects (64%) reported treatment emergent adverse events, the most common being headache (5/33; 15%) and dizziness (4/33; 12%). All adverse events were considered as mild to moderate in severity. There were no serious adverse events or deaths reported in this study. The incidence of adverse events was similar among the four treatments. 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:**

**Title of the Study:** SCH 58235: Assessment of a Multiple-Dose Drug Interaction Between SCH 58235 and Pravastatin in Healthy Volunteers (Protocol No. P00447)

**Pharmacodynamics:**

The mean (SE) percent change from Baseline in serum lipid concentrations following once-daily oral administration of pravastatin 20 mg in combination with ezetimibe 10 mg, pravastatin 20 mg, ezetimibe 10 mg or placebo administered for 14 days to healthy hypercholesterolemic volunteers is shown in the following table:

| Treatment | Day | LDL-C | Total-C | HDL-C | Triglycerides |
|---|---|---|---|---|---|
| Pravastatin 20 mg + Ezetimibe 10 mg (n=8) | 7 | -28.7 (4.4)[a,c] | -23.7 (4.1)[a,c] | -10.2 (5.5) | -14.9 (7.1) |
| | 14 | -28.0 (4.6)[a] | -21.4 (4.4)[a] | -10.5 (5.8)[b] | -0.7 (7.2) |
| Pravastatin 20 mg (n=8) | 7 | -18.3 (3.3)[b] | -15.0 (2.7)[a] | -4.3 (3.7) | 0.3 (11.0) |
| | 14 | -29.1 (5.6)[a] | -20.3 (4.6)[a] | -0.7 (4.0) | -0.5 (9.0) |
| Ezetimibe 10 mg (n=8) | 7 | -19.1 (3.9)[b] | -15.7 (2.9)[a] | -9.8 (3.3) | 16.9 (16.3) |
| | 14 | -17.2 (4.5) | -12.3 (4.7)[d] | -8.1 (4.8) | 7.6 (11.5) |
| Placebo (n=9) | 7 | -5.7 (3.6) | -1.9 (2.8) | -5.1 (2.8) | 49.5 (53.1) |
| | 14 | -5.9 (4.1) | -1.1 (2.9) | 3.6 (4.2) | 13.0 (20.8) |

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

b: $p < 0.05$ vs. placebo.

c: $p = 0.07$ vs. pravastatin 20 mg.

d: $p = 0.06$ vs. placebo.

The administration of pravastatin 20 mg caused a significantly ($p<0.05$) greater mean percent reduction in LDL-C and total-cholesterol vs. placebo on Days 7 and 14. Ezetimibe 10 mg also decreased LDL-C and total-cholesterol vs. placebo, however this only reached significance ($p<0.05$) on Day 7. There were no significant ($p>0.05$) changes in HDL-C or triglycerides after treatment with pravastatin 20 mg or ezetimibe 10 mg vs. placebo. The coadministration of pravastatin 20 mg plus ezetimibe 10 mg caused a significantly ($p<0.01$) greater mean percent reduction in LDL-C and total-cholesterol vs. placebo on Days 7 and 14. The coadministration of pravastatin and ezetimibe resulted in a greater mean percent reduction in LDL-C and total-cholesterol on Day 7 vs. pravastatin 20 mg or ezetimibe 10 mg, however this did not reach statistical significance ($p \geq 0.07$). This trend towards greater reduction in LDL-C and total-cholesterol for the coadministration vs. pravastatin 20 mg alone was not observed on Day 14, and may be due to pharmacodynamic outliers. The coadministration of pravastatin and ezetimibe resulted in a greater percent reduction in LDL-C (mean -10.8%) on Day 14 vs. ezetimibe 10 mg, however this did not reach statistical significance ($p=0.12$). The coadministration of pravastatin and ezetimibe had no significant ($p>0.05$) effect on triglycerides vs. placebo. In this inpatient study HDL-C levels tended to decrease in all treatment groups with the exception of placebo on Day 14, likely due to restricted physical activity. The decrease in HDL-C levels on Day 14 became significant ($p<0.05$) for the coadministration group compared to placebo.

**Pharmacokinetics:** The mean (%CV) pharmacokinetic parameters and statistical comparison of the log-transformed Cmax and AUC values for pravastatin are presented in the table below:

| Parameter | Unit | Pravastatin 20 mg + Ezetimibe 10 mg | | Pravastatin 20 mg | | Point Estimate[a] (%) | 90% Confidence Interval |
|---|---|---|---|---|---|---|---|
| Cmax | ng/mL | 31.2 | (73) | 37.1 | (65) | 76.0 | 39 - 147 |
| Tmax[b] | hr | 1.0 | — | 1.0 | — | -- | -- |
| AUC(0-24 hr) | ng·hr/mL | 69.8 | (73) | 76.0 | (47) | 79.9 | 45 - 141 |

a: Expressed as a percent ratio of Treatment A (pravastatin + ezetimibe) to Treatment B (pravastatin alone).

b: Median (range).

n=8 per treatment.

**Title of the Study:** SCH 58235: Assessment of a Multiple-Dose Drug Interaction Between SCH 58235 and Pravastatin in Healthy Volunteers (Protocol No. P00447)

There were no significant differences in the mean pravastatin pharmacokinetic parameters (Cmax and AUC) between the two treatments, considering the parallel study design, small sample size (n=8 per group), and considerable overlap in the data. The relative oral bioavailability of pravastatin after coadministration of pravastatin and ezetimibe compared to pravastatin alone was approximately 76 and 80% based on log-transformed Cmax and AUC values, respectively. The 90% confidence intervals for the relative oral bioavailability ranged from 39-147% and 45-141% based on log-transformed Cmax and AUC values, respectively.

The mean (%CV) pharmacokinetic parameters and statistical comparison of the log-transformed Cmax and AUC values for ezetimibe, conjugated ezetimibe, and total ezetimibe are presented in the table below:

| Parameter | Unit | Pravastatin 20 mg + Ezetimibe 10 mg | | Ezetimibe 10 mg | | Point Estimate[a] (%) | 90% Confidence Interval |
|---|---|---|---|---|---|---|---|
| **Total Ezetimibe** | | | | | | | |
| Cmax | ng/mL | 95.1 | (42) | 74.9 | (32) | 123 | 86 - 175 |
| Tmax[b] | hr | 1.0 | | 1.0 | | – | – |
| AUC(0-24 hr) | ng·hr/mL | 711 | (40) | 677 | (48) | 107 | 69 - 166 |
| **Conjugated Ezetimibe** | | | | | | | |
| Cmax | ng/mL | 92.0 | (43) | 70.8 | (31) | 125 | 87 - 178 |
| Tmax[b] | hr | 1.0 | | 1.0 | | – | – |
| AUC(0-24 hr) | ng·hr/mL | 653 | (41) | 610 | (51) | 110 | 70 - 175 |
| **Ezetimibe** | | | | | | | |
| Cmax | ng/mL | 5.01 | (40) | 4.52 | (53) | 115 | 77 - 171 |
| Tmax[b] | hr | 2.0 | | 4.5 | | – | – |
| AUC(0-24 hr) | ng·hr/mL | 57.9 | (36) | 65.4 | (45) | 90.1 | 62 - 130 |

a: Expressed as a percent ratio of Treatment A (pravastatin + ezetimibe) to Treatment C (ezetimibe alone).

b: Median (range).

NA = not applicable for geometric mean.

n=8 per treatment.

There were no significant differences in the mean pharmacokinetic parameters (Cmax and AUC) of ezetimibe and total ezetimibe between the two treatments, considering the parallel study design, small sample size (n=8 per group), and considerable overlap in the data. The relative oral bioavailability of ezetimibe and total ezetimibe after coadministration of pravastatin and ezetimibe compared to ezetimibe alone was 115% and 123%, respectively, based on log-transformed Cmax, and 90% and 107%, respectively, based on log-transformed AUC. The 90% confidence interval for ezetimibe and total ezetimibe was 77-171% and 86-175%, respectively, based on log-transformed Cmax, and was 62-130% and 69-166%, respectively, based on log-transformed AUC.

**Title of the Study:** SCH 58235: Assessment of a Multiple-Dose Drug Interaction Between SCH 58235 and Pravastatin in Healthy Volunteers (Protocol No. P00447)

**CONCLUSIONS:**

- Ezetimibe (SCH 58235) 10 mg administered concurrently with pravastatin 20 mg once-daily for 14 days to healthy subjects with hypercholesterolemia was safe and well tolerated.
- Pravastatin 20 mg significantly ($p \leq 0.01$) decreased LDL-C and total-cholesterol vs. placebo, without significantly affecting serum HDL-C or triglycerides.
- Ezetimibe 10 mg decreased LDL-C and total-cholesterol vs. placebo ($p \leq 0.02$ on Day 7), without significantly affecting serum HDL-C or triglycerides.
- The coadministration of pravastatin 20 mg and ezetimibe 10 mg caused significantly ($p \leq 0.01$) greater mean percent reductions in LDL-C and total-cholesterol vs. placebo.
- The coadministration of pravastatin 20 mg and ezetimibe 10 mg caused greater mean percent reductions in LDL-C, total-cholesterol, and HDL-C on Day 14 vs. ezetimibe alone.
- The coadministration of pravastatin 20 mg and ezetimibe 10 mg caused greater percent reductions in LDL-C and total-cholesterol on Day 7 vs. pravastatin 20 mg alone, but this incremental reduction did not reach statistical significance ($p=0.07$). This incremental decrease for the coadministration vs. pravastatin alone was not observed on Day 14 and may be related to the small sample size.
- There was no clinically significant pharmacokinetic drug interaction between pravastatin and ezetimibe.

| | |
|---|---|
| **Title of the Study:** | SCH 58235: Assessment of a Multiple-Dose Drug Interaction Between SCH 58235 and Atorvastatin in Healthy Volunteers (Protocol No. P00460) |
| **Investigator(s):** | [redacted] |
| **Study Center(s):** | |
| **Publications:** | Kosoglou T, Seiberling M, Statkevich P et al. Pharmacodynamic interaction between the new selective cholesterol absorption inhibitor ezetimibe and atorvastatin. *JACC* 2001;37(Suppl. A):229A.<br>Zhu Y, Statkevich P, Kosoglou T et al. Lack of pharmacokinetic interaction between ezetimibe and atorvastatin. *Clin Pharmacol Ther* 2001;69:P68. |
| **Studied Period:** | 07 AUG 1999 to 20 OCT 1999 — **Clinical Phase:** 1 |
| **Objective:** | The primary objectives were to evaluate the safety, tolerance and pharmacodynamic effects of the coadministration of ezetimibe (SCH 58235) and atorvastatin in healthy subjects at clinically-relevant doses. The secondary objective was to evaluate the potential for a pharmacokinetic drug interaction of ezetimibe on atorvastatin. |

**Methodology:** This was a 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 four treatments (n=8/treatment): **Treatment A**: Atorvastatin 10 mg + ezetimibe 10 mg; **Treatment B**: Atorvastatin 10 mg; **Treatment C**: Ezetimibe 10 mg; or **Treatment D**: placebo. All doses were administered orally with 200 mL of noncarbonated, 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 pharmacodynamic, pharmacokinetic, and safety evaluations.

Blood samples for pharmacodynamic evaluation (LDL-C, total-C, HDL-C, triglycerides) were collected at screening, on Days -1, 1 (Baseline), 7, 14, and 15 (24 hours after the last dose of study treatment). Subjects fasted for at least eight 8 hours prior to the blood sample collection. Serum concentrations of total-C, HDL-C, and triglycerides were determined using commercially available direct quantitative assay methods. LDL-C concentrations were calculated using the Friedewald equation.

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 the determination of atorvastatin and its active metabolites, orthohydroxy atorvastatin and parahydroxy atorvastatin, pharmacokinetics 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 Tmax for total ezetimibe) after the last dose (Day 14) for determination of plasma ezetimibe and total ezetimibe concentrations. Plasma atorvastatin, orthohydroxy atorvastatin and parahydroxy atorvastatin concentrations were determined using [redacted] The lower limits of quantitation (LOQ) were [redacted] for atorvastatin, orthohydroxy atorvastatin and parahydroxy atorvastatin, respectively. Linear ranges were [redacted] and [redacted] for atorvastatin, orthohydroxy atorvastatin and parahydroxy atorvastatin, respectively. Plasma ezetimibe (unconjugated) and total ezetimibe (ezetimibe plus conjugated ezetimibe) concentrations were determined using [redacted] assays with LOQs of [redacted] and linear ranges of [redacted] 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.

**Number of Subjects:** Thirty-two subjects were enrolled and completed the study.

**Title of the Study:** SCH 58235: Assessment of a Multiple-Dose Drug Interaction Between SCH 58235 and Atorvastatin in Healthy Volunteers (Protocol No. P00460)

**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 at screening calculated serum LDL-C concentration of ≥130 mg/dL and triglycerides not greater than 400 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, 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. Atorvastatin (Sortis® 10 distributed by Warner-Lambert [Schweiz] AG, 6341 Baar, Switzerland, for Pfizer Zürich, Switzerland) tablets, 10 mg, oral, Batch No. 0180039; expiration date 02/2001.

**Duration of Treatment:** Ezetimibe 10 mg tablet with atorvastatin 10 mg tablet, atorvastatin 10 mg tablet, ezetimibe 10 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 coadministration of ezetimibe and atorvastatin was LDL-C. The potential for a pharmacokinetic interaction of ezetimibe on atorvastatin was assessed by evaluating the pharmacokinetic parameters (Cmax and AUC) of atorvastatin and its metabolites 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-C, HDL-C and triglycerides were evaluated. Analysis of variance (ANOVA) models extracting treatment effect were performed to compare the four 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 ≥50%, and the distribution of subjects in each category were tabulated. The probability levels presented on all tables are nominal values.

Summary statistics including means, standard deviations and coefficients of variation were provided for the drug concentration data at each time point and the derived pharmacokinetic parameters. ANOVA was performed on the original scale and log-transformed Cmax and AUC values to evaluate the potential pharmacokinetic interaction between ezetimibe and atorvastatin. The relative oral bioavailability of ezetimibe or atorvastatin administered in combination relative to each drug administered alone was expressed as the Cmax 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 $\alpha$ level of 0.05 (two-tailed) were computed.

**SUMMARY-CONCLUSIONS:**

**RESULTS:** This study originally intended to evaluate the effect of ezetimibe on the pharmacokinetics of atorvastatin, however, since there was sufficient plasma after the completion of the atorvastatin assays, it was decided to assay all pharmacokinetic samples for ezetimibe and total ezetimibe concentrations so that the effect of atorvastatin on ezetimibe pharmacokinetics could also be evaluated. Thus, in addition to the first set of 32 plasma samples (one sample/subject), as described in the protocol, which were collected and analyzed for ezetimibe and total ezetimibe, a second set of 352 plasma samples (11 samples/subject), were also analyzed for ezetimibe and total ezetimibe. The decision to assay the plasma samples for complete ezetimibe pharmacokinetic evaluation was made prior to database lock and unblinding of the study. This decision was not in violation of the subjects' informed consent.

**Safety:** Overall 12 subjects (38%) reported treatment emergent adverse events, the most common being fatigue (5/32; 16%), headache (4/32; 13%) and flatulence (3/32; 9%). The incidence of adverse events was similar among the four treatments. All adverse events were considered as mild to moderate in severity. All adverse events resolved spontaneously without medical intervention. 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.

**Title of the Study:** SCH 58235: Assessment of a Multiple-Dose Drug Interaction Between SCH 58235 and Atorvastatin in Healthy Volunteers (Protocol No. P00460)

**Clinical Pharmacology:**

**Pharmacodynamics:** The mean (SE) percent change from Baseline in serum lipid concentrations following once-daily oral administration of atorvastatin 10 mg with ezetimibe 10 mg, atorvastatin 10 mg, ezetimibe 10 mg or placebo administered for 14 days to healthy hypercholesterolemic volunteers is shown in the following table:

| Treatment | Day | LDL-C | Total-C | HDL-C | Triglycerides |
|---|---|---|---|---|---|
| Atorvastatin 10 mg + Ezetimibe 10 mg (n=8) | 7 | -49.5 (3.3)[a,c,d] | -35.3 (2.5)[a,c,d] | -1.9 (3.7) | -20.3 (5.8)[b] |
| | 14 | -55.7 (2.0)[a,c,d] | -38.0 (2.4)[a,d] | -1.1 (5.0) | -8.6 (7.1) |
| Atorvastatin 10 mg (n=8) | 7 | -30.0 (2.1)[a] | -21.9 (3.4)[a] | 1.7 (8.6) | -4.2 (10.6) |
| | 14 | -40.0 (5.1)[a] | -28.4 (4.6)[a] | -0.5 (7.7) | 0.5 (14.0) |
| Ezetimibe 10 mg (n=8) | 7 | -24.4 (3.4)[a] | -18.3 (3.1)[a] | -8.2 (3.5) | 3.1 (9.8) |
| | 14 | -22.7 (5.2)[b] | -15.4 (4.6) | -11.3 (2.6) | 32.8 (15.6) |
| Placebo (n=8) | 7 | -9.1 (3.7) | -6.7 (2.2) | -7.5 (2.3) | 10.7 (11.4) |
| | 14 | -6.9 (4.6) | -6.1 (3.7) | -12.8 (2.2) | 22.6 (21.1) |

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

b: $p \leq 0.03$ vs. placebo.

c: $p \leq 0.02$ vs. atorvastatin 10 mg.

d: $p < 0.01$ vs. ezetimibe 10 mg.

The administration of atorvastatin 10 mg caused a significantly ($p \leq 0.01$) greater mean percent reduction in LDL-C and total-C vs. placebo. Ezetimibe 10 mg significantly ($p \leq 0.03$) decreased LDL-C vs. placebo, and lowered total-C, however this effect reached statistical significance ($p \leq 0.01$) only on Day 7. There were no significant ($p > 0.05$) changes in HDL-C or triglycerides after treatment with atorvastatin 10 mg or ezetimibe 10 mg vs. placebo. The coadministration of atorvastatin 10 mg and ezetimibe 10 mg caused a significantly ($p < 0.01$) greater mean percent reduction in LDL-C and total-cholesterol vs. placebo. The coadministration of atorvastatin and ezetimibe resulted in a significantly ($p \leq 0.02$) greater mean percent reduction in LDL-C than either drug alone, with a mean reduction of 15.7% more than atorvastatin. The coadministration also caused a significantly ($p \leq 0.02$) greater reduction in total-C than either drug alone, however this effect was not statistically significant on Day 14 vs. atorvastatin. In this inpatient study HDL-C levels tended to decrease in all treatment groups, likely due to restricted physical activity. Of note, the decrease in HDL-C levels was less in the coadministration and atorvastatin alone treatment groups compared to the ezetimibe alone or placebo. The coadministration of atorvastatin and ezetimibe caused a decrease in triglyceride concentrations, however this effect was only significant ($p = 0.03$) on Day 7 compared to placebo.

**Pharmacokinetics:** The mean (%CV) pharmacokinetic parameters and statistical comparisons of the log-transformed Cmax and AUC values for atorvastatin and orthoxydroxy atorvastatin are presented in the table below. Plasma parahydroxy atorvastatin concentrations were either slightly above or below the assay LOQ for all subjects, therefore the mean calculations and statistical comparisons for this atorvastatin metabolite were not conducted.

**Title of the Study:** SCH 58235: Assessment of a Multiple-Dose Drug Interaction Between SCH 58235 and Atorvastatin in Healthy Volunteers (Protocol No. P00460)

| Parameter | Unit | Atorvastatin 10 mg + Ezetimibe 10 mg | | Atorvastatin 10 mg | | Point Estimate[a] (%) | 90% Confidence[c] Interval |
|---|---|---|---|---|---|---|---|
| **Atorvastatin** | | | | | | | |
| Cmax | ng/mL | 3.29 | (67) | 2.70 | (29) | 107 | 72 - 159 |
| Tmax[b] | hr | 0.75 | | 0.50 | | -- | -- |
| AUC(0-24 hr) | ng·hr/mL | 22.1 | (58) | 21.3 | (29) | 95.6 | 68 - 134 |
| **Orthohydroxy atorvastatin** | | | | | | | |
| Cmax | ng/mL | 1.62 | (35) | 1.24 | (10) | 125 | 102 - 154 |
| Tmax[b] | hr | 3.00 | | 3.00 | | -- | -- |
| AUC(0-24 hr) | ng·hr/mL | 18.8 | (27) | 15.0 | (7) | 122 | 103 - 144 |

a: Expressed as a percent ratio of Treatment A (atorvastatin + ezetimibe) to Treatment B (atorvastatin alone).

b: Median (range).

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

n=8 per treatment.

There were no significant differences in the mean atorvastatin and orthohydroxy atorvastatin pharmacokinetic parameters (Cmax and AUC) between the two treatments, considering the parallel study design, small sample size (n=8 per group), and considerable overlap in the data. The relative oral bioavailability of atorvastatin and orthohydroxy atorvastatin after coadministration of atorvastatin and ezetimibe as compared to atorvastatin alone was 96% and 122% based on log-transformed AUC values, respectively.

The mean (%CV) pharmacokinetic parameters and statistical comparison of the log-transformed Cmax and AUC values for total ezetimibe, conjugated ezetimibe, and ezetimibe, are presented in the table below:

| Parameter | Unit | Atorvastatin 10 mg + Ezetimibe 10 mg | | Ezetimibe 10 mg | | Point Estimate[a] (%) | 90% Confidence[c] Interval |
|---|---|---|---|---|---|---|---|
| **Total Ezetimibe** | | | | | | | |
| Cmax | ng/mL | 87.3 | (50) | 73.0 | (28) | 112 | 80 - 157 |
| Tmax[b] | hr | 0.50 | | 0.75 | | -- | -- |
| AUC(0-24 hr) | ng·hr/mL | 707 | (41) | 681 | (25) | 98.5 | 72 - 134 |
| **Conjugated Ezetimibe** | | | | | | | |
| Cmax | ng/mL | 83.3 | (52) | 70.0 | (28) | 110 | 78 - 157 |
| Tmax[b] | hr | 0.50 | | 0.75 | | -- | -- |
| AUC(0-24 hr) | ng·hr/mL | 632 | (44) | 619 | (26) | 95.4 | 68 - 134 |
| **Ezetimibe** | | | | | | | |
| Cmax | ng/mL | 6.07 | (42) | 4.65 | (38) | 131 | 98 - 176 |
| Tmax[b] | hr | 4.50 | | 6.00 | | -- | -- |
| AUC(0-24 hr) | ng·hr/mL | 75.7 | (45) | 62.2 | (39) | 121 | 88 - 166 |

a: Expressed as a percent ratio of Treatment A (atorvastatin + ezetimibe) to Treatment B (atorvastatin alone).

b: Median (range).

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

n=8 per treatment.

**Title of the Study:** SCH 58235: Assessment of a Multiple-Dose Drug Interaction Between SCH 58235 and Atorvastatin in Healthy Volunteers (Protocol No. P00460)

There were no significant differences in the mean pharmacokinetic parameters (Cmax and AUC) of total ezetimibe, conjugated ezetimibe, and ezetimibe between the two treatments, considering the parallel study design, small sample size (n=8 per group), and considerable overlap in the data. The relative oral bioavailability of total ezetimibe and ezetimibe after coadministration of atorvastatin and ezetimibe compared to ezetimibe alone was 98.5% and 121% based on log-transformed AUC values, respectively.

**CONCLUSIONS:**

- Ezetimibe (SCH 58235) 10 mg administered with atorvastatin 10 mg once daily for 14 days to healthy subjects with hypercholesterolemia was safe and well tolerated.
- Atorvastatin 10 mg significantly ($p \leq 0.01$) decreased LDL-C and total-C vs. placebo, without significantly affecting serum HDL-C or triglycerides.
- Ezetimibe 10 mg significantly ($p \leq 0.03$) decreased LDL-C and lowered total-C vs. placebo, however the effect on total-C was not statistically significant on Day 14.
- The coadministration of atorvastatin 10 mg and ezetimibe 10 mg caused significantly ($p \leq 0.01$) greater mean percent reductions in LDL-C and total-C vs. placebo, without significantly affecting HDL-C levels.
- The coadministration of atorvastatin 10 mg and ezetimibe 10 mg resulted in a significantly ($p \leq 0.02$) greater mean percent reduction in LDL-C than either drug alone, with a mean reduction of 15.7% more than atorvastatin.
- The coadministration of atorvastatin 10 mg and ezetimibe 10 mg caused a decrease in triglyceride concentrations, however this effect was not significant ($p > 0.05$) from placebo on Day 14.
- There was no clinically significant pharmacokinetic drug interaction between atorvastatin and ezetimibe.

| | |
|---|---|
| **Title of the Study:** | SCH 58235: Assessment of a Multiple-Dose Drug Interaction Between SCH 58235 and Cerivastatin in Healthy Volunteers (Protocol No. P00754) |
| **Investigator(s):** | [redacted] |
| **Study Center:** | |
| **Publication(s):** | None |
| **Studied Period:** | 18 FEB 2000 to 07 OCT 2000 — **Clinical Phase:** 1 |
| **Objective:** | The primary objectives of this study were to evaluate pharmacodynamic effects and safety of the co-administration of ezetimibe (SCH 58235) and cerivastatin in healthy hypercholesterolemic subjects at clinically relevant doses. A secondary objective was to evaluate the potential for a pharmacokinetic drug interaction between ezetimibe and cerivastatin. |

**Methodology:** This was a single-center, randomized, third-party blind, placebo-controlled, multiple-dose parallel-group study in healthy, hypercholesterolemic subjects (Screening LDL-C ≥130 mg/dL). 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 four treatments (n=8/treatment): **Treatment A**: cerivastatin 0.3 mg + ezetimibe 10 mg; **Treatment B**: cerivastatin 0.3 mg; **Treatment C**: ezetimibe 10 mg; **Treatment D**: placebo. 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 pharmacodynamic, pharmacokinetic, and safety evaluations.

Blood samples for pharmacodynamic evaluation (LDL-C, total-C, HDL-C, triglycerides) were collected at Screening and on Day -1, and just prior to dosing on Days 1, 7, and 14 and Day 15 (24 hours after the last dose of study treatment). Subjects fasted for at least 8 hours prior to the blood sample collection. Lipid concentrations were determined using commercially available direct quantitative assay methods [redacted]

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.

Blood samples for cerivastatin and ezetimibe 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. Plasma concentrations of cerivastatin, and its pharmacologically active metabolites hydroxycerivastatin and O-desmethylcerivastatin were determined using a [redacted] with lower limits of quantitation (LOQ) of [redacted] and standard curve concentrations ranging from [redacted] respectively. Plasma ezetimibe (unconjugated) and total ezetimibe (ezetimibe plus conjugated ezetimibe) concentrations were determined using [redacted] assays with LOQ of [redacted], and standard curve concentration ranges of [redacted] to [redacted] 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.

**Number of Subjects:** Thirty-two subjects were enrolled and completed the study as planned.

**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, 10 mg, oral, Batch No. 75882-090, expiration date 02/2001.

**Title of the Study:** SCH 58235: Assessment of a Multiple-Dose Drug Interaction Between SCH 58235 and Cerivastatin in Healthy Volunteers (Protocol No. P00754)

**Reference Therapy, Dose, Mode of Administration, Batch No(s):** Placebo tablets matching ezetimibe, oral, Batch No. 75882-062, expiration date 06/2001. Cerivastatin (LIPOBAY® 0.3 mg manufactured by Bayer AG, Germany and distributed by Bayer (Schweiz) AG, Zürich, Switzerland) tablets, 0.3 mg, oral, Batch No. CBGNV1, expiration date 05/2002.

**Duration of Treatment:** Ezetimibe 10 mg tablets with cerivastatin 0.3 mg tablet, cerivastatin 0.3 mg tablet, ezetimibe 10 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 cerivastatin was LDL-C. The potential for a pharmacokinetic interaction between ezetimibe and cerivastatin was assessed by evaluating the pharmacokinetic parameters (Cmax and AUC) of cerivastatin and its metabolites, ezetimibe, conjugated ezetimibe, and total ezetimibe on Day 14 of treatment.

**Statistical Methods:** Summary statistics including means and standard errors (S.E.) were provided for the demographic and pharmacodynamic data. Actual values, changes from Baseline and percent changes from Baseline for lipid parameters LDL-C, total-C, HDL-C, and triglycerides were evaluated. Analysis of variance (ANOVA) models extracting treatment effect were performed to compare the 4 treatment groups at Baseline (Day 1), Day 7, Day 14, and Day 15. Pairwise comparisons 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 ≥50%, and the distribution of subjects in each category was 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 Cmax and AUC values to evaluate the effect of ezetimibe on the pharmacokinetics of cerivastatin. The relative oral bioavailability of ezetimibe or cerivastatin administered in combination relative to each drug administered alone was expressed as the Cmax 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 $\alpha$ level of 0.05 (two-tailed) were computed.

**SUMMARY-CONCLUSIONS:**

**RESULTS:**

**Safety:** Overall, 5 out of the 32 subjects enrolled (16%) reported treatment emergent adverse events that included constipation, diarrhea, flatulence, and skin rash. The incidence of adverse events was similar among treatments groups. All adverse events were considered as mild to moderate in severity and resolved spontaneously. All of the adverse events reported were considered by the investigator to be treatment-related. There were no serious adverse events or death 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 cerivastatin 0.3 mg in combination with ezetimibe 10 mg, cerivastatin 0.3 mg, ezetimibe 10 mg or placebo administered for 14 days to healthy hypercholesterolemic volunteers is shown in the following table:

APPEARS THIS WAY
ON ORIGINAL

**Title of the Study:** SCH 58235: Assessment of a Multiple-Dose Drug Interaction Between SCH 58235 and Cerivastatin in Healthy Volunteers (Protocol No. P00754)

| Treatment | Day | LDL-C | Total-C | HDL-C | Triglycerides |
|---|---|---|---|---|---|
| Cerivastatin 0.3 mg + Ezetimibe 10 mg (n=8) | 7 | -32.6 (2.63)[a,c] | -23.8 (3.14)[a,c,e] | -7.10 (3.46) | -0.71 (10.5) |
| | 14 | -33.3 (6.38)[a,d] | -23.0 (5.72)[a,d] | 2.20 (4.10) | 3.18 (15.2) |
| Cerivastatin 0.3 mg (n=8) | 7 | -5.76 (3.32)[b] | -3.41 (2.02) | -0.06 (3.75) | 12.98 (10.9) |
| | 14 | -14.7 (4.41)[a] | -9.11 (3.94)[b] | 2.05 (3.82) | 0.60 (11.3) |
| Ezetimibe 10 mg (n=8) | 7 | -16.1 (4.05)[a] | -10.7 (3.53)[a] | 1.39 (2.51) | 4.25 (11.4) |
| | 14 | -19.8 (5.87)[a] | -11.8 (5.32)[a] | -2.21 (3.96) | 4.63 (11.3) |
| Placebo (n=8) | 7 | 5.72 (5.44) | 2.27 (2.47) | -4.52 (2.67) | 31.34 (29.0) |
| | 14 | 7.80 (4.46) | 6.01 (2.35) | -1.48 (1.86) | 29.24 (18.7) |

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

b: $p \leq 0.05$ vs. placebo

c: $p \leq 0.01$ vs. cerivastatin 0.3 mg.

d: $p < 0.05$ vs. cerivastatin 0.3 mg.

e: $p \leq 0.01$ vs. ezetimibe 10 mg.

Cerivastatin 0.3 mg, ezetimibe 10 mg, and the co-administration of ezetimibe 10 mg plus cerivastatin 0.3 mg caused significantly ($p \leq 0.03$) greater mean percent reductions in LDL-C and total-cholesterol than placebo at Day 14. The co-administration of cerivastatin and ezetimibe resulted in a significantly (p=0.02) greater incremental mean percent reduction of 19% in LDL-C than cerivastatin 0.3 mg alone. The coadministration of cerivastatin and ezetimibe was numerically better than ezetimibe 10 mg alone by a mean of -14%, however this did not reach statistical significance (p=0.09). There were no statistically significant changes in HDL-C or triglycerides with any of the active treatment groups vs. placebo.

**Pharmacokinetics:** The mean (%CV) pharmacokinetic parameters and statistical comparison of the log-transformed Cmax and AUC values for cerivastatin and its metabolites are presented in the following table:

| Parameter | Unit | Ezetimibe + Cerivastatin | Cerivastatin | Relative Bioavailability[a] | 90% Confidence Interval |
|---|---|---|---|---|---|
| | | | Cerivastatin | | |
| Cmax | ng/mL | 3.61 (27) | 2.72 (32) | 133 | 101-176 |
| Tmax[b] | hr | 2.00 [redacted] | 3.00 [redacted] | -- | -- |
| AUC (0-24 hr) | ng·hr/mL | 22.3 (33) | 18.1 (42) | 124 | 88-175 |
| | | | Hydroxycerivastastin | | |
| Cmax | ng/mL | 0.45 (23) | 0.37 (34) | 123 | 95-161 |
| Tmax[b] | hr | 6.00 [redacted] | 6.00 [redacted] | -- | -- |
| AUC (0-24 hr) | ng·hr/mL | 4.57 (30) | 4.06 (45) | 117 | 85-162 |
| | | | O-desmethylcerivastatin | | |
| Cmax | ng/mL | 0.16 (37) | 0.14 (34) | 111 | 81-151 |
| Tmax[b] | hr | 3.00 [redacted] | 3.00 [redacted] | -- | -- |
| AUC (0-24 hr) | ng·hr/mL | 1.25 (34) | 1.25 (60) | 108 | 76-153 |

a: Ratio of the mean value of Treatment A (Ezetimibe + Cerivastatin) to Treatment B (Cerivastatin).

b: Median (range).

n=8 per treatment

**Title of the Study:** SCH 58235: Assessment of a Multiple-Dose Drug Interaction Between SCH 58235 and Cerivastatin in Healthy Volunteers (Protocol No. P00754)

There were no significant differences in the mean cerivastatin and active metabolite pharmacokinetic parameters (Cmax and AUC) between the two treatments, considering the parallel study design, small sample size (n=8 per group), and considerable overlap in the data. The relative oral bioavailability and the corresponding 90% confidence intervals (90% CI) based on the log-transformed AUC values were 124% (88-175%), 117% (85-162%) and 108% (76-153%) for cerivastatin, hydroxycerivastatin and O-desmethylcerivastatin, respectively. The point estimate and the corresponding 90% CI for the log-transformed Cmax values were 133% (101-176%), 123% (95-161%) and 111% (81-151%) for cerivastatin, hydroxycerivastatin, and O-desmethylcerivastatin, respectively.

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

| Parameter | Unit | Cerivastatin + Ezetimibe | Ezetimibe | Relative Bioavailability[a] | 90% Confidence Interval |
|---|---|---|---|---|---|
| | | | Total Ezetimibe | | |
| Cmax | ng/mL | 81.6 (24) | 84.2 (36) | 99.7 | 76-130 |
| Tmax[b] | hr | 1.0 | 1.0 | -- | -- |
| AUC(0-24hr) | ng·hr/mL | 727 (26) | 733 (32) | 100 | 78-129 |
| | | | Conjugated Ezetimibe | | |
| Cmax | ng/mL | 79.0 (24) | 80.8 (39) | 102 | 76-135 |
| Tmax[b] | hr | 1.0 | 1.0 | -- | -- |
| AUC(0-24hr) | ng·hr/mL | 676 (26) | 652 (36) | 106 | 81-139 |
| | | | Ezetimibe | | |
| Cmax | ng/mL | 4.06 (34) | 5.71 (30) | 69.5 | 50-96 |
| Tmax[b] | hr | 6.0 | 6.0 | -- | -- |
| AUC(0-24hr) | ng·hr/mL | 50.5 (29) | 80.9 (36) | 63.4 | 47-86 |

a: Ratio of the mean value of Treatment A (Ezetimibe + Cerivastatin) to Treatment C (Ezetimibe).

b: Median (range).

n=8 per group.

Cerivastatin co-administered with ezetimibe had no significant effect on the pharmacokinetics of ezetimibe, based on total ezetimibe Cmax and AUC concentrations. The point estimates (90% CI) based on the log-transformed AUC values for total and conjugated ezetimibe were 100% (78-129%) and 106% (81-139%), respectively. Co-administration of cerivastatin with ezetimibe resulted in an approximately 38% decrease in the exposure to ezetimibe (based on non-transformed AUC), however, there was considerable overlap of the data. The point estimates (90% CI) for log-transformed Cmax and AUC values were 69.5% (50-96%) and 63.4% (47-86%), respectively. The point estimates (90% CI) for total ezetimibe were within 50-200%, suggesting a lack of clinically significant interaction.

**Title of the Study:** SCH 58235: Assessment of a Multiple-Dose Drug Interaction Between SCH 58235 and Cerivastatin in Healthy Volunteers (Protocol No. P00754)

**CONCLUSIONS:**

- Ezetimibe (SCH 58235) administered at a daily dose of 10 mg concurrently with cerivastatin 0.3 mg for 14 consecutive days to healthy hypercholesterolemic subjects was safe and well tolerated.
- Cerivastatin 0.3 mg, ezetimibe 10 mg, and the co-administration of cerivastatin 0.3 mg and ezetimibe 10 mg caused significantly ($p \leq 0.03$) greater mean percent reductions in LDL-C and total-cholesterol than placebo.
- The co-administration of cerivastatin 0.3 mg and ezetimibe 10 mg caused a significantly ($p=0.02$) greater mean percent reduction in LDL-C than cerivastatin 0.3 mg alone, with a mean reduction of 19% more for the combination treatment.
- The co-administration of cerivastatin 0.3 mg and ezetimibe 10 mg achieved a greater mean percent reduction of 14% in LDL-C than ezetimibe 10 mg alone, however this did not reach statistical significance ($p=0.09$).
- Ezetimibe did not significantly alter the pharmacokinetics of cerivastatin and its metabolites, hydroxycerivastatin and O-desmethylcerivastatin. Cerivastatin had no significant effect on the bioavailability of ezetimibe, based on total ezetimibe AUC.
- There was no clinically significant pharmacokinetic drug interaction between cerivastatin and ezetimibe.

| | |
|---|---|
| **Title of the Study:** | SCH 58235: Assessment of a Multiple-Dose Drug Interaction Between SCH 58235 and Fluvastatin in Healthy Volunteers (Protocol No. P00755) |
| **Investigator(s):** | [ ] |
| **Study Center:** | |
| **Publication(s):** | Kosoglou T, Meyer I, Musiol B, Anderson L, Reyderman L, Statkevich P, et al. Pharmacodynamic interaction between fluvastatin and ezetimibe has favorable clinical implications [abstract P171]. Atherosclerosis Suppl 2001;2(2):89. |
| **Studied Period:** | 02 MAR 2000 to 20 JUN 2000 — **Clinical Phase:** 1 |

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

**Methodology:** This was a single-center, randomized, evaluator-blind, placebo-controlled, multiple-dose parallel-group study in healthy, hypercholesterolemic volunteers. The study consisted of an outpatient Screening phase of up to 4 weeks, an outpatient NCEP Step 1 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 1 Diet was maintained. On Day 1, after an overnight fast, each subject received one of the following four treatments (n=8/treatment): **Treatment A**: fluvastatin 20 mg plus ezetimibe 10 mg; **Treatment B**: fluvastatin 20 mg; **Treatment C**: ezetimibe 10 mg; **Treatment D**: placebo. All doses were administered orally with 200 mL of noncarbonated, 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 pharmacodynamic, pharmacokinetic, and safety evaluations. Blood samples for pharmacodynamic evaluation (LDL-C, total-C, HDL-C, triglycerides) were collected at Screening and on Day -1, and just prior to dosing on Days 1, 7, and 14 and Day 15 (24 hours after the last dose of study treatment). Subjects fasted for at least 8 hours prior to the blood sample collection for the pharmacodynamic evaluations. Lipid concentrations were determined using commercially available direct quantitative assay methods [redacted]. 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. Blood samples for fluvastatin and ezetimibe 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. Plasma fluvastatin concentrations were determined using a [redacted] with a lower limit of quantitation (LOQ) of [redacted] and a linear range of [redacted] Plasma ezetimibe (unconjugated) and total ezetimibe (ezetimibe plus conjugated ezetimibe) concentrations were determined using [redacted] assays with LOQs of [redacted], and the linear ranges of [redacted] and [redacted] 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.

**Number of Subjects:** Thirty-two volunteers were enrolled and completed the study as planned.

**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, 10 mg, oral, Batch No. 75882-090.

**Reference Therapy, Dose, Mode of Administration, Batch No(s):** Placebo tablets matching ezetimibe, oral, Batch No. 75882-062; Fluvastatin (LOCOL® 20 manufactured by Novartis Pharma GmbH, Nürnberg, Germany) capsules, 20 mg, oral, Lot No. B9004, expiration date April 2002.

**Title of the Study:** SCH 58235: Assessment of a Multiple-Dose Drug Interaction Between SCH 58235 and Fluvastatin in Healthy Volunteers (Protocol No. P00755)

**Duration of Treatment:** Ezetimibe 10 mg tablets with fluvastatin 20 mg capsule, fluvastatin 20 mg capsule, ezetimibe 10 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 predose 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 coadministration of ezetimibe and fluvastatin was LDL-C. The potential for a pharmacokinetic interaction between ezetimibe and fluvastatin was assessed by evaluating the pharmacokinetic parameters (Cmax and AUC) of fluvastatin, ezetimibe, conjugated ezetimibe, and total ezetimibe on Day 14 of treatment.

**Statistical Methods:** Summary statistics including means and standard errors (SE) 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 4 treatment groups at Baseline (Day 1), Day 7, Day 14, and Day 15. Pairwise comparisons 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 ≥50%, and the distribution of subjects in each category was 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 with one factor (treatment) was performed on the original scale and log-transformed Cmax and AUC values to evaluate the effect of ezetimibe on the pharmacokinetics of fluvastatin. The relative oral bioavailability of ezetimibe or fluvastatin administered in combination relative to each drug administered alone was expressed as the Cmax and AUC ratio of the treatments based on log-transformed data. Ninety percent confidence intervals for these estimates of relative bioavailability and the power to detect a 20% difference between treatment means for an $\alpha$ level of 0.05 (two-tailed) were computed.

**SUMMARY-CONCLUSIONS:**

**RESULTS:**

**Clinical Pharmacology:**

**Safety:** Overall 8 subjects (25%) reported treatment emergent adverse events that included headache, dizziness, diarrhea, loose stools, and pharyngitis. The incidence of adverse events was similar among the four treatments groups. All adverse events were considered mild in severity and resolved spontaneously. Most of the adverse events reported were considered by the investigator to be possibly related to study medication. 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.

**Pharmacodynamics:** The mean (SE) percent change from Baseline in serum lipid concentrations following once-daily oral administration of fluvastatin 20 mg in combination with ezetimibe 10 mg, fluvastatin 20 mg, ezetimibe 10 mg or placebo administered for 14 days to healthy hypercholesterolemic volunteers is shown in the following table:

| Treatment | Day | LDL-C | Total-C | HDL-C | Triglycerides |
|---|---|---|---|---|---|
| Fluvastatin 20 mg + Ezetimibe 10 mg (n=8) | 7 | -32.8 (3.36) | -22.6 (2.01) | -19.0 (5.08) | 0.92 (12.4) |
| | 14 | -32.0 (3.69) | -25.3 (2.98) | -8.21 (5.08) | -3.94 (10.4) |
| Fluvastatin 20 mg (n=8) | 7 | -13.5 (6.79) | -10.2 (3.86) | -12.1 (4.62) | 2.83 (9.29) |
| | 14 | -12.8 (6.55 | -12.0 (3.29) | -11.1 (4.47) | 6.61 (11.8) |
| Ezetimibe 10 mg (n=8) | 7 | -25.0 (4.44) | -16.5 (2.47) | -19.2 (2.94) | 3.52 (6.83) |
| | 14 | -20.2 (4.35) | -14.6 (3.40) | -14.8 (4.83) | 1.07 (14.4) |
| Placebo (n=8) | 7 | -16.2 (3.35) | -7.15 (2.61) | -17.2 (2.79) | 13.28 (9.04) |
| | 14 | -0.64 (3.41) | 0.21 (3.35) | -12.1 (3.62) | 5.38 (14.7) |

**Title of the Study:** SCH 58235: Assessment of a Multiple-Dose Drug Interaction Between SCH 58235 and Fluvastatin in Healthy Volunteers (Protocol No. P00755)

Ezetimibe 10 mg significantly ($p \leq 0.01$) decreased total-cholesterol and LDL-C concentrations compared to placebo at Day 14. Fluvastatin 20 mg also caused a significant ($p=0.01$) reduction in total-cholesterol and a decrease in LDL-C at Day 14 compared to placebo, however the decrease in LDL-C did not reach statistical significance ($p=0.08$). The coadministration of ezetimibe 10 mg and fluvastatin 20 mg caused significantly ($p \leq 0.01$) greater mean percent reductions in LDL-C and total-cholesterol than fluvastatin 20 mg alone or placebo at Day 14. The mean percent reductions in LDL-C were 32%, 13%, 20%, and 1% for the combination of fluvastatin and ezetimibe, fluvastatin alone, ezetimibe alone, and placebo, respectively. The coadministration of fluvastatin and ezetimibe resulted in a statistically ($p=0.01$) greater incremental mean percent reduction of 19% in LDL-C than fluvastatin 20 mg alone. Furthermore, 4/8 subjects in the fluvastatin 20 mg plus ezetimibe 10 mg treatment group achieved a 35 to 50% reduction in LDL-C on Day 14, compared to 1/8 subjects treated with fluvastatin or ezetimibe alone, and 0/8 subjects treated with placebo. There were no statistically significant changes in HDL-C or triglycerides with any of the active treatments vs. placebo. In this inpatient study HDL-C levels tended to decrease in all treatment groups and are likely due to restricted physical activity.

**Pharmacokinetics:** The mean (%CV) pharmacokinetic parameters and statistical comparison of the log-transformed Cmax and AUC values for fluvastatin are presented in the table below:

| Parameter | Unit | Fluvastatin 20 mg + Ezetimibe 10 mg | Fluvastatin 20 mg | Relative Bioavailability[a] | 90% Confidence Interval |
|---|---|---|---|---|---|
| Cmax | ng/mL | 62.2 (34) | 94.1 (68) | 73.0 | 49-109 |
| Tmax[b] | hr | 0.75 | 1.0 | -- | -- |
| AUC(tf) | ng·hr/mL | 92.4 (27) | 183 (75) | 61.1 | 38-97 |

a: Ratio of the mean value of Treatment A (Ezetimibe + Fluvastatin) to Treatment B (Fluvastatin).

b: Median value (range).

n=8 per treatment.

The relative oral bioavailability based on the log-transformed Cmax and AUC values for fluvastatin was 73 and 61.1%, respectively, for fluvastatin coadministered with ezetimibe vs. fluvastatin alone. The corresponding 90% confidence intervals for these point estimates were 49-109% and 38-97% based on the log-transformed Cmax and AUC, respectively. The apparently large mean differences for Cmax and AUC values are primarily due to the two pharmacokinetic outliers. Otherwise, there is considerable overlap in the data and the mean differences are minimal. The range of confidence intervals and the low power is due to the high intersubject variability in the Cmax and AUC values (%CV range from 27 and 75%), the sample size (n=8 subjects/group) and the parallel study design.

The mean (%CV) pharmacokinetic parameters and statistical comparison of the log-transformed Cmax and AUC values for total ezetimibe, conjugated ezetimibe, and ezetimibe are presented in the table below:

**Title of the Study:** SCH 58235: Assessment of a Multiple-Dose Drug Interaction Between SCH 58235 and Fluvastatin in Healthy Volunteers (Protocol No. P00755)

| Parameter | Unit | Fluvastatin 20 mg + Ezetimibe 10 mg | Ezetimibe 10 mg | Relative Bioavailability[a] | 90% Confidence Interval |
|---|---|---|---|---|---|
| | | Total Ezetimibe | | | |
| Cmax | ng/mL | 77.1 (41) | 71.0 (31) | 107 | 78-148 |
| Tmax[b] | hr | 1.00 | 1.00 | – | – |
| AUC(0-24 hr) | ng·hr/mL | 618 (57) | 692 (30) | 81.0 | 54-122 |
| | | Conjugated Ezetimibe | | | |
| Cmax | ng/mL | 73.2 (43) | 68.7 (33) | 105 | 75-147 |
| Tmax[b] | hr | 1.00 | 1.00 | – | – |
| AUC(0-24 hr) | ng·hr/mL | 556 (61) | 636 (33) | 79.3 | 52-122 |
| | | Ezetimibe | | | |
| Cmax | ng/mL | 4.71 (35) | 4.04 (24) | 114 | 89-146 |
| Tmax[b] | hr | 4.00 | 7.00 | – | – |
| AUC(0-24 hr) | ng·hr/mL | 62.0 (47) | 56.2 (19) | 99.9 | 69-144 |
| CL/F | L/hr | 211 (68) | 185 (23) | – | – |

a: Ratio of the mean value of Treatment A (Ezetimibe + Fluvastatin) to Treatment C (Ezetimibe).

b: Median value (range).

n=8 per treatment.

Fluvastatin coadministered with ezetimibe had no clinically significant effect on the pharmacokinetics of ezetimibe. The relative oral bioavailability based on the log-transformed Cmax and AUC values were 105-114% and 79-100%, respectively, for fluvastatin coadministered with ezetimibe vs. ezetimibe alone. The corresponding 90% confidence intervals for these point estimates were 75-148% and 52-144% based on the log-transformed Cmax and AUC, respectively.

**CONCLUSIONS:**

- Ezetimibe (SCH 58235) administered at a daily dose of 10 mg concurrently with fluvastatin 20 mg for 14 consecutive days to healthy subjects with hypercholesterolemia was safe and well tolerated.
- Ezetimibe caused significantly ($p \leq 0.01$) greater percent reductions in LDL-C and total-cholesterol compared to placebo, without significantly affecting serum HDL-C or triglycerides.
- Fluvastatin 20 mg caused a significant ($p=0.01$) reduction in total-cholesterol and a decrease in LDL-C compared to placebo, however the decrease in LDL-C did not reach statistical significance ($p=0.08$).
- The coadministration of fluvastatin 20 mg with ezetimibe caused significantly ($p \leq 0.01$) greater percent reductions in LDL-C and total-cholesterol compared to fluvastatin 20 mg alone or placebo, without significantly affecting serum HDL-C or triglycerides.
- The coadministration of fluvastatin and ezetimibe caused a significantly ($p=0.01$) greater percent reduction in serum LDL-C than fluvastatin 20 mg alone, with a mean additional reduction of 19% more for the combination treatment.
- Fluvastatin had no clinically significant effect on the pharmacokinetics of ezetimibe. On average, ezetimibe appeared to decrease the rate and extent of fluvastatin bioavailability, however, this is likely due to the parallel study design and two pharmacokinetic outliers.

| | |
|---|---|
| **Title of the Study:** | SCH 58235: Assessment of a Multiple-Dose Drug Interaction Between SCH 58235 and Fenofibrate in Hypercholesterolemic Volunteers (Protocol No. P00753) |
| **Investigator(s):** | Michel Guillaume, M.D. |
| **Study Center:** | Aster-Cephac, 3 & 5 rue Eugene Millon, 75015 Paris, France |
| **Publication(s):** | Kosoglou T, Guillaume M, Sun S, Pember LJC, Reyderman L, Statkevich P, et al. Pharmacodynamic interaction between fenofibrate and the cholesterol absorption inhibitor ezetimibe [abstract W6.1]. Atherosclerosis Suppl 2001;2(2):38.<br>Kosoglou T, Fruchart J-C, Guillaume M, Pember LJC, Sun S, Picard G, et al. Coadministration of ezetimibe and fenofibrate leads to favorable effects on Apo CIII and LDL subfractions (abstract P172). Atherosclerosis Suppl 2001;2(2):89. |
| **Studied Period:** | 08 FEB 2000 to 24 MAY 2000 **Clinical Phase:** 1 |
| **Objective:** | The primary objectives of this study were to evaluate the pharmacodynamic effects and safety of the coadministration of ezetimibe (SCH 58235) and fenofibrate in healthy hypercholesterolemic subjects at clinically-relevant doses. A secondary objective was to evaluate the potential for a pharmacokinetic drug interaction between ezetimibe and fenofibrate. |

**Methodology:** This was a randomized, investigator/evaluator-blind, placebo-controlled, multiple-dose parallel-group study in healthy, hypercholesterolemic subjects (Screening LDL-C ≥130 mg/dL [3.37 mmol/L]). The study consisted of an outpatient Screening phase of up to 4 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. Beginning in the morning of Day 1, after an overnight fast, each subject received one of the following four treatments (n=8/treatment): **Treatment A**: fenofibrate 200 mg plus ezetimibe 10 mg; **Treatment B**: fenofibrate 200 mg; **Treatment C**: ezetimibe 10 mg; and **Treatment D**: placebo. All doses were administered orally with 200 mL of noncarbonated, room-temperature water, once-daily in the morning for 14 consecutive days. Subjects continued fasting until two hours postdose, at which time standardized meals (NCEP) 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, on Days -1, 1 (Baseline), 7, 14, and 15 (24 hours after the last dose of study treatment). In addition to these evaluations, a 10 mL blood sample was collected predose on Days 1, 7, and 14 and the resulting plasma sample was to be assayed for lipoprotein particle size distribution. Subjects fasted for at least eight hours prior to the blood sample collection. Lipid concentrations were determined using commercially available direct quantitative assay methods [redacted]. Serum apolipoproteins, lipoproteins containing apolipoproteins, and lipid subfractions were determined using validated assays.

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 fenofibrate (fenofibric acid) and ezetimibe 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. Plasma concentrations of fenofibric acid were determined using a [redacted] method with an LOQ of [redacted] and a concentration of [redacted] Plasma ezetimibe (unconjugated) and total ezetimibe (ezetimibe plus conjugated ezetimibe) concentrations were determined using [redacted] assays with the lower limits of quantitation (LOQ) of [redacted] plasma, respectively. The concentration ranges were [redacted] 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.

**Title of the Study:** SCH 58235: Assessment of a Multiple-Dose Drug Interaction Between SCH 58235 and Fenofibrate in Hypercholesterolemic Volunteers (Protocol No. P00753)

**Number of Subjects:** Thirty-three subjects were enrolled and 32 completed the study. One subject (Subject No. 30, allocated to Treatment C [ezetimibe 10 mg]) withdrew for personal reasons unrelated to the study and was replaced.

**Diagnosis and Criteria for Inclusion:** Adult male and female volunteers between 18-50 years of age inclusive and having a Body Mass Index (BMI) between 19-31 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), and have a Screening LDL-C ≥130 mg/dL (3.37 mmol/L). 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, 10 mg, oral, Batch No. 75882-090.

**Reference Therapy, Dose, Mode of Administration, Batch No(s):** Placebo tablets matching ezetimibe, 0 mg, oral, Batch No. 75882-062. Fenofibrate (LIPANTHYL®, Laboratoires Fournier SCA, Dijon, France) capsules, 200 mg, oral, Batch No. 61136, expiration date November 2002.

**Duration of Treatment:** Each subject who completed the study received either ezetimibe 10 mg tablet with one fenofibrate 200 mg capsule, fenofibrate 200 mg capsule, ezetimibe 10 mg tablet, or placebo tablets 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 eight hours prior to the blood sample collection) serum lipids (LDL-C, total-C, HDL-C, triglycerides) collected predose 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 coadministration of ezetimibe and fenofibrate was LDL-C. The potential for a pharmacokinetic interaction between ezetimibe and fenofibrate was assessed by evaluating the pharmacokinetic parameters (Cmax and AUC) of fenofibric acid, ezetimibe, conjugated ezetimibe, and total ezetimibe 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 four treatment groups at Baseline, Day 7, Day 14, and Day 15. Pairwise comparisons of fenofibrate 200 mg alone versus placebo, ezetimibe 10 mg alone versus placebo, and the combination of ezetimibe/fenofibrate versus each individual arm were tested using the least square mean procedures. In addition, percent changes in LDL-cholesterol were categorized as follows: <10%, 10 to <25%, 25 to <35%, 35 to <50%, and ≥50%, and the distribution of subjects in each category were tabulated. The probability levels presented on all tables are nominal levels.

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 on Day 14. ANOVA was performed on both original scale and log-transformed Cmax and AUC values to evaluate the oral bioavailability of either ezetimibe or fenofibrate in combination relative to each drug administration alone. The point estimate was expressed as the percent Cmax and AUC ratio of Treatments A to C, or A to B based on the log-transformed data for ezetimibe and fenofibric acid, respectively. 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:** Overall, 9 subjects (27%) reported treatment emergent adverse events, the most common being gastrointestinal complaints (constipation, diarrhea, eructation, abdominal distension, and abdominal pain), headache, and paresthesias. Vasovagal reactions were reported for two subjects, however these were not considered by the investigator to be related to treatment. The incidence of adverse events was similar among the four treatments. All adverse events were mild to moderate in severity and resolved spontaneously. No concomitant medication was used by any subject during this study. No subject discontinued participation in this study due to adverse events. 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.

**Title of the Study:** SCH 58235: Assessment of a Multiple-Dose Drug Interaction Between SCH 58235 and Fenofibrate in Hypercholesterolemic Volunteers (Protocol No. P00753)

**Pharmacodynamics:** The mean (SE) Day 14 percent (%) change from Baseline in serum lipids following once-daily oral administration of ezetimibe 10 mg alone, fenofibrate 200 mg alone, the coadministration of fenofibrate 200 mg and ezetimibe 10 mg or placebo for 14 days to healthy hypercholesterolemic subjects is shown in the table below:

| Treatment | LDL-C | Total-C | HDL-C | TG |
|---|---|---|---|---|
| Placebo (n=8) | -10.1 (4.78) | -8.38 (3.97) | -14.1 (2.18) | 19.1 (13.9) |
| Ezetimibe 10 mg (n=8) | -22.3 (5.66)[c] | -19.6 (4.00)[b] | -13.3 (4.40) | -4.57 (12.8) |
| Fenofibrate 200 mg (n=8) | -13.5 (3.11) | -13.0 (2.43) | -6.09 (3.63) | 0.28 (11.4) |
| Fenofibrate 200 mg + Ezetimibe 10 mg (n=8) | -36.3 (3.48)[a,d,f] | -27.8 (1.69)[a,d] | -1.97 (4.67)[b,f] | -32.4 (4.50)[a,e] |

a: $p<0.01$ vs. placebo.

b: $p\leq0.03$ vs. placebo

c: $p=0.06$ vs. placebo.

d: $p<0.01$ vs. fenofibrate 200 mg.

e: $p=0.05$ vs. fenofibrate 200 mg.

f: $p\leq0.05$ vs. ezetimibe 10 mg.

The administration of fenofibrate 200 mg caused a small decrease in LDL-C concentrations but this effect was not different from placebo ($p>0.5$). Ezetimibe 10 mg significantly ($p=0.04$) decreased LDL-C concentrations on Day 7 vs. placebo, but this effect was not achieved on Day 14 ($p=0.06$). The coadministration of fenofibrate 200 mg and ezetimibe 10 mg caused a significantly greater ($p<0.05$) mean percent reduction in LDL-C compared to either drug alone or placebo, with a mean Day 14 reduction of approximately 23% and 14% more for the combination treatment vs. fenofibrate or ezetimibe alone, respectively. Furthermore, 6 of the 8 subjects in the fenofibrate plus ezetimibe treatment group achieved ≥35% reduction in LDL-C on Day 14, compared to 0/8 treated with fenofibrate alone and 2/8 treated with ezetimibe alone. The administration of fenofibrate 200 mg had no significant effect ($p>0.3$) on total-C concentrations vs. placebo. Ezetimibe 10 mg caused a significantly ($p\leq0.02$) greater mean percent reduction in total-C compared to placebo. The coadministration of fenofibrate plus ezetimibe caused a significantly greater ($p\leq0.05$) mean percent reduction in total-C and triglycerides compared to fenofibrate alone or placebo. In this inpatient study HDL-C levels tended to decrease in all treatment groups, likely due to restricted physical activity. Of note, the decrease in HDL-C levels was less in the coadministration treatment group compared to the ezetimibe alone or placebo treatment groups ($p\leq0.05$).

The mean (SE) Day 14 percent (%) change from Baseline in serum apolipoproteins and LDL subfractions is shown in the table below:

| Treatment | Apo C-III | Apo A-I | Lp A-I | Lp A-I:A-II | LDL-I | LDL-II | LDL-III |
|---|---|---|---|---|---|---|---|
| Placebo (n=8) | 4.36 (8.95) | 3.43 (11.6) | -16.2 (4.00) | 12.7 (17.9) | -8.90 (9.15) | -5.96 (13.4) | 5.59 (8.39) |
| Ezetimibe 10 mg (n=8) | -20.9 (4.24) | -10.1 (3.02) | -20.5 (3.92) | -5.36 (4.41) | -27.4 (8.16) | -20.9 (6.82) | -7.89 (3.91) |
| Fenofibrate 200 mg (n=8) | -12.5 (4.87) | 2.48 (2.98) | -21.3 (7.28) | 17.7 (5.28) | -27.0 (9.30) | -5.53 (14.0) | 7.99 (15.3) |
| Fenofibrate 200 mg + Ezetimibe 10 mg (n=8) | -27.4 (4.59) | -1.42 (3.18) | -25.0 (5.04) | 12.8 (4.89) | -28.4 (7.97) | -8.12 (13.6) | -36.9 (5.95) |

Ezetimibe alone and ezetimibe plus fenofibrate caused significantly greater reductions ($p\leq0.01$) in total apo C-III concentrations compared to placebo. The coadministration of fenofibrate and ezetimibe caused a significant reduction ($p\leq0.05$) in LDL-III compared to either drug alone or placebo. The changes in total A-I, Lp A-I, and Lp A-I:A-II concentrations are consistent with the decrease in HDL-C, and published fenofibrate data.

**Title of the Study:** SCH 58235: Assessment of a Multiple-Dose Drug Interaction Between SCH 58235 and Fenofibrate in Hypercholesterolemic Volunteers (Protocol No. P00753)

**Pharmacokinetics:** The mean (%CV) Day 14 pharmacokinetic parameters and statistical comparisons of the log-transformed Cmax and AUC values for ezetimibe after multiple-dose oral administration of ezetimibe 10 mg alone and with fenofibrate 200 mg in healthy hypercholestrolemic subjects are summarized in the table below:

| Parameter | Units | Treatment A Ezetimibe + Fenofibrate | | Treatment C Ezetimibe + Placebo | | Relative Bioavailability (%)[a] | 90% Confidence Interval |
|---|---|---|---|---|---|---|---|
| Total Ezetimibe | | | | | | | |
| Cmax | ng/mL | 114 | (34) | 70.1 | (36) | 164 | 117 - 230 |
| Tmax[b] | hr | 0.75 | | 1.0 | | – | – |
| AUC(0-24 hr) | ng·hr/mL | 1070 | (32) | 785 | (54) | 148 | 99 - 219 |
| Conjugated Ezetimibe | | | | | | | |
| Cmax | ng/mL | 110 | (35) | 66.5 | (37) | 168 | 119 - 237 |
| Tmax[b] | hr | 0.75 | | 1.0 | | – | – |
| AUC(0-24 hr) | ng·hr/mL | 997 | (34) | 717 | (58) | 152 | 101 - 230 |
| Ezetimibe | | | | | | | |
| Cmax | ng/mL | 5.13 | (47) | 4.50 | (41) | 114 | 79 - 164 |
| Tmax[b] | hr | 6.0 | | 4.5 | | -- | – |
| AUC(0-24 hr) | ng·hr/mL | 72.9 | (48) | 68.6 | (37) | 106 | 72 - 154 |

a: Ratio of the mean value for Treatment A (Ezetimibe + Fenofibrate) to Treatment C (Ezetimibe + Placebo).

b: Median (range).

n=8 per treatment.

The coadministration of ezetimibe and fenofibrate had no apparent effect on ezetimibe concentrations but resulted in an approximately 50% mean increase in the exposure to total and conjugated ezetimibe (based on log-transformed AUC); the magnitude of this effect is not considered to be clinically significant. Due to the parallel study design, small sample size (n=8 per group) and moderate intersubject variability, there was considerable overlap in the data.

Ezetimibe was rapidly absorbed and extensively conjugated following oral administration. Plasma ezetimibe and total ezetimibe concentrations exhibited multiple peaks, suggesting enterohepatic recycling. Ezetimibe exposure was 3-14% of the total ezetimibe based on the ratio of plasma AUC values.

The mean (%CV) Day 14 fenofibric acid pharmacokinetic parameters and statistical comparison based on log-transformed Cmax and AUC values are summarized in the following table:

| Parameter | Units | Treatment A Ezetimibe + Fenofibrate | | Treatment B Fenofibrate + Placebo | | Relative Bioavailability (%)[a] | 90% Confidence Interval |
|---|---|---|---|---|---|---|---|
| Cmax | ng/mL | 5798 | (33) | 5317 | (28) | 107 | 80 - 143 |
| Tmax[b] | hr | 6.0 | | 3.0 | | – | – |
| AUC(0-24 hr) | ng·hr/mL | 108500 | (38) | 96726 | (31) | 111 | 78 - 158 |

a: Ratio of the mean value for Treatment A (Ezetimibe + Fenofibrate) to Treatment B (Fenofibrate + Placebo).

b: Median (range).

n=8 per treatment.

**Title of the Study:** SCH 58235: Assessment of a Multiple-Dose Drug Interaction Between SCH 58235 and Fenofibrate in Hypercholesterolemic Volunteers (Protocol No. P00753)

The coadministration of fenofibrate with ezetimibe had no apparent effect on the pharmacokinetics of fenofibric acid. The mean oral bioavailability (based on log-transformed AUC) of fenofibric acid after coadministration of fenofibrate and ezetimibe relative to fenofibrate administered alone was 111%.

**CONCLUSIONS:**

- Ezetimibe (SCH 58235) 10 mg administered with fenofibrate 200 mg once-daily for 14 days to healthy subjects with hypercholesterolemia was safe and well tolerated.
- The administration of fenofibrate 200 mg decreased LDL-C and total-C concentrations, but the effect was not significant ($p>0.3$) from placebo.
- Ezetimibe 10 mg significantly ($p<0.05$) decreased LDL-C and total-C concentrations vs. placebo, but the effect on LDL-C was not achieved on Day 14 ($p=0.06$).
- The coadministration of fenofibrate 200 mg and ezetimibe 10 mg caused a significantly greater ($p<0.01$) mean percent reduction in serum LDL-C, total-C, and triglycerides vs. placebo.
- The coadministration of fenofibrate 200 mg and ezetimibe 10 mg caused a significantly greater ($p<0.05$) percent reduction in serum LDL-C compared to either drug alone, with a mean additional reduction of 23% and 14% more for the combination treatment vs. fenofibrate 200 mg or ezetimibe 10 mg, respectively.
- The coadministration of ezetimibe and fenofibrate caused a significant ($p\leq0.05$) reductions in serum LDL-III subfraction and apolipoprotein C-III levels than either drug alone or placebo. Elevated levels of these subfractions are markers for increased risk of atherogenesis.
- Ezetimibe did not significantly alter the pharmacokinetics of fenofibrate. Fenofibrate had no clinically significant effect on the pharmacokinetics of ezetimibe.

| | |
|---|---|
| **Title of the Study:** | SCH 58235: Assessment of a Multiple-Dose Drug Interaction Between Ezetimibe and Cholestyramine in Healthy Hypercholesterolemic Subjects (Protocol No. P00776) |
| **Investigator(s):** | [redacted] |
| **Study Center:** | |
| **Publication(s):** | None |
| **Studied Period:** | 05 FEB 2001 to 23 MAY 2001 — **Clinical Phase:** 1 |
| **Objective:** | The primary objective was to evaluate the pharmacodynamic effects of the coadministration of cholestyramine and ezetimibe in healthy hypercholesterolemic subjects at clinically relevant doses. Secondary objectives were: 1) to evaluate the effect of cholestyramine on ezetimibe absorption, and, 2) to evaluate the incremental pharmacodynamic effects of simvastatin added to the coadministration of cholestyramine and ezetimibe. |

**Methodology:** This was a single-center, randomized, evaluator-blind, placebo-controlled, multiple-dose parallel-group study in healthy, hypercholesterolemic volunteers. The study consisted of an outpatient screening phase of up to 4 weeks, an outpatient NCEP Step 1 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 1 Diet was maintained. On Day 1, after an overnight fast, each subject received one of the following five treatments (n=8/treatment): **Treatment A**: Ezetimibe placebo (two tablets) PO QD at 8 AM, followed by anhydrous cholestyramine 4 g (one packet) suspended in 200 mL of orange juice, PO Q12H at 9 AM and 9 PM; **Treatment B**: Ezetimibe 10 mg (one tablet) plus ezetimibe placebo (one tablet) PO QD at 8 AM, followed by 200 mL of orange juice, PO Q12H at 9 AM and 9 PM; **Treatment C**: Ezetimibe 10 mg (one tablet) plus ezetimibe placebo (one tablet) PO QD at 8 AM, followed by anhydrous cholestyramine 4 g (one packet) suspended in 200 mL of orange juice, PO Q12H at 9 AM and 9 PM; **Treatment D**: Ezetimibe 10 mg (one tablet) plus simvastatin 20 mg (one tablet) PO QD at 8 AM, followed by anhydrous cholestyramine 4 g (one packet) suspended in 200 mL of orange juice, PO Q12H at 9 AM and 9 PM; or **Treatment E**: Ezetimibe placebo (two tablets) PO QD at 8 AM, followed by 200 mL of orange juice, PO Q12H at 9 AM and 9 PM. Tablets were administered orally with 200 mL of non-carbonated, room-temperature water. All doses were administered for 14 consecutive days. Cholestyramine oral suspension or orange juice was administered one hour after the administration of the tablets. Subjects continued fasting until 2 hours the 8 AM dose, 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 Day -1, and just prior to dosing on Days 1, 7, and 14 and Day 15 (24 hours after the last dose of study treatment). Subjects fasted for at least 8 hours prior to the blood sample collection. Lipid concentrations were determined using commercially available direct quantitative assay methods [redacted]

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.

Blood samples for ezetimibe pharmacokinetic evaluations 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. Plasma ezetimibe and total ezetimibe (ezetimibe plus conjugated ezetimibe) concentrations were determined using [redacted] assays with lower limits of quantitation (LOQ) of [redacted] and linear ranges of [redacted] 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.

**Number of Subjects:** Forty (40) subjects were enrolled and completed the study as planned.

**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

**Title of the Study:** SCH 58235: Assessment of a Multiple-Dose Drug Interaction Between Ezetimibe and Cholestyramine in Healthy Hypercholesterolemic Subjects (Protocol No. P00776)

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 (3.37 mmol/L). 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, 10 mg, oral, Batch No. 75882-090.

**Reference Therapy, Dose, Mode of Administration, Batch No(s):** Placebo tablets matching ezetimibe, oral, Batch No. 75882-062. Cholestyramine (QUESTRAN® Bristol-Myers Squibb, France) powder for oral suspension, 4 g, oral, Lot No. 4947, expiration date December 2003. Simvastatin (ZOCOR® MSD Merck Sharp & Dohme GmbH, Germany) tablets, 20 mg, oral, Lot No. 995849, Expiration Date October 2002.

**Duration of Treatment:** Cholestyramine 4 g Q12H, ezetimibe 10 mg QD, cholestyramine 4 g Q12H plus ezetimibe 10 mg QD, cholestyramine 4 g Q12H plus ezetimibe 10 mg QD and simvastatin 20 mg QD, or placebo were administered 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 predose 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 coadministration of cholestyramine and ezetimibe was LDL-C. The potential for a pharmacokinetic interaction of cholestyramine on ezetimibe was assessed by evaluating the pharmacokinetic parameters (Cmax and AUC) of ezetimibe, conjugated ezetimibe, and total ezetimibe on Day 14 of treatment.

**Statistical Methods:** Summary statistics including means and standard errors (SE) 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 5 treatment groups at baseline (Day 1), Day 7, Day 14, and Day 15. Pairwise comparisons 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 ≥50%, and the distribution of subjects in each category was tabulated. The probability levels presented on all tables are nominal levels.

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 Cmax and AUC values to evaluate the effect of cholestyramine on the pharmacokinetics of each ezetimibe. The relative oral bioavailability of ezetimibe given in combination with cholestyramine (Treatments C and D) compared to ezetimibe given alone (Treatment B) was expressed as the ratio of Treatments C or D to Treatment B based on log-transformed Cmax and AUC values. Additionally, the relative oral bioavailability of ezetimibe when given in combination with cholestyramine and simvastatin (Treatment D) vs. with cholestyramine only (Treatment C), was expressed as the ratio of Treatments D to Treatment C based on log-transformed Cmax and AUC values. Ninety percent (90%) confidence intervals for these estimates and the power to detect a 20% difference between treatment means for an $\alpha$ level of 0.05 (two-tailed) were computed.

**SUMMARY-CONCLUSIONS:**

**RESULTS:**

**Clinical Pharmacology:**

**Safety:**

Overall, 24 subjects (60%) reported treatment emergent adverse events, predominantly consisting of gastrointestinal system disorders which included flatulence, abdominal pain, and diarrhea. The incidence of subjects reporting adverse events was similar among the five treatments groups. The majority (16/24; 67%) of these subjects reported adverse events that were considered mild in severity, and the rest (8/24; 33%) reported adverse events that were considered moderate in severity. Six subjects received concomitant therapy for the treatment of their adverse events such as headache, dental and back pain, superficial vascular pain of the leg, constipation, and conjunctivitis. There were no severe or serious adverse events or deaths reported in this study. There were no discontinuations 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 tests, including those tests assessing muscle and liver function, except for one subject (Subject No. 27, a 42 year old woman allocated to cholestyramine plus ezetimibe) who had a transient increase in

SGPT (maximum 3.4 x the upper limit of normal [ULN]), as well as SGOT (2.1 x ULN) and GGT (1.2 x ULN). This subject's liver function tests normalized within 9 days of study completion.

**Pharmacodynamics:**

The mean (SE) percent change from baseline in serum lipid concentrations following oral administration of cholestyramine, ezetimibe, the coadministration of cholestyramine and ezetimibe with or without simvastatin, or placebo for 14 days to healthy hypercholesterolemic volunteers is shown in the following table:

| Treatment | Day | LDL-C | Total-C | HDL-C | Triglycerides |
|---|---|---|---|---|---|
| Cholestyramine 4 g Q12H (n=8) | 7 | -31.4 (3.10)[a] | -12.4 (2.99)[b] | -5.15 (2.39) | 60.27 (23.6) |
| | 14 | -22.5 (1.76)[a] | -10.1 (3.08) | -0.34 (7.11) | 84.59 (30.7) |
| Ezetimibe 10 mg QD (n=8) | 7 | -22.4 (3.70)[a] | -14.5 (1.71)[a] | -13.6 (2.96) | 6.93 (9.15) |
| | 14 | -11.6 (7.07) | -12.6 (4.17)[b] | -8.36 (8.35) | 17.82 (9.86) |
| Cholestyramine 4 g Q12H + Ezetimibe 10 mg QD (n=8) | 7 | -39.8 (3.35)[a,c] | -21.1 (2.64)[a,d] | -6.61 (2.64) | 55.31 (18.3)[c] |
| | 14 | -33.4 (4.18)[a,c] | -19.7 (3.46)[a] | 2.84 (8.44) | 49.52 (19.6) |
| Cholestyramine 4 g Q12H + Ezetimibe 10 mg QD + Simvastatin 20 mg QD (n=8) | 7 | -53.0 (4.74)[e] | -30.9 (4.49)[e] | -1.29 (5.39) | 18.95 (8.57) |
| | 14 | -48.5 (6.15)[f] | -30.1 (5.45) | 6.93 (10.2) | 21.79 (7.22) |
| Placebo (n=8) | 7 | -5.01 (3.48) | -2.49 (3.15) | -13.6 (5.33) | 32.71 (11.8) |
| | 14 | 0.64 (7.82) | 0.38 (3.78) | -12.4 (7.81) | 49.05 (20.1) |

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

b: $p \leq 0.03$ vs. placebo.

c: $p \leq 0.03$ vs. ezetimibe.

d: $p = 0.06$ vs. cholestyramine.

e: $p \leq 0.03$ vs. cholestyramine plus ezetimibe.

f: $p = 0.07$ vs. cholestyramine plus ezetimibe.

The administration of cholestyramine 4 g twice-daily caused significantly ($p \leq 0.01$) greater mean percent reductions in LDL-C compared to placebo. Ezetimibe 10 mg/day also significantly ($p < 0.01$) decreased LDL-C on Day 7 vs. placebo, but this effect was not significant ($p = 0.15$) on Day 14. The coadministration of cholestyramine and ezetimibe caused significantly ($p \leq 0.01$) greater mean percent reductions in LDL-C than ezetimibe alone or placebo. There was a trend towards greater percent reductions in LDL-C with the coadministration of cholestyramine and ezetimibe compared to cholestyramine alone, however the difference did not reach statistical significance ($p > 0.1$). The coadministration of cholestyramine, ezetimibe and simvastatin caused a significant ($p = 0.02$) incremental percent reduction in serum LDL-C on Day 7 compared to cholestyramine plus ezetimibe, but this effect did not reach statistical significance ($p = 0.07$) on Day 14. The mean additional reduction in LDL-C on Day 14 for the triple combination treatment was 15% more than the coadministration of cholestyramine plus ezetimibe. Seven of the 8 subjects in the cholestyramine plus ezetimibe treatment group achieved a ≥25% reduction in LDL-C on Day 14, compared to 3/8 in the cholestyramine alone treatment group, 3/8 in the ezetimibe alone treatment group, and 1/8 subjects treated with placebo. Of note, 5/8 subjects in the triple combination treatment group achieved a ≥50% reduction in LDL-C on Day 14.

The administration of cholestyramine 4 g twice-daily caused significantly ($p = 0.03$) greater mean percent reductions in total-C on Day 7 vs. placebo, but this effect was not significant ($p = 0.08$) on Day 14. Ezetimibe 10 mg/day caused significantly ($p \leq 0.03$) greater mean percent reductions in total-C vs. placebo. There was a trend towards greater percent reductions in total-C with the coadministration of cholestyramine and ezetimibe compared to either drug alone, however the difference did not reach statistical significance ($p > 0.1$). The coadministration of cholestyramine, ezetimibe and simvastatin caused a significant ($p = 0.03$) incremental percent reduction in serum total-C on Day 7 compared to cholestyramine plus ezetimibe, but this effect did not reach statistical significance ($p = 0.08$) on Day 14.

There were no statistically significant differences in the percent changes from baseline in HDL-C or triglycerides with any of the active treatments vs. placebo.

**Title of the Study:** SCH 58235: Assessment of a Multiple-Dose Drug Interaction Between Ezetimibe and Cholestyramine in Healthy Hypercholesterolemic Subjects (Protocol No. P00776)

**Pharmacokinetics:**

The mean (%CV) pharmacokinetic parameters of total ezetimibe, conjugated ezetimibe, and ezetimibe are presented in the table below:

| Parameter | Unit | Treatment B (Ezetimibe Alone) | | Treatment C (Cholestyramine + Ezetimibe) | | Treatment D (Cholestyramine + Ezetimibe + Simvastatin) | |
|---|---|---|---|---|---|---|---|
| | | Mean[a] | %CV | Mean[a] | %CV | Mean[a] | %CV |
| **Total Ezetimibe** | | | | | | | |
| Cmax | ng/mL | 76.5 | (40) | 72.8 | (36) | 91.2 | (34) |
| Tmax[b] | hr | 1.0 | [illegible] | 1.0 | [illegible] | 0.75 | [illegible] |
| AUC(0-24hr) | ng·hr/mL | 755 | (31) | 333 | (27) | 317 | (21) |
| **Conjugated Ezetimibe** | | | | | | | |
| Cmax | ng/mL | 72.8 | (43) | 71.6 | (36) | 88.6 | (35) |
| Tmax[b] | hr | 1.0 | [illegible] | 1.0 | [illegible] | 0.75 | [illegible] |
| AUC(0-24hr) | ng·hr/mL | 668 | (37) | 316 | (27) | 297 | (23) |
| **Ezetimibe** | | | | | | | |
| Cmax | ng/mL | 5.77 | (34) | 1.61 | (51) | 2.53 | (28) |
| Tmax[b] | hr | 8.0 | [illegible] | 0.5 | [illegible] | 0.5 | [illegible] |
| AUC(0-24hr) | ng·hr/mL | 86.7 | (33) | 17.0 | (34) | 20.6 | (36) |

a: n=8

b: Median (range).

The statistical comparison of the log-transformed Cmax and AUC values for total ezetimibe, conjugated ezetimibe, and ezetimibe are presented in the table below:

| Analyte | Parameter | Comparison[a] | Relative Bioavailability[b] (%) | Confidence Interval[c] |
|---|---|---|---|---|
| Ezetimibe | Cmax | C/B | 26.5 | 19-36 |
| | | D/B | 44.5 | 32-61 |
| | AUC(0-24 hr) | C/B | 19.6 | 15-26 |
| | | D/B | 23.5 | 18-31 |
| Conjugated Ezetimibe | Cmax | C/B | 101 | 73-140 |
| | | D/B | 127 | 91-176 |
| | AUC(0-24 hr) | C/B | 48.6 | 38-62 |
| | | D/B | 46.1 | 36-59 |
| Total Ezetimibe | Cmax | C/B | 96.4 | 70-132 |
| | | D/B | 123 | 90-169 |
| | AUC(0-24 hr) | C/B | 44.5 | 36-55 |
| | | D/B | 43.0 | 35-53 |

a: Ratio of the mean value for Treatment C (Cholestyramine + Ezetimibe) or Treatment D (Cholestyramine + Ezetimibe + Simvastatin) to Treatment B (Ezetimibe Alone).

b: Ratio of the mean values.

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

**Title of the Study:** SCH 58235: Assessment of a Multiple-Dose Drug Interaction Between Ezetimibe and Cholestyramine in Healthy Hypercholesterolemic Subjects (Protocol No. P00776)

Cholestyramine significantly (p=0.001) decreased the systemic exposure (based on AUC) to ezetimibe, conjugated ezetimibe, and total ezetimibe. The effect on ezetimibe bioavailability was more pronounced (mean reduction of approximately 80% based on log-transformed AUC) than the effect on total ezetimibe (mean reduction approximately 55%). Cholestyramine also significantly (p=0.001) reduced ezetimibe Cmax, but had no apparent effect on total ezetimibe Cmax. Enterohepatic recycling, as observed by multiple peaks in the plasma concentration-time profiles, was less apparent following coadministration of ezetimibe and cholestyramine as compared to ezetimibe alone. The pharmacokinetic data from this study are consistent with the in vitro binding of ezetimibe and ezetimibe-glucuronide to cholestyramine, resulting in less absorption and reabsorption of ezetimibe.

**CONCLUSIONS:**

- Ezetimibe (SCH 58235) 10 mg once-daily administered with cholestyramine 4 g twice-daily with or without concurrent simvastatin 20 mg once-daily for 14 days to healthy subjects with hypercholesterolemia was safe and well tolerated.
- The coadministration of cholestyramine 4 g Q12H and ezetimibe 10 mg caused significantly ($p \leq 0.03$) greater percent reduction in LDL-C compared to ezetimibe 10 mg alone or placebo, without significantly affecting serum HDL-C or triglycerides.
- There was a trend towards greater percent reductions in LDL-C and total-C with the coadministration of cholestyramine and ezetimibe compared to cholestyramine alone, however the difference did not reach statistical significance.
- The coadministration of cholestyramine, ezetimibe and simvastatin caused an incremental percent reduction in serum LDL-C compared to cholestyramine plus ezetimibe, with a mean additional reduction of 15% more for the triple combination treatment (p=0.07).
- Cholestyramine significantly decreased the systemic exposure to ezetimibe, conjugated ezetimibe, and total ezetimibe, with a mean reduction of approximately 55% in total ezetimibe bioavailability (based on AUC).
- The coadministration of the selective cholesterol absorption inhibitor ezetimibe and anion-exchange resins may lead to greater percent reductions in LDL-C than either drug alone. However, the triple combination of ezetimibe, a resin, and an HMG-CoA reductase inhibitor such as simvastatin may not cause greater reductions in LDL-C than the coadministration of ezetimibe or a resin plus a statin.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

MERCK RESEARCH LABORATORIES

SCH 58235
Ezetimibe, Tablet
Hypercholesterolemia

# CLINICAL STUDY REPORT
## I. SYNOPSIS

**PROTOCOL TITLE/NO.:** A Randomized, Double-Blind, Placebo-Controlled, 2-Period, Crossover Study to Evaluate Ezetimibe (SCH 58235) as an Inhibitor of Intestinal Cholesterol Absorption #P02484

**INVESTIGATOR(S)/STUDY CENTER:**

[redacted]

**PRIMARY THERAPY PERIOD:** 28-May-2001 to 06-Aug-2001. The study is complete. All investigator certified data was received in-house by 17-Sep-01. Frozen file: 12-Sep-2001.

**CLINICAL PHASE:** IIa

**DURATION OF TREATMENT:** Two 2-week treatment periods for a total of 4 weeks. A 2-week washout period separated each treatment period.

**OBJECTIVE(S):** Primary: To evaluate the effect of 2 weeks of treatment with ezetimibe 10 mg/day on intestinal cholesterol absorption in patients with mild-to-moderate hypercholesterolemia. Secondary: To evaluate the tolerability of short-term treatment with ezetimibe 10 mg/day. Exploratory: To evaluate whether ezetimibe 10 mg/day leads to changes in indices of cholesterol biosynthesis.

**STUDY DESIGN:** Single-center, randomized, double-blind, placebo-controlled, 2-period, crossover study. Following a 2-week placebo run-in period, eligible patients were randomized to 1 of 2 treatment sequences: either ezetimibe 10 mg/day in Treatment Period 1 followed by placebo in Treatment Period 2 or placebo in Treatment Period 1 followed by ezetimibe 10 mg/day in Treatment Period 2. A washout period of 2 weeks separated each treatment period.

**SUBJECT ACCOUNTING:**

| | |
|---|---|
| ENTERED: Total | 18 |
| Male (age range) | 18 (24 to 58) |
| COMPLETED: | 18 |
| DISCONTINUED: Total | 0 |

**DOSAGE/FORMULATION NOS.:** Oral administration of ezetimibe 10 mg or matching placebo tablet once daily in the morning during each of the 2 treatment periods. Oral administration of 1 placebo tablet in the morning during the placebo run-in and washout periods.

**DIAGNOSIS/INCLUSION CRITERIA:** Healthy adult men, 18 to 55 years of age, having a body mass index (BMI) between 19 $kg/m^2$ and 30 $kg/m^2$ with plasma low-density lipoprotein cholesterol (LDL-C) ≥130 mg/dL (3.36 mmol/L) and ≤180 mg/dL (4.65 mmol/L) and triglycerides (TG) ≤250 mg/dL (2.83 mmol/L). Patients were required to have ≥1 but not more than 2 bowel movements per day. The dietary intake of calculated cholesterol was required to be >200 mg/day but <500 mg/day.

**EVALUATION CRITERIA:** Primary Endpoint: Change in fractional cholesterol absorption following treatment with ezetimibe 10 mg/day for 2 weeks relative to placebo. Exploratory Endpoints: Fecal sterol balance estimates and plasma lathosterol concentrations were determined as indices of cholesterol synthesis (data not available). Lipid Endpoints: Percent change from baseline in LDL-C, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and TG following treatment with ezetimibe 10 mg/day for 2 weeks. Safety: Clinical evaluation including vital signs, ECG, and physical examinations. Laboratory safety tests including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatine kinase (CK). Clinical and laboratory safety evaluations were performed continuously during the study.

**STATISTICAL PLANNING AND ANALYSIS:** Fractional cholesterol absorption was analyzed using an analysis-of-variance (ANOVA) model appropriate for a 2-period, crossover design with terms sequence, patient within sequence, period, and treatment. A 90% confidence interval (CI) was computed for the geometric mean ratio (GMR) of treatment means (ezetimibe 10 mg/placebo). Fractional cholesterol absorption values were log transformed.

**RESULTS:**

**EFFICACY:** Primary Endpoint: Treatment with ezetimibe 10 mg/day for 2 weeks reduced fractional cholesterol absorption by 54% as compared with placebo. After 2 weeks of treatment with ezetimibe 10 mg/day or placebo, the geometric mean fractional cholesterol absorption values were 22.7% and 49.8%, respectively. The difference between ezetimibe 10 mg and placebo treatments was significant ($p<0.001$). The summary statistics and GMR with corresponding 90% CI for the fractional cholesterol absorption after 2 weeks of treatment with ezetimibe 10 mg/day or placebo are shown in the table below.

| Treatment | Geometric Mean | Between-Subject SD | Between Treatment p-Value | GMR | 90% CI for GMR |
|---|---|---|---|---|---|
| Ezetimibe 10 mg/day | 22.7 | 25.84 | <0.001 | 0.46 | (0.35, 0.60) |
| Placebo | 49.8 | 13.80 | | | |

Root mean square error (RMSE) from analysis of variance model=0.463 (within-subject variation).
GMR = Geometric mean ratio (ezetimibe/placebo).
CI = Confidence interval.
SD = Back-transformed standard deviation.

Exploratory Endpoints: Results for indices of cholesterol biosynthesis were not available for the preparation of this report. Lipid Endpoints: For LDL-C, LS mean changes from baseline after 2 weeks of treatment were -20.4% and 1.9% for ezetimibe 10 mg/day and placebo, respectively. The treatment difference between ezetimibe 10 mg/day and placebo in percent change from baseline to endpoint was significant for LDL-C, TC, and non-HDL-C concentrations ($p<0.001$) but was not significant for TG and HDL-C concentrations.

**SAFETY:** Treatment with ezetimibe 10 mg/day for 2 weeks was safe and well tolerated. There were no serious adverse experiences reported and no patients were discontinued because of adverse experiences. No patient experienced an elevation of ALT, AST >3 times ULN (upper limit of normal) or CK>5 times ULN during the study.

**CONCLUSIONS:** (1) Ezetimibe 10 mg/day significantly inhibited intestinal cholesterol absorption by 54% as compared with placebo. (2) Ezetimibe 10 mg/day significantly reduced plasma LDL-C and TC concentrations as compared with placebo. (3) Oral administration of ezetimibe 10 mg/day for 14 days was safe and well tolerated in healthy adult males with mild-to-moderate hypercholesterolemia.

**AUTHORS:** [redacted]

APPEARS THIS WAY
ON ORIGINAL

| | | |
|---|---|---|
| **Title of the Study:** | SCH 58235: Assessment of a Multiple-Dose Pharmacodynamic Drug Interaction Between SCH 58235 and Simvastatin in Healthy Volunteers (Protocol P00300) | |
| **Investigator(s):** | [redacted] | |
| **Publication(s):** | None | |
| **Studied Period:** | 06 APR 1999 to 09 JUN 1999 | **Clinical Phase:** I |

**Objective:** The objective of this study was to evaluate the safety and pharmacodynamic effects of the co-administration of SCH 58235 and simvastatin in healthy subjects at clinically relevant doses.

**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 three treatments (n=8/treatment): **Treatment A:** Simvastatin 20 mg + SCH 58235 10 mg; **Treatment B:** Simvastatin 20 mg + SCH 58235 placebo; and **Treatment C:** SCH 58235 10 mg + SCH 58235 placebo. 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 pharmacodynamic and safety evaluations. Blood samples for pharmacodynamic evaluation (LDL-C, total-C, HDL-C, triglycerides) were collected prior to the first dose (Day 1, Baseline) and just prior to the dose (0 hour) on Days 7, 14 and 15 (24 hours after the last dose of study treatment). Blood and urine samples for safety evaluation (CBC, blood chemistries, urinalysis) were collected prior to the first dose (Day -1, Baseline) and at the conclusion of the study (Day 15, 24 hours after the last dose of study treatment). In addition, blood samples were collected for safety evaluations (SGPT, SGOT, GGT, CPK, Alk. Phos.) pre-dose on Days 3, 7 and 10. Subjects were continuously observed and questioned throughout the study for possible occurrence of adverse events.

**Number of Subjects:** Twenty-four (24) volunteers were enrolled and completed the study as planned.

**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.

**Test Product, Dose, Mode of Administration, Batch No(s):** 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. 52123-048; Simvastatin (ZOCOR® 20, MSD) 20 mg, tablets, Lot No. 985681, Exp. Date October 2001.

**Duration of Treatment:** SCH 58235 10 mg tablets were administered alone or administered with simvastatin 20 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 treatment made up the population data set for the primary pharmacodynamic comparisons. Summary statistics and adverse reaction tabulation are included for all treated subjects. Demographic and Baseline variables are listed and summarized using descriptive statistics. These variables are also summarized for each treatment group.

**Statistical Methods:** Summary statistics including means, standard deviations or standard errors and coefficients of variation were provided for the demographic 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 models extracting treatment effect were performed to compare the 3 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 of every two treatments 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 >=50%, and the distribution of subjects in each category were tabulated.

| Title of the Study: | SCH 58235: Assessment of a Multiple-Dose Pharmacodynamic Drug Interaction Between SCH 58235 and Simvastatin in Healthy Volunteers (Protocol P00300) |
|---|---|

**SUMMARY-CONCLUSIONS:**

**RESULTS:**

**Clinical Pharmacology:**

**Safety:**

Ten (10) out of the 24 subjects enrolled (42%) reported treatment emergent adverse events, including headache, nausea, flatulence, diarrhea, and viral or bacterial infections. The incidence of adverse events was similar among the three treatments, with no evidence of increased AEs during co-administration of simvastatin and SCH 58235. Most adverse events were characterized as mild in intensity and resolved spontaneously. Two subjects complained of adverse events characterized as moderate in intensity and required additional therapy. One subject was treated with iodine dressings for paronychia (redness, tenderness and swelling at the base of a finger nail), and the other subject required treatment with acetaminophen for his headache. All adverse events resolved without sequelae. There were no serious or significant adverse events or deaths reported in this study.

**Pharmacodynamics:**

The mean (S.E.) percent change from Baseline in serum lipid concentrations following once-daily oral administration of simvastatin 20 mg alone, SCH 58235 10 mg alone (with placebo) or in combination administered for 14 days to healthy hypercholesterolemic volunteers is shown in the following table.

| Treatment | Day | LDL-C | Total-C | HDL-C | Triglycerides |
|---|---|---|---|---|---|
| Simvastatin 20 mg + SCH 58235 10 mg (n=8) | 7<br>14 | -48.4 (3.0)<br>-58.7 (3.3) | -36.1 (1.4)<br>-43.2 (3.5) | -13.5 (3.1)<br>-13.8 (3.6) | -11.2 (7.3)<br>-16.1 (5.3) |
| Simvastatin 20 mg + SCH 58235 placebo (n=8) | 7<br>14 | -32.9 (3.4)<br>-40.8 (3.7) | -21.7 (4.0)<br>-26.9 (2.9) | -11.0 (3.2)<br>-14.4 (3.7) | 6.6 (18.3)<br>-5.9 (16.8) |
| SCH 58235 10 mg + SCH 58235 placebo (n=8) | 7<br>14 | -25.8 (4.0)<br>-33.6 (3.7) | -16.4 (2.3)<br>-19.3 (3.9) | -13.8 (5.0)<br>-13.8 (5.6) | 12.3 (15.8)<br>3.1 (15.1) |

The administration of simvastatin 20 mg plus SCH 58235 10 mg caused a statistically ($p \leq 0.01$) greater mean percent reduction in LDL-C than either simvastatin 20 mg or SCH 58235 10 mg alone, with a mean Day 14 reduction of 17.9% more for the combination than simvastatin 20 mg alone. Furthermore, 6 of the 8 subjects in the simvastatin 20 mg plus SCH 58235 10 mg treatment group achieved ≥50% reduction in LDL-C on Day 14, compared to only 1/8 and 0/8 subjects treated with simvastatin 20 mg alone or SCH 58235 10 mg alone, respectively.

**CONCLUSIONS:**

- SCH 58235 administered at a daily dose of 10 mg concurrently with simvastatin 20 mg for 14 consecutive days to healthy male subjects was safe and well tolerated.
- The co-administration of SCH 58235 10 mg with simvastatin 20 mg caused a significantly ($p \leq 0.01$) greater percent reduction in serum LDL-C and total cholesterol than either simvastatin 20 mg or SCH 58235 10 mg alone.
- The co-administration of SCH 58235 and HMGCo-A reductase inhibitor simvastatin did not increase the incidence of liver transaminase or CPK abnormalities.

| | |
|---|---|
| **Title of Study:** | **PILOT DOSE-RANGING STUDY OF THE SAFETY AND EFFICACY OF SCH 58235 COMPARED TO PLACEBO AND LOVASTATIN IN PATIENTS WITH PRIMARY HYPERCHOLESTEROLEMIA** (Protocols C96-411 and C96-345). |
| **Investigators:** | Multicenter |
| **Study Centers:** | 12 centers in the USA |
| **Publication:** | None |
| **Studied Period:** | 17 APR 1997 to 26 AUG 1998 — **Clinical Phase:** II |

**Objectives:** The primary objective, as stated in the protocol, was as follows:

- to evaluate the efficacy and safety of SCH 58235 compared to placebo in lowering LDL cholesterol (LDL-C) when administered orally in doses of ~ mg, 10 mg, ~ mg, once a day for eight weeks, to subjects with primary hypercholesterolemia

The secondary objectives, as stated in the protocol, were as follows:

- establish the cholesterol-lowering effect dose-response relationship of SCH 58235
- compare the cholesterol-lowering effect of lovastatin 40 mg once daily with placebo as an internal reference arm for study design validation

**Methodology:** Randomized, double-blind, fixed-dose, parallel-groups comparison conducted in conformance with Good Clinical Practices.

**Number of Subjects:** 124 subjects, 66 men and 58 women aged 30-71 years, received randomized treatment assignment; 16 to 20 subjects were in each of the 7 treatment groups.

**Diagnosis and Criteria for Inclusion:** Otherwise healthy subjects with primary hypercholesterolemia; plasma LDL-C calculated via Friedewald equation (calculated LDL-C) 160-220 mg/dl (≈4.1-5.7 mmol/l) and triglycerides ≤250 mg/dl (≈2.8 mmol/l); National Cholesterol Education Program Step I diet; adequate washout of previous lipid-lowering medication.

**Test Product, Dose, Mode of Administration, Batch No(s):** SCH 58235 oral ~ mg; batch 37750-015. ~mg; batch 37750-010. ~ mg; batch 37750-011.

SCH 58235 ~ 10, ~ mg taken once daily in the morning before breakfast.

**Duration of Treatment:** 8 to 16 weeks no-treatment washout; 4 weeks single-blind placebo run-in; 8 weeks double-blind investigational treatment.

**Reference Therapy, Dose, Mode of Administration, Batch No(s):** Placebo oral ~ batches 36809-118 and 36809-119. Encapsulated lovastatin (Mevacor®) 40-mg tablet; batch 36809-122.

Taken once daily in the morning before breakfast.

**Criteria for Evaluation:** The primary efficacy evaluation was percent change from baseline to treatment endpoint (each subject's last lipid sample) in plasma LDL-C measured by ~ (direct LDL-C) for SCH 58235 40 mg versus placebo; if the difference was significant, other comparisons between active treatments and placebo could be made. Percent change from baseline was also determined for calculated and direct LDL-C, HDL-C, total cholesterol, and triglycerides after 2, 4, and 8 weeks of treatment, and for subfractions $HDL_2$-C and $HDL_3$-C, apolipoproteins $A_1$ and B, and lipoprotein(a) at end of treatment. Treatment was to be held until after samples were collected on visit days.

**Statistical Methods:** Analysis of variance extracting treatment effect only was used at treatment endpoint and Weeks 2, 4, and 8 test for overall differences, whereas pairwise comparisons between active treatments and placebo were performed using the least-square-means procedure. A repeated-measurement analysis was performed on direct LDL-C data to test for a significant treatment-by-visit interaction.

**SUMMARY-CONCLUSIONS:**

**RESULTS:**

**Efficacy:** Comparison of percent change from baseline to treatment endpoint for SCH 58235 40 mg versus placebo was significant ($p<.01$), and additional comparisons were made. All active treatments decreased direct LDL-C significantly compared with placebo, the mean decreases ranging from approximately 15%-20% for SCH 58235 ~ mg. As expected, lovastatin 40 mg decreased direct LDL-C by slightly more than 30%, thus validating the study design. A summary of all efficacy results appears in **Table 1**.

**Table 1**
Percent Changes (S.E.M.) From Baseline to Treatment Endpoint
in Plasma Concentrations of Various Lipid-Related Variables in the Intent-to-Treat Data Set

| Variables | Placebo (n=17) | SCH 58235 ~ mg (n=17) | SCH 58235 ~ mg (n=20) | SCH 58235 10 mg (n=18) | SCH 58235 ~ mg (n=16) | SCH 58235 ~ mg (n=18) | Lovastatin 40 mg (n=18) |
|---|---|---|---|---|---|---|---|
| Direct LDL-C | +3.8 (2.5) | -14.6 (2.4) | -15.7 (1.6) | -16.4 (2.2) | -17.9 (2.0) | -20.0 (2.0) | -31.8 (2.8) |
| Calculated LDL-C | +1.3 (2.5) | -16.0 (2.4) | -18.0 (1.4) | -17.6 (2.2) | -19.8 (2.2) | -22.1 (2.1) | -33.2 (2.6) |
| Apolipoprotein B | +3.4 (1.6) | -12.5 (2.5) | -13.5 (2.0) | -7.9 (3.4) | -13.5 (2.2) | -12.5 (2.6) | -25.3 (3.1) |
| HDL-C | +4.4 (2.6) | +4.6 (1.7) | +3.8 (2.0) | +4.4 (3.3) | +2.5 (2.7) | +1.8 (2.5) | +7.1 (2.1) |
| $HDL_2$-C | +0.4 (8.6) | +7.5 (6.0) | -1.9 (5.1) | +13.7 (10.0) | +1.3 (6.5) | -0.1 (6.5) | +14.9 (5.4) |
| $HDL_3$-C | +6.8 (3.4) | +3.3 (3.8) | +5.6 (3.0) | +2.7 (4.6) | +8.8 (4.9) | +7.4 (4.3) | +4.1 (3.3) |
| Apolipoprotein $A_1$ | -0.6 (2.0) | +4.6 (1.9) | +2.3 (2.0) | +9.6 (2.7) | +0.9 (2.7) | +3.4 (2.6) | +4.4 (2.1) |
| Total Cholesterol | +0.9 (2.1) | -10.3 (1.8) | -11.8 (1.2) | -10.4 (1.9) | -14.2 (1.9) | -15.8 (1.8) | -22.8 (2.3) |
| Triglycerides | -6.4 (5.2 ) | -0.9 (5.3) | +2.9 (7.0) | +13.1 (9.4) | -7.8 (5.3) | -8.3 (4.6) | -15.4 (5.6) |
| Lipoprotein(a) | +1.9 (7.8) | -2.6 (6.1) | -1.3 (4.6) | 0.0 (7.5) | -8.9 (7.2) | +7.3 (5.2) | -4.7 (4.5) |

S.E.M. = standard error of the mean.
Not every subject had an end-of-treatment measurement for every variable; "n" sizes varied from 15 to 20.

All active treatments decreased all measures of LDL-C and total cholesterol from baseline, while having no adverse effect on measures of HDL-C. SCH 58235 had no apparent effect on triglycerides or lipoprotein(a).

The action of SCH 58235 had relatively rapid onset and appeared to be durable: maximum or near-maximum effects were observed at the first assay point during treatment, Week 2, and continued for the next 6 weeks. Repeated-measures analysis revealed no treatment-by-visit interaction.

**Safety:** Slightly less than two thirds of all subjects had treatment-emergent adverse events reported, without indication of a meaningful difference in incidence among the seven groups. No adverse event was particularly common and many were reported by only one subject overall. Nothing unusual or unexpected was observed. All treatments appeared to be equally well tolerated by this population of subjects. Table 2 contains a summary of the most common adverse events.

**Table 2**
Number (%) of Subjects Reporting the Most Common Treatment-Emergent Adverse Events

| | Placebo (n=17) | SCH 58235 ~ mg (n=17) | SCH 58235 ~ mg (n=20) | SCH 58235 10 mg (n=18) | SCH 58235 ~ mg (n=16) | SCH 58235 ~ mg (n=18) | Lovastatin 40 mg (n=18) |
|---|---|---|---|---|---|---|---|
| upper respiratory tract infection | 0 | 4 (24) | 1 (5) | 1 (6) | 4 (25) | 1 (6) | 1 (6) |
| infection, viral | 4 (24) | 1 (6) | 1 (5) | 1 (6) | 2 (13) | 1 (6) | 2 (11) |
| headache | 1 (6) | 1 (6) | 2 (10) | 2 (11) | 0 | 2 (11) | 2 (11) |
| arthralgia | 1 (6) | 0 | 0 | 3 (17) | 1 (6) | 2 (11) | 1 (6) |
| myalgia | 1 (6) | 1 (6) | 2 (10) | 1 (6) | 1 (6) | 1 (6) | 0 |

Six subjects discontinued treatment because of adverse events: 1 each treated with placebo or SCH 58235 mg; and 2 each treated with lovastatin 40 mg or SCH 58235 10 mg. The subject treated with SCH 58235 ng had mild urticaria (hives plus rash) that resolved with diphenhydramine. The other events were not unexpected for a middle-aged population observed for an extended period (eg, headache, diarrhea).

Results of the additional measures of safety — laboratory tests, vital signs, ECGs, cardiopulmonary and general physical examinations, and tests for fecal occult blood — revealed no evidence of an adverse effect of active treatment compared with placebo.

**CONCLUSIONS:** The following conclusions may be drawn based on results of oral administration of SCH 58235 10, mg, or lovastatin 40 mg once a day before breakfast for 8 weeks:

- SCH 58235 was effective in reducing the mean plasma concentration of low-density-lipoprotein cholesterol as measured by by approximately 15% to 20% at the end of treatment.
- SCH 58235 had a relatively rapid onset of action; maximal or near-maximal response occurred within 2 weeks of initiation of dosing.
- The response to SCH 58235 was relatively stable between 2 and 8 weeks after initiation of dosing.
- A small numerical increase in response was observed with doses of SCH 58235 increasing from mg QD, suggesting that this range is close to the plateau of maximum effect; this range does not include a "no-effect" dose.
- SCH 58235 also reduced the plasma concentrations of apolipoprotein B and total cholesterol relative to placebo.
- SCH 58235 had no effect on plasma concentration of high-density-lipoprotein cholesterol as indicated by changes in total HDL-C, subfractions $HDL_2$-C and $HDL_3$-C, and apolipoprotein $A_1$.
- SCH 58235 had no consistent effect on plasma concentrations of triglycerides or lipoprotein(a).
- Results for lovastatin 40 mg QD were in the range expected from product labeling, thus validating the study design.
- SCH 58235 was well tolerated and had an overall adverse event profile similar to that of placebo.
- SCH 58235 had no adverse effect on subjects as indicated by results of all additional measures of safety.

**Date of the Report:** 15 MAR 1999

| | |
|---|---|
| **Title of Study:** | A PHASE II DOUBLE-BLIND DOSE-RESPONSE INVESTIGATION OF THE EFFICACY AND SAFETY OF FOUR DOSES OF SCH 58235 COMPARED WITH PLACEBO IN SUBJECTS WITH PRIMARY HYPERCHOLESTEROLEMIA (Protocol C98-010). |
| **Investigators:** | Multicenter |
| **Study Centers:** | 27 centers in the USA |
| **Publication:** | None |
| **Studied Period:** | 05 NOV 1998 to 12 JUL 1999 — **Clinical Phase:** II |

**Objectives:** Primary objective:

- to confirm the efficacy and safety of a range of doses as determined by a pilot study (C96-411/C96-345) of SCH 58235 compared to placebo in lowering LDL cholesterol (LDL-C) when administered orally, once a day for 12 weeks, to subjects with primary hypercholesterolemia

Secondary objective:

- to determine the dose-response relationship of the LDL-C-lowering effect of SCH 58235

**Methodology:** Randomized, double-blind, fixed-dose, balanced-parallel-groups comparison conducted in conformance with Good Clinical Practices.

**Number of Subjects:** 243 subjects, 139 men and 104 women aged 28-75 years, received randomized treatment assignment; 46 to 52 subjects were in each of the 5 treatment groups.

**Diagnosis and Criteria for Inclusion:** Otherwise healthy subjects with primary hypercholesterolemia; plasma LDL-C calculated via Friedewald equation (calculated LDL-C) 130-250 mg/dl (≈3.4-6.5 mmol/l) and triglycerides ≤300 mg/dl (≈3.4 mmol/l); National Cholesterol Education Program Step I diet or stricter; adequate washout of previous lipid-lowering medication.

**Test Product, Dose, Mode of Administration, Batch Nos.:** SCH 58235 oral tablets. — mg; batch 37750-063. — ng; batch 37750-055 —ng; batch 37750-056. 10 mg; batch 37750-057.

SCH 58235 — or 10 mg taken once daily before a morning meal.

**Duration of Treatment:** Up to 10 weeks no-treatment washout (if needed); 6 weeks single-blind placebo run-in; 12 weeks double-blind investigational treatment.

**Reference Therapy, Dose, Mode of Administration, Batch Nos.:** Placebo oral tablets. Batches 37750-053 and 39554-030 during placebo run-in. Batch 37750-053 during randomized treatment.

Taken once daily before a morning meal.

**Criteria for Evaluation:** The primary efficacy evaluation was percent change from baseline to study endpoint in plasma LDL-C measured by ——— (direct LDL-C). If the result of the linear trend test was significant (see below), comparisons between active treatments and placebo could be made. Percent change from baseline was also determined for calculated and direct LDL-C, high-density lipoprotein cholesterol (HDL-C), total cholesterol, and triglycerides after 1, 2, 4, 8, and 12 weeks of treatment, and for subfractions $HDL_2$-C and $HDL_3$-C, apolipoproteins $A_1$ and B, and lipoprotein(a) at end of treatment. Treatment was to be held until after samples were collected on visit days.

**Statistical Methods:** The primary efficacy analysis was based on a linear trend test of the treatment means, obtained from a two-way analysis of variance model extracting treatment and center effect. Pairwise comparisons between response to active treatment and response to placebo were performed using the least-square-means procedure.

**SUMMARY – CONCLUSIONS:**

**RESULTS:**

**Efficacy:** Results of the linear trend test were statistically significant, and additional comparisons were made without penalty for multiple comparisons. All active treatments decreased direct LDL-C significantly compared with placebo, and response was related to dose. A summary of all efficacy results appears in **Table 1**.

**Table 1**
Percent Changes (S.E.M.) From Baseline to Study Endpoint in Plasma Concentrations of Various Lipid-Related Variables in the Intent-to-Treat Data Set

| | | SCH 58235 | | | |
|---|---|---|---|---|---|
| Variables | Placebo (n=52) | — mg (n=47) | — mg (n=49) | — mg (n=49) | 10 mg (n=46) |
| Direct LDL-C | +4.3 (1.4) | -9.9 (1.5) | -12.6 (1.5) | -16.4 (1.4) | -18.7 (1.5) |
| Calculated LDL-C | +3.6 (1.4) | -9.3 (1.5) | -13.9 (1.5) | -18.4 (1.5) | -18.9 (1.5) |
| Apolipoprotein B | +2.4 (1.6) | -6.3 (1.7) | -11.7 (1.7) | -15.1 (1.6) | -15.2 (1.7) |
| HDL-C | +2.2 (1.4) | +4.1 (1.5) | +2.8 (1.4) | +2.7 (1.4) | +4.5 (1.5) |
| $HDL_2$-C | +16.1 (5.9) | +15.0 (6.4) | +10.4 (6.3) | +16.9 (6.1) | +11.7 (6.5) |
| $HDL_3$-C | -0.1 (2.7) | +2.6 (2.9) | -2.2 (2.8) | -0.7 (2.7) | -0.2 (2.9) |
| Apolipoprotein $A_1$ | -2.9 (1.7) | +1.2 (1.8) | -2.9 (1.8) | -1.6 (1.7) | +0.7 (1.8) |
| Total Cholesterol | +2.2 (1.1) | -6.8 (1.2) | -10.3 (1.2) | -12.6 (1.1) | -12.6 (1.2) |
| Triglycerides | -2.9 (3.7) | -7.7 (4.0) | -10.4 (3.9) | -5.4 (3.8) | -3.8 (4.0) |
| Lipoprotein(a) | +9.1 (6.9) | +12.6 (7.4) | +7.7 (7.4) | +6.3 (7.0) | -2.8 (7.5) |

S.E.M. = standard error of the least-square mean.

Not every subject had an end-of-treatment measurement for every variable; "n" sizes varied from 43 to 51.

All active treatments decreased LDL-C and total cholesterol concentrations from baseline, while having no adverse effect on measures of HDL-C, triglycerides, or lipoprotein(a).

The action of SCH 58235 had relatively rapid onset, with approximately 65% to 75% of the maximum decrease in direct LDL-C observed at Week 1, the earliest measurement after randomization. Near-maximum effect was observed at Week 2 with SCH 58235 — mg, and 10 mg. The response to SCH 58235 was relatively stable between 2 and 12 weeks after initiation of dosing.

**Safety:** Fifty-eight percent of all subjects had treatment-emergent adverse events reported, without clinically meaningful difference in incidence among the five groups. No adverse event was particularly common and many were reported by only one subject overall. Nothing unusual or unexpected was observed. All treatments appeared to be equally well tolerated by this population of subjects. **Table 2** contains a summary of the most common adverse events.

APPEARS THIS WAY
ON ORIGINAL

**Table 2**
Number (%) of Subjects Reporting the Most Common Treatment-Emergent Adverse Events

| | | SCH 58235 | | | |
|---|---|---|---|---|---|
| | Placebo (n=52) | — mg (n=47) | — mg (n=49) | — mg (n=49) | 10 mg (n=46) |
| headache | 4 (8) | 2 (4) | 2 (4) | 2 (4) | 5 (11) |
| arthralgia | 3 (6) | 2 (4) | 2 (4) | 5 (10) | 3 (7) |
| infection, viral | 2 (4) | 1 (2) | 1 (2) | 6 (12) | 4 (9) |
| upper respiratory tract infection | 2 (4) | 3 (6) | 7 (14) | 0 | 2 (4) |

Three subjects discontinued treatment because of adverse events: 1 treated with placebo (elevated liver enzymes; Day 65), 1 treated with SCH 58235 — mg (arthralgia, edema dependent, paroniria [wild dreams], and skin disorder [red blotches on face]; Day 43), and 1 treated with SCH 58235 — mg (thrombocytopenia; Day 35).

Results of the additional measures of safety – laboratory tests, vital signs, electrocardiograms, cardiopulmonary and general physical examinations, and tests for fecal occult blood – revealed no evidence of an adverse effect of active treatment compared with placebo.

**CONCLUSIONS:** The following conclusions may be drawn based on results of oral administration of SCH 58235 — or 10 mg once a day before a morning meal for 12 weeks to subjects with primary hypercholesterolemia:

- The degree of decrease in plasma concentration of low-density-lipoprotein cholesterol was directly related to the dose of SCH 58235.
- SCH 58235 — mg to 10 mg was effective in reducing the mean plasma concentration of low-density-lipoprotein cholesterol by approximately 10% to 19% at the end of treatment.
- SCH 58235 had a relatively rapid onset of action, with approximately 65% to 75% of the maximum decrease in direct LDL-C observed at Week 1, the earliest measurement after randomization.
- The magnitude of the response to SCH 58235 was maintained between 2 and 12 weeks after initiation of dosing.
- SCH 58235 reduced the plasma concentrations of apolipoprotein B and total cholesterol relative to placebo.
- SCH 58235 had no effect on plasma concentration of high-density-lipoprotein cholesterol as indicated by changes in total HDL-C, subfractions HDL2-C and HDL3-C, and apolipoprotein A1.
- SCH 58235 had no effect on the plasma concentrations of triglycerides or lipoprotein(a).
- SCH 58235 was well tolerated and had an overall adverse event profile similar to that of placebo.
- SCH 58235 had no adverse effect on subjects as indicated by results of safety laboratory tests, measurements of vital signs, ECGs, and cardiopulmonary and general physical examinations.

**Date of the Report:** 17 JAN 2000

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/

Wei Qiu
9/17/02 12:54:03 PM
PHARMACOLOGIST

Hae-Young Ahn
9/18/02 09:33:46 AM
BIOPHARMACEUTICS

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

# *Office of Clinical Pharmacology and Biopharmaceutics*
# *New Drug Application Filing and Review Form*

**General Information About the Submission**

| | Information | | Information |
|---|---|---|---|
| **NDA Number** | **21-445** | **Brand Name** | **Zetia (proposed)** |
| **OCPB Division (I, II, III)** | **II** | **Generic Name** | **Ezetimibe** |
| **Medical Division** | **510** | **Drug Class** | **Lipid lowering** |
| **OCPB Reviewer** | **Wei Qiu, Ph.D.** | **Indication(s)** | **Hypercholesterolemia with and without an HMG-CoA reductase inhibitor; hypercholesterolemia in patients with homozygous familial hypercholesterolemia; elevated sitosterol and campesterol in patients with homozygous sitosterolemia.** |
| **OCPB Team Leader** | **Hae-Young Ahn** | **Dosage Form** | **tablets** |
| **Related IND(s)** | **—** | **Dosing Regimen** | **10 mg** |
| **Date of Submission** | **27 Dec. 01** | **Route of Administration** | **Oral** |
| **Estimated Due Date of OCPB Review** | **Aug. 17, 2002** | **Sponsor** | **MSP Singapore Co., LLC** |
| **PDUFA Due Date** | **Oct. 27, 2002** | **Priority Classification** | **regular** |
| **Division Due Date** | **Sept. 17, 2002** | | |

**Clin. Pharm. and Biopharm. Information**

| | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments If any |
|---|---|---|---|---|
| **STUDY TYPE** | | | | |
| **Table of Contents present and sufficient to locate reports, tables, data, etc.** | X | | | |
| **Tabular Listing of All Human Studies** | X | | | |
| **HPK Summary** | X | | | |
| **Labeling** | X | | | |
| **Reference Bioanalytical and Analytical Methods** | X | | | |
| **I. Clinical Pharmacology** | | | | |
| **Mass balance:** | | 1 | 1 | |
| **Isozyme characterization:** | | | | |
| **Blood/plasma ratio:** | | | | |
| **Plasma protein binding:** | | | | |
| **Pharmacokinetics (e.g., Phase I) -** | | | | |
| ***Healthy Volunteers-*** | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| ***Patients-*** | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| **Dose proportionality -** | | | | |
| fasting / non-fasting single dose: | | 2 | 2 | |
| fasting / non-fasting multiple dose: | | 1 | 1 | |
| **Drug-drug interaction studies -** | | | | |
| In-vivo effects on primary drug: | | 2 | 2 | |
| In-vivo effects of primary drug: | | 3 | 3 | |
| Mutual: | | 12 | 12 | |
| In-vitro: | | | | |
| **Subpopulation studies -** | | | | |
| ethnicity: | | | | |
| gender: | | 1 | 1 | |
| pediatrics: | | 1 | 1 | adolescent |
| geriatrics: | | 1 | 1 | |
| renal impairment: | | 1 | 1 | |
| hepatic impairment: | | 2 | 2 | |
| Meta Analysis: | | 1 | 1 | |
| **PD:** | | | | |
| Phase 2: | | 1 | 1 | |
| Phase 3: | | | | |
| **PK/PD:** | | | | |
| Phase 1 and/or 2, proof of concept: | | | | |
| Phase 3 clinical trial: | | | | |
| **Population Analyses -** | | | | |
| Data rich: | | | | |

| | | | | |
|---|---|---|---|---|
| Data sparse: | | | | |
| **II. Biopharmaceutics** | | | | |
| **Absolute bioavailability:** | | | | |
| **Relative bioavailability -** | | | | |
| *solution as reference:* | | | | |
| alternate formulation as reference: | | 1 | 1 | |
| **Bioequivalence studies -** | | | | |
| traditional design; single / multi dose: | | | | |
| replicate design; single / multi dose: | | | | |
| **Food-drug interaction studies:** | | 2 | 1 | 1 pivotal |
| **Dissolution:** | x | | | |
| **(IVIVC):** | | | | |
| **Bio-wavier request based on BCS** | | | | |
| **BCS class** | | | | |
| **III. Other CPB Studies** | | | | |
| **Genotype/phenotype studies:** | | | | |
| **Chronopharmacokinetics** | | | | |
| **Pediatric development plan** | | | | |
| **Literature References** | | | | |
| **Total Number of Studies** | | 32 | 31 | |
| | | | | |

| **Filability and QBR comments** | | |
|---|---|---|
| | **"X" if yes** | **Comments** |
| **Application filable ?** | x | The clinical formulation is the same as the to-be-marketed one. It was noted that there was no BA study for this new chemical entity in this submission. However, since only one dose (10 mg) was proposed, no food effect was observed, and a mass balance study was conducted, no BA study is requested at this moment after consulting with OCPB/DPEII director Dr. Hank Malinowski. |
| **Comments sent to firm ?** | x | The sponsor submitted dissolution results of 10 mg tablets under only one condition using the medium of [redacted]. However, the medium of the proposed dissolution method is [redacted]. In order to obtain an appropriate dissolution method and specification for this product, the sponsor is recommended to submit dissolution profiles for the 10 mg tablets from 3 batches (12 units/batch) under three different conditions. In addition, the amount of surfactant should be justified. The sponsor should provide a solubility profile as well. |
| **QBR questions (key issues to be considered)** | **1. ADME<br>2. Dose proportionality<br>3. Food effect<br>4. Drug drug interaction<br>5. PK in special populations** | |
| **Other comments or information not included above** | | |
| **Primary reviewer Signature and Date** | | |
| **Secondary reviewer Signature and Date** | | |

On Dec 27, 2001, Schering Corp. submitted an original NDA for ZETIA™ (ezetimibe) tablets for the following treatments on behalf of the MSP Singapore Co. LLC, a joint venture between Merck & Co., Inc. and Schering Corporation:

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

Ezetimibe (SCH58235) is the first of a novel class of compounds that selectively inhibit the intestinal absorption of cholesterol and related phytosterols.

There were 32 clinical pharmacology studies conducted in support of this application that are provided in the following table. In addition, relevant dissolution data and analytical validation reports were included. However, the dissolution method and specification validation data were not provided.

| BA/PK Studies | Drug Interaction Studies |
|---|---|
| Radiolabeled 14C-AME (C97-136) | Effect on CYP450 Enzymes (I97137) |
| Tablet formulation selection (C97-221) | PK interaction with Antacid (P00748) |
| Dose proportionality (P00750) | PK interaction with Cimetidine (P00746) |
| Food effect on tablet (P00751) | PK interaction with Gemfibrozil (P00252) |
| Pilot food effect (C97-026) | PK interaction with Lovastatin (P01382) |
| **PK Studies in Special Populations** | PK interaction with Oral Contraceptives (P00267) |
| | PK and PD interaction with Digoxin (C98-114) |
| Effect of Gender on PK (C98-107) | PK and PD interaction with Glipizide (P00752) |
| Effect of Age on PK (C98-115) | PK and PD interaction with Warfarin (I98-106) |
| PK in Adolescent Children (P00774) | PD interaction with Simvastatin (P00300) |
| Effect of Renal Disease on PK (P00749) | PD and PK interaction with Simvastatin (I98-311) |
| Effect of Liver Disease on PK (P00251) | PD and PK interaction with Lovastatin (P00250) |
| Effect of Moderate Liver Disease on MD PK (P01912) | PD and PK interaction with Atorvastatin (P00460) |
| **Special Studies** | PD and PK interaction with Pravastatin (P00447) |
| | PD and PK interaction with Fluvastatin (P00755) |
| Rising single-dose safety/tolerance (I96-088) | PD and PK interaction with Cerivastatin (P00754) |
| Rising multiple-dose safety/tolerance (I96-139) | PD and PK interaction with Fenofibrate (P00753) |
| Effect on Cholesterol absorption (P02484) | PD and PK interaction with Cholestyramine (P00776) |

The pharmacokinetic results of Ezetimibe are summarized as follows:

1. Following oral administration, ezetimibe was rapidly absorbed and conjugated and slowly eliminated. The profiles for both ezetimibe and total ezetimibe concentrations exhibited multiple peaks suggesting enterohepatic recycling.
2. Ezetimibe was extensively conjugated to the glucuronide; unchanged plasma ezetimibe concentrations were only approximately 10% of total ezetimibe concentrations.
3. The half-life of ezetimibe and ezetimibe-glucuronide was approximately 22 hours; steady state was attained by Day 10.
4. AUC(0-24 hr) and Cmax values of ezetimibe and total ezetimibe were dose related between 10 and — mg, but did not appear to be dose-proportional.
5. The concomitant administration of antacid and ezetimibe can affect the rate of absorption but has no significant effect on ezetimibe bioavailability.
6. Ezetimibe is neither an inhibitor nor an inducer of common cytochrome P450 drug-metabolizing enzymes.
7. Ezetimibe administered at clinically relevant doses does not have a clinically significant effect on the pharmacokinetics of several drugs including simvastatin, lovastatin, atorvastatin, pravastatin, fluvastatin, cerivastatin, fenofibrate, gemfibrozil, glipizide, digoxin, warfarin, and oral contraceptives.
8. The concomitant administration of cimetidine and ezetimibe can affect the rate of absorption but has no significant effect on ezetimibe bioavailability.
9. Cholestyramine significantly decreased the systemic exposure to ezetimibe (mean reduction ~55% based on total ezetimibe AUC).
10. There are no clinically significant pharmacokinetic differences for ezetimibe between males and females.
11. There are no clinically significant pharmacokinetic differences for ezetimibe between young and older subjects. The pharmacokinetics in children >=10 years old appears similar to young adults.
12. The pharmacokinetics of ezetimibe is not dependent on race or body weight.
13. Patients with severe chronic renal insufficiency had approximately 50% higher exposure to ezetimibe and total ezetimibe compared with matched healthy controls. However, this is not considered to be clinically significant, and therefore no dosage adjustment is necessary for renally impaired patients. Severe chronic renal insufficiency did not affect the protein binding of total ezetimibe.
14. Patients with moderate and severe chronic liver disease had approximately 4-fold higher exposure to ezetimibe and total ezetimibe compared to matched healthy controls. The increase in exposure to ezetimibe and total ezetimibe appeared to relate directly with the severity of liver disease. Moderate chronic liver disease did not affect the protein binding of total ezetimibe. No dosage adjustment is necessary for patients with mild hepatic insufficiency. Ezetimibe is not recommended for patients with moderate or severe hepatic disease.
15. In vivo human plasma protein binding for total ezetimibe is approximately 94% and is not affected by severe chronic renal disease or moderate chronic liver failure.

---

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

---

/s/

---

Wei Qiu
2/14/02 03:29:54 PM
PHARMACOLOGIST

Hae-Young Ahn
3/8/02 02:05:02 PM
BIOPHARMACEUTICS

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL