SUMMARY

ASTRAZENECA

FINISHED PRODUCT: CRESTOR

ACTIVE INGREDIENT: Rosuvastatin calcium

Trial title (number): A Phase I, Single Center, Randomized, Double-blind, Placebo-controlled, 2-Way Crossover Trial to Assess the Effect of Gemfibrozil on the Pharmacokinetics of a Single Oral Dose of Rosuvastatin 80 mg in Healthy Men and Women (4522IL/0095).

Developmental phase: I

First subject recruited: 21 November 2001
Last subject completed: 22 December 2001
AstraZeneca approval date: 20 February 2002

Publications: none at the time of writing this report

OBJECTIVES

The primary objective of this trial was to assess the effect of gemfibrozil 1200 mg daily (highest approved dose; administered to steady state) on the pharmacokinetics of a single oral dose of rosuvastatin 80 mg as measured by C_{max} and AUC of rosuvastatin. The secondary objectives of the trial were to assess the effect of steady state gemfibrozil on the pharmacokinetics of a single oral dose of rosuvastatin 80 mg as measured by AUC(0-t), $t_{1/2}$, and t_{max} of rosuvastatin; evaluate the effect of steady state gemfibrozil on the pharmacokinetics of the rosuvastatin metabolites, rosuvastatin lactone and N-desmethyl rosuvastatin, by measuring AUC, AUC(0-t), C_{max}, t_{max}, and $t_{1/2}$ for each metabolite; assess the pharmacokinetics of gemfibrozil coadministered with a single dose of rosuvastatin 80 mg by measuring $C_{ss,min}$, AUC(0-12), C_{max}, t_{max}; and assess safety by measuring the incidence and severity of adverse events and abnormal laboratory values.

METHODS

Design: This was a randomized, double-blind, placebo-controlled, 2-way crossover trial conducted at a single center. The trial consisted of 2 gemfibrozil/placebo seven-day treatment periods (Periods A and B), with rosuvastatin dosing separated by an 11-day washout period.

During Period A, subjects were given gemfibrozil 600 mg twice a day or placebo twice a day for 7 days. In Period B subjects were crossed over to the treatment they had not received in Period A. On trial Day 4 of each period, a single oral dose of rosuvastatin 80 mg was given with the morning dose of gemfibrozil or placebo. Subjects resided in the trial center from admission (Day 0) through the end of the trial (Day 23).

Population: Twenty healthy men or women between the ages of 18 and 55 years, inclusive, were enrolled to obtain at least 16 evaluable subjects.

Key inclusion criteria: negative screens for hepatitis B surface antigen, hepatitis C antibody and human immunodeficiency virus (HIV) antibody. No clinically significant abnormalities identified from the medical history, physical examination and electrocardiogram (ECG) as evaluated by the investigator; body mass index (BMI) between 18 and 29, inclusive; nonsmokers.

Key exclusion criteria: clinically significant abnormalities in clinical chemistry, hematology or urinalysis; history of or presence of gastrointestinal, hepatic, or renal disease or other condition known to interfere with the absorption, distribution, metabolism or excretion of drugs; definite or suspected history of adverse drug reactions or hypersensitivity to drugs with a similar chemical structure to rosuvastatin (or related statins) or gemfibrozil (or other fibric acid derivatives) or lactose.

Dosage: During Period A, subjects received oral doses of gemfibrozil 1200 mg (600 mg twice daily; Lopid™, Parke-Davis Inc, NDC 0071–0737–20) or placebo (CEBO-CAPS™, Forest Pharmaceuticals Inc, NDC 00456070801) twice a day for seven days in a blinded fashion. In Period B, subjects were crossed over to the treatment they had not received in Period A. On the fourth day of each blinded trial treatment, a single oral dose of rosuvastatin 80 mg (formulation F12822, batch 2000027481) was taken with the morning dose of gemfibrozil or placebo; the doses of rosuvastatin were separated by 11 days.

Key assessments:

Pharmacokinetic: Blood samples were taken at specified times during the trial to examine the primary pharmacokinetic endpoints, AUC and C_{max} of rosuvastatin, and the secondary endpoints AUC(0-t), $t_{1/2}$, and t_{max} of rosuvastatin and AUC(0-t), C_{max}, $t_{1/2}$, t_{max} of N-desmethyl rosuvastatin and rosuvastatin lactone. AUC(0-t) was to be considered a primary endpoint —rather than AUC— if AUC data from each treatment (gemfibrozil and placebo) were not available for 16 or more subjects. The AUC and C_{max} values of rosuvastatin were analyzed using an analysis of variance model fitting for the effects of treatment (gemfibrozil or placebo), period, sequence, and subject within sequence as a random effect. The results of the analysis are presented in terms of geometric least squares means (glsmean), treatment effect (ratio of glsmean: gemfibrozil + rosuvastatin / placebo + rosuvastatin) and 90% confidence interval (CI). Power calculations show that for a trial including 16 subjects there would be 80% power for C_{max} and greater than 80% power for AUC that the 90% confidence interval (CI) for the ratio of glsmean (gemfibrozil + rosuvastatin / placebo + rosuvastatin) would be contained within the interval of 0.70 to 1.43. Blood samples were obtained before each morning dose on Days 2, 3, 4, 13, 14 and 15 to assess gemfibrozil steady-state plasma concentrations ($C_{ss,\ min}$). The C_{max}, t_{max} and AUC(0-12) for gemfibrozil were also estimated as secondary endpoints on Day 4 of the gemfibrozil treatment period.

Safety: Safety assessments included adverse event reports, clinical laboratory data, ECGs, vital signs and physical examination.

RESULTS

Demography: Seventeen men (3 Caucasian, 14 Hispanic) and 3 women (all Hispanic) entered this trial. The mean age, height and weight was 41.2 years (range 27 to 53 years), 172.3 cm (range 158 to 185 cm) and 76.0 kg (range 56 to 94 kg), respectively. The mean BMI was 25.6 kg/m^2 (range 20 to 29). There were no withdrawals during the trial. The trial was conducted at a single center.

Pharmacokinetics: A summary of the key pharmacokinetic findings is presented in Table I. As AUC data were not available for 16 or more subjects for each treatment (gemfibrozil and placebo), AUC(0-t) was considered a primary endpoint, rather than AUC, as specified in the protocol.

Table I Statistical comparison for plasma AUC(0-t) and C_{max} of rosuvastatin in the presence and absence of gemfibrozil

Primary endpoints	Gemfibrozil + rosuvastatin		Placebo + rosuvastatin		Ratio of glsmeans[a]	90% CI for ratio[a]
	glsmean	N	glsmean	N		
AUC(0-t) (ng·h/ml)	771	20	410	20	1.88	1.60 to 2.21
C_{max} (ng/ml)	109	20	49.5	20	2.21	1.81 to 2.69

Data derived from Table T4.7.

[a] Ratio and 90% CI are expressed as a ratio of glsmean (gemfibrozil + rosuvastatin) / glsmean (placebo + rosuvastatin); glsmean = geometric least squares mean; AUC(0-t) = area under the curve up to time t; C_{max} = maximum plasma concentration; CI = confidence interval; N = number of subjects.

Gemfibrozil increased exposure to rosuvastatin, based on AUC(0-t) and C_{max}, 1.88 fold and 2.21 fold, respectively, compared with placebo. When the AUC(0-t) and C_{max} were compared statistically**,** the 90% CIs for the AUC(0-t) and C_{max} treatment ratios were 1.60 to 2.21 and 1.81 to 2.69, respectively. These data indicate that gemfibrozil increased the systemic exposure of rosuvastatin approximately 2 fold.

With respect to the rosuvastatin metabolites, statistical analyses showed a 48% reduction in AUC(0-t) and a 39% reduction in C_{max} of N-desmethyl rosuvastatin when rosuvastatin was administered in combination with gemfibrozil. Statistical analyses of AUC (0-t) and C_{max} for rosuvastatin lactone showed that gemfibrozil had no effect on the pharmacokinetics of this metabolite.

The observed plasma concentrations of gemfibrozil were as expected for gemfibrozil 600 mg twice daily. Individual and mean trough plasma concentrations of gemfibrozil indicated that gemfibrozil was at steady state when rosuvastatin was administered.

Safety: There were no deaths and no serious adverse events during the trial. There were no cases of myopathy or hepatic adverse events and no clinically significant elevations in ALT or AST (>3 x ULN) or CK (>10 x ULN). Three subjects had asymptomatic rises in ALT that did not exceed 3 x ULN during treatment with gemfibrozil and rosuvastatin; the changes resolved and were not observed during treatment with placebo and rosuvastatin. A 4th subject had ALT

values slightly >1 x ULN during placebo and rosuvastatin treatment (Period B), with the highest value (1.1 x ULN) occurring before rosuvastatin dosing.
One adverse event (constipation) was reported during the trial; the adverse event was mild, considered by the investigator to be related to trial treatments, and resolved without intervention.