SUMMARY

ZENECA PHARMACEUTICALS

FINISHED PRODUCT:

ACTIVE INGREDIENT: ZD4522

Trial title (number): A Randomised, Non-controlled, Single-centre, Open-label, 3-way Crossover Trial to Assess the Effect of Co-administration of ZD4522 and Fenofibrate on the Pharmacokinetics of Each Compound in Healthy Male Volunteers (4522IL/0022).

Developmental phase: I

First volunteer recruited: 18 August 1999
Last volunteer completed: 15 November 1999
Zeneca approval date: 26 March 2000

Publications: None at the time of writing this report.

OBJECTIVES

The primary objective of this trial was to assess the effect of co-administration of ZD4522 and fenofibrate on the pharmacokinetics of both ZD4522 and fenofibrate. There were no secondary objectives for this trial.

METHODS

Design: This was a randomised, non-controlled, open-label, 3-way crossover trial conducted at a single centre. The trial consisted of three 7-day treatment periods (Trial Periods A, B and C). During Trial Periods A, B and C, volunteers received in randomised order, single daily oral doses of ZD4522 10 mg, 3 daily oral doses of fenofibrate 67 mg (morning, afternoon and evening) or ZD4522 10 mg + fenofibrate (3 x 67 mg; morning, afternoon and evening) in combination. When the drugs were given in combination, ZD4522 was taken with the morning dose of fenofibrate. Each trial period was separated by a 3-week washout period.

Population: Healthy male volunteers. A total of 14 volunteers were recruited with the expectation that at least 12 would complete the trial. A total sample size of 12 volunteers gave a 93% chance of showing that the 90% confidence intervals (CIs) for the comparisons of AUC(0-24) and C_{max} of ZD4522 in the presence and absence of fenofibrate and the AUC(0-8) and C_{max} of fenofibrate in the presence and absence of ZD4522 were between 0.67 and 1.5. If the 90% CIs for the comparisons were outside the pre-specified intervals, a pharmacokinetic (drug-drug) interaction was concluded. Confidence intervals outside of 0.5 to 2.0 would indicate a clinically relevant interaction.

Key inclusion criteria: Men aged between 18 and 65 years inclusive; negative screens for serum hepatitis B surface antigen, hepatitis C antibody and HIV and a normal screen for ferritin; no clinically significant abnormalities identified from the medical history, physical examination, and electrocardiogram (ECG) as evaluated by the investigator; weight not differing by more than 20% from the desirable weight.

Key exclusion criteria: Any clinically significant abnormalities in clinical chemistry, haematology or urinalysis; total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and creatine kinase (CK) outside the normal reference range at the start of the trial; history or presence of gastrointestinal, hepatic, biliary or renal disease or other condition known to interfere with the absorption, distribution, metabolism or excretion of drugs; treatment with any drug known to have a well-defined potential for hepatotoxicity in the 3 months before the start of the trial; definite or suspected history of adverse drug reactions or hypersensitivity to drugs with a similar chemical structure to ZD4522, related statins or fenofibrate and related fibrate drugs.

Dosage: Each volunteer was given ZD4522 10 mg (formulation F12420, batch 63682B99) once-daily or fenofibrate 67 mg (formulation F12575, batch 63519C99) three-times daily, or ZD4522 10 mg once-daily and fenofibrate 67 mg three-times daily in combination for 7 days, in randomised order during Trial Periods A, B and C.

Key assessments:

Pharmacokinetic: Blood samples were taken at specified times on Trial Days 1, 2, 3, 6 and 7 both before dosing and following dosing with trial treatment, to examine the primary pharmacokinetic end-points of ZD4522 (AUC(0-24) and C_{max}) in the presence and absence of fenofibrate, and of fenofibric acid (AUC(0-8) and C_{max}) in the presence and absence of ZD4522. Secondary end-points also assessed were t_{max} and C_{min} of ZD4522 in the presence and absence of fenofibrate and t_{max}, $t_{1/2}$ and C_{min} of fenofibric acid in the presence and absence of ZD4522. The log transformed values of AUC(0-24) and C_{max} of ZD4522 and AUC(0-8) and C_{max} of fenofibric acid were analysed using an analysis of variance model fitted for the effects of volunteer, period and treatment. The results of the analyses were presented in terms of geometric least square means (glsmeans) for each group (ie, ZD4522 or fenofibrate alone as 1 group and ZD4522 + fenofibrate in combination as the other), the treatment ratios (ZD4522 + fenofibrate) / (ZD4522) for the ZD4522 parameters and (ZD4522 + fenofibrate) / (fenofibrate) for the fenofibric acid parameters and their 90% CIs. The effect of fenofibrate on AUC(0-24) and C_{max} of ZD4522 and the effect of ZD4522 on AUC(0-8) and C_{max} of fenofibric acid was assessed using the 90% CIs for the treatment ratios. If the 90% CIs fell outside the pre-specified intervals of 0.67 to 1.50, a pharmacokinetic interaction was concluded and if they fell outside the interval 0.5 to 2.0 a clinically relevant interaction was concluded.

Safety: Safety and tolerability were assessed during the trial by collection of adverse events, specific clinical chemistry laboratory tests (eg, hepatic, muscle and renal), physical examination, periodic vital signs measurements and ECGs. Safety assessment data were summarised.

RESULTS

Demography: Fourteen male Caucasians entered this trial. The first volunteer entered the trial on 18 August 1999 and the last volunteer completed on 15 November 1999. Their mean age, height and weight were 38.3 years (range 23 to 64 years), 176.9 cm (range 166 to 186 cm) and 79.2 kg (range 60 to 93 kg), respectively. There were no withdrawals during the trial. The trial was conducted at a single centre.

Pharmacokinetics: The results of the statistical analysis comparing AUC(0-24) and C_{max} of ZD4522 in the presence and absence of fenofibrate and the AUC(0-8) and C_{max} of fenofibric acid in the presence and absence of ZD4522 are presented in Table I.

Table I Summary of key pharmacokinetic findings

Comparison	ZD4522 + fenofibrate		ZD4522		Ratio of glsmeans[a]	90% CI[a]
Parameter	glsmean	n	glsmean	n		
ZD4522						
AUC(0-24) (ng·h/ml)	40.7	14	38.0	14	1.07	1.00 to 1.15
C_{max} (ng/ml)	5.29	14	4.36	14	1.21	1.14 to 1.28
	ZD4522 + fenofibrate		Fenofibrate		Ratio of glsmeans[b]	90% CI[b]
	glsmean	n	glsmean	n		
Fenofibric acid						
AUC(0-8) (µg·h/ml)	54.3	14	56.5	13	0.96	0.90 to 1.02
C_{max} (µg/ml)	8.23	14	9.00	13	0.91	0.84 to 1.00

Data derived from Tables T4.3 and T5.3

[a] Ratio and 90% CI are expressed as a ratio of the glsmean (ZD4522 + fenofibrate) / glsmean (ZD4522)

[b] Ratio and 90% CI are expressed as a ratio of the glsmean (ZD4522 + fenofibrate) / glsmean (fenofibrate)

AUC(0-24) = area under the curve from 0 to 24 hours; n = number of volunteers;
AUC(0-8) = area under the curve from 0 to 8 hours; C_{max} = maximum plasma concentration;
glsmean = geometric least squares mean; CI = confidence interval

The 90% CIs for C_{max} and AUC(0-24) for ZD4522 fell within the pre-specified limits, indicating that fenofibrate did not have a significant pharmacokinetic or clinically relevant interaction with ZD4522. The 90% CIs for C_{max} and AUC(0-8) for fenofibric acid also fell within the pre-determined limits, indicating that ZD4522 did not have a significant pharmacokinetic or clinically relevant interaction with fenofibric acid.

Safety: Co-administration of ZD4522 and fenofibrate was well tolerated. More volunteers reported adverse events when the two drugs were co-administered (8 volunteers) compared with when ZD4522 or fenofibrate were given alone (4 and 5 volunteers, respectively). However, no consistent adverse event profile was established for any treatment group and none of the adverse events reported were unexpected or considered to be causally related to trial medication. The

most commonly reported adverse event was headache (2, 4 and 4 volunteers reported headache whilst receiving ZD4522 alone, fenofibrate alone and ZD4522 + fenofibrate in combination, respectively). Two volunteers showed slight elevations in ALT levels (one also showed elevations in AST levels) during the trial (both whilst receiving ZD4522 alone) and one volunteer had slightly raised CK levels (whilst receiving fenofibrate alone); all elevations were small (largest elevation was 1.6 x upper limit of normal [ULN] for ALT and 1.1 x ULN for CK) and transient and were not considered to be clinically significant. There were no signs and symptoms suggestive of muscle damage and no clinically significant effects on uric acid levels associated with co-administration of ZD4522 + fenofibrate. The reduction observed in mean cholesterol levels following administration of ZD4522 plus fenofibrate was greater than when ZD4522 or fenofibrate were given alone. This suggests the possibility of an additive pharmacodynamic response on cholesterol levels when ZD4522 and fenofibrate are dosed together.