SUMMARY

ASTRAZENECA

FINISHED PRODUCT:

ACTIVE INGREDIENT: ZD4522

Trial title (number): A Single Centre, Randomised, Double-blind, 2-Way Crossover Trial to Assess the Effect of Fluconazole, a CYP2C9/2C19 Inhibitor, on the Pharmacokinetics of a Single Dose of ZD4522 80 mg in Healthy Male Volunteers (4522IL/0048).

Developmental phase: I

First volunteer recruited: 22 March 2000
Last volunteer completed: 16 May 2000
AstraZeneca approval date: 25 September 2000

Publications: None at the time of writing this report.

OBJECTIVES

The primary objective of this trial was to assess the effect of fluconazole on the pharmacokinetics of a single dose of ZD4522 80 mg. The secondary objectives were to assess the effect of fluconazole on the pharmacokinetics of total and active HMG-CoA reductase inhibitors and to assess the contribution of ZD4522 to total and active HMG-CoA reductase inhibitors. In addition the safety of all volunteers was ensured by clinical monitoring.

METHODS

Design: This was a randomised, double-blind, 2-way crossover, placebo-controlled trial conducted at a single centre. The trial consisted of two 11-day treatment periods (Periods A and B). During Period A, volunteers received once-daily doses of either fluconazole 200 mg

or placebo for 11 days. During Period B, volunteers crossed over to whichever treatment they did not receive in Period A. On the eighth day of dosing (Trial Day 8) in each treatment period, volunteers also received a single oral dose of ZD4522 80 mg at the same time as dosing with fluconazole or placebo. A 2-week washout period separated Periods A and B.

Population: Healthy male volunteers. A total of 14 volunteers were recruited with the expectation that at least 12 would complete the trial.

Key inclusion criteria: Men aged between 18 and 65 years inclusive; negative screens for serum hepatitis B surface antigen and hepatitis C antibody 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.

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 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 or other statins, and fluconazole or related antifungals.

Dosage: Each volunteer received daily doses of fluconazole 200 mg (batch 992151) or placebo (formulation F12132, batch 00789A98) for 11 days during Period A. During Period B, volunteers received whichever treatment they did not receive in Period A. On the eighth day of dosing in each treatment period, volunteers also received a single oral dose of ZD4522 80 mg (formulation F12568, batch 70235I00).

Key assessments:

Pharmacokinetic: Blood samples were taken at specific times during Trial Day 8 of each trial period, following dosing with trial treatment, to examine the primary pharmacokinetic end-points (AUC and C_{max} of ZD4522) and the secondary pharmacokinetic end-points (AUC(0-t), AUC(0-ct) and t_{max} of ZD4522 and total and active HMG-CoA reductase inhibitors, $t_{1/2}$ of ZD4522, AUC(0-t) and C_{max} of desmethyl ZD4522, C_{max} and $t_{1/2}$ of total and active HMG-CoA reductase inhibitors and C_{min} of fluconazole). The log-transformed values of AUC and C_{max} of ZD4522 were analysed using an analysis of variance (ANOVA) model fitting for the effects of volunteer, period and treatment. The results of the analysis were presented in terms of geometric least square means (glsmeans), the treatment ratio (ZD4522 + fluconazole) / (ZD4522 + placebo) and the 90% confidence interval (CI) for the treatment ratio. If the 90% CI fell within the pre-specified interval of 0.5 to 2.0 then no clinically relevant interaction was concluded.

Safety: Standard safety assessments included adverse event reports, clinical laboratory data (hepatic biochemistry, CK, renal biochemistry, haematology, urinalysis), vital signs, ECGs and physical examination. All data were summarised.

RESULTS

Demography: Fourteen male volunteers entered this trial, all of whom were Caucasian. The mean age, height and weight of the volunteers were 36.6 years (range 29 to 51 years), 179 cm (range 172 to 188 cm) and 81.2 kg (range 70 to 92 kg), respectively. One volunteer withdrew from the trial due to an adverse event/concurrent illness during Trial Period B whilst receiving fluconazole but before receiving the single dose of ZD4522.

Pharmacokinetic: A summary of the key pharmacokinetic findings is presented in Table I. Since fewer than 12 volunteers had AUC data available for both treatments (ie, fluconazole and placebo), AUC(0-t) was considered to be the primary end-point and was subject to formal statistical analysis.

Table I Statistical comparison for plasma AUC(0-t) and C_{max} of ZD4522 80 mg when given with and without fluconazole 200 mg daily

Parameter (units)	ZD4522 + fluconazole		ZD4522 + placebo		Ratio of glsmeans[a]	90% CI for ratio[a]
	glsmean	N	glsmean	N		
AUC(0-t) (ng·h/ml)	370	13	325	14	1.139	0.967 to 1.341
C_{max} (ng/ml)	45.1	13	41.4	14	1.089	0.874 to 1.355

Data derived from Table T4.2.3

[a] Ratio and 90% CI are expressed as a ratio of glsmean (ZD4522 + fluconazole) / glsmean (ZD4522 + placebo)
glsmean = geometric least square mean; AUC(0-t) = area under the curve up to time t;
C_{max} = maximum plasma concentration; CI = confidence interval; N = number of volunteers

Geometric mean AUC(0-t) and C_{max} of ZD4522 were higher following dosing with fluconazole compared with placebo, however, the 90% CIs for the treatment ratios fell within the pre-determined limits of 0.5 to 2.0, indicating that there was no clinically relevant interaction between ZD4522 and fluconazole. A comparison of the individual plasma concentration profiles of ZD4522 between treatment periods indicates that the shapes of the profiles, including the terminal elimination phase, are similar. Median t_{max} values for ZD4522 with and without fluconazole were 4.0 and 5.0 hours, respectively. Mean half-life values for ZD4522 with and without fluconazole were 19.1 and 18.6 hours, respectively. Comparison of the AUC(0-ct) gmean ratios for ZD4522 and total and active HMG-CoA reductase inhibitors within each treatment period suggests that ZD4522 was the major active circulating component, accounting for approximately all of the circulating active HMG-CoA reductase inhibitors. Steady state plasma concentrations of fluconazole were achieved before dosing with ZD4522 and during sampling after ZD4522 administration.

From the limited data obtained for desmethyl ZD4522, it was observed that there was a 25% reduction in C_{max} values in volunteers dosed with fluconazole compared with volunteers dosed with placebo, with no corresponding increase in ZD4522 concentrations. This is consistent with the metabolism of ZD4522 being a minor route of clearance. Also, the apparent decrease in metabolite is not particularly large considering that CYP2C9 was the major P450 enzyme associated with ZD4522 metabolism during in vitro studies. This suggests that multiple P450 enzymes could be capable of metabolism of ZD4522 to the N-desmethyl derivative.

Safety: ZD4522 and fluconazole were well tolerated when co-administered. There was no evidence of adverse events associated with liver function abnormalities or myopathy. Headache was the most commonly reported adverse event during the trial. There were no serious adverse

events or deaths during the trial. One volunteer was withdrawn from the trial due to an adverse event (flu syndrome) which occurred when the volunteer was receiving fluconazole 200 mg alone, before ZD4522 was administered. None of the adverse events reported during the trial were considered, by the investigator, to be related to trial treatment. The adverse event profile of ZD4522 in this trial was as expected with no new safety issues being raised.