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 Itraconazole, a CYP3A4 Inhibitor, on the Pharmacokinetics of a Single Dose of ZD4522 80 mg in Healthy Male Volunteers (4522IL/0053).

Developmental phase: I

First volunteer recruited: 31 January 2000
Last volunteer completed: 4 April 2000
AstraZeneca approval date: 22 September 2000

Publications: None at the time of writing this report.

OBJECTIVES

The primary objective of the trial was to assess the effect of itraconazole on the pharmacokinetics of a single dose of 80 mg ZD4522. The secondary objectives of the trial were to assess the effect of itraconazole 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 inhibitor concentrations. In addition, the safety of volunteers was assured by clincal 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 5-day treatment periods (Periods A and

B). During Period A volunteers received 5 daily doses of itraconazole 200 mg or placebo. During Period B, volunteers were crossed over to which-ever treatment they did not receive in Period A. On the fourth day of dosing in each treatment period, volunteers also received a single oral dose of ZD4522 80 mg, 1 hour after the dose of itraconazole or placebo. A 4-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 itraconazole or related antifungal agents.

Dosage: Each volunteer received either itraconazole 200 mg (2 x 100 mg; batch 99FV213) or placebo (formulation F12132, batch 00789A98) once-daily for 5 days during Period A. During Period B volunteers were crossed over to whichever treatment they did not receive in Period A. On the fourth 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 4 of each trial period, following dosing with trial treatment, to examine the primary pharmacokinetic end-points (AUC(0-t) and C_{max} of ZD4522) and the secondary pharmacokinetic end-points (AUC, AUC(0-ct), t_{max} and $t_{1/2}$ of ZD4522, AUC(0-t), AUC(0-ct), C_{max}, t_{max} and $t_{1/2}$ of total and active HMG-CoA reductase inhibitors and AUC(0-72), C_{max} and t_{max} of itraconazole and hydroxyitraconazole). The log-transformed values of AUC(0-t) 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 glsmeans, the treatment ratio (ZD4522 + itraconazole) / (ZD4522 + placebo) and the 90% confidence interval (CI) for the treatment ratio. If the 90% CI fell outside the pre-specified interval of 0.7 to 1.43, then a pharmacokinetic interaction was concluded.

Safety: Safety and tolerability were assessed during the trial by recording of adverse events, specific clinical 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. Their mean age, height and weight were 38.4 years (range 25 to 56 years), 178.4 cm (range 168 to 186 cm) and 78.4 kg (range 59 to 88 kg), respectively. There were no withdrawals during the trial. The trial was conducted at a single centre.

Pharmacokinetics: A summary of the key pharmacokinetic findings is presented in Table I.

Table I Statistical comparison for plasma AUC(0-t) and C_{max} of ZD4522 in the presence and absence of itraconazole

Parameter (units)	ZD4522 + itraconazole		ZD4522 + placebo		Ratio of glsmeans[a]	90% CI for ratio[a]
	glsmean	N	glsmean	N		
AUC(0-t) (ng·h/ml)	508	14	397	14	1.280	1.149 to 1.426
C_{max} (ng/ml)	61.3	14	53.5	14	1.145	0.949 to 1.381

Data derived from Table T4.1.3

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

Itraconazole increased exposure to ZD4522, based on AUC(0-t) by approximately 28% and C_{max} by approximately 15%. When the AUC(0-t) and C_{max} were assessed statistically, the 90% CIs were within the pre-determined limits of 0.7 to 1.43. This indicated that there was no significant pharmacokinetic interaction between ZD4522 and itraconazole with respect to the AUC(0-t) and C_{max} of ZD4522. It was not possible to define the terminal elimination phase and hence estimate the $t_{1/2}$ of ZD4522 for all volunteers. However, comparison of the individual plasma concentration profiles between treatment periods indicates that the shapes of the profiles, including the terminal elimination phase (where defined) are similar.

Comparison of the AUC(0-ct) gmean ratios for ZD4522 and total and active HMG-CoA reductase inhibitors within each treatment period, dosed with or without itraconazole, showed that ZD4522 was the major active circulating component, accounting for approximately all of the circulating active HMG-CoA reductase inhibitors, which suggests only a small amount of circulating active metabolite. Active HMG-CoA reductase inhibitors accounted for approximately 82 to 85% of total HMG-CoA reductase inhibitors (in both treatment groups) indicating the presence of only a small proportion of circulating drug-related lactone(s) with the potential to generate pharmacologically active species. As a consequence of ZD4522 accounting for all of the active HMG-CoA reductase inhibitor, observed changes, following dosing with itraconazole, in the pharmacokinetics of total and active HMG-CoA reductase inhibitors are relative to the changes observed in the pharmacokinetics of ZD4522.

Appropriate plasma concentrations of itraconazole and hydroxyitraconazole were observed for 200 mg daily dosing of itraconazole.

Safety: ZD4522 and itraconazole were well tolerated when co-administered. There was no evidence of adverse events associated with liver function abnormalities or myopathy and there were no serious adverse events or deaths during the trial. Pharyngitis was the most commonly reported adverse event during the trial. None of the adverse events reported 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.