

## SUMMARY

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**ASTRAZENECA**

**FINISHED PRODUCT:**

**ACTIVE INGREDIENT:** ZD4522

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**Trial title (number):** A Single Centre, Randomised, Double-blind, 2-Way Crossover Trial to Assess the Effect of Ketoconazole, a CYP3A4 Inhibitor, on the Pharmacokinetics of a Single Oral Dose of ZD4522 80 mg in Healthy Male Volunteers (4522IL/0057).

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**Developmental phase: I**

**First volunteer recruited:** 25 April 2000

**Last volunteer completed:** 13 June 2000

**AstraZeneca approval date:** 09 November 2000

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**Publications:** None at the time of writing this report.

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### OBJECTIVES

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

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### METHODS

**Design:** This was a randomised, double-blind, placebo-controlled, 2-way crossover trial conducted at a single centre. The trial consisted of two seven-day treatment periods (Periods A and B), separated by a washout period of at least two weeks. During Period A volunteers received oral doses of ketoconazole 200 mg twice a day or placebo twice a day for seven days.

In Period B, volunteers crossed over to the treatment they had not received in Period A. On Trial Day 4 of each period a single oral dose of ZD4522 80 mg was taken with the morning dose of ketoconazole or placebo.

**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, hepatitis C antibody and human immunodeficiency virus (HIV) 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; weight not differing by more than 20% from the desirable weight; non-smoker or casual smoker (<10 cigarettes a day).

**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 three 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 related statins, and ketoconazole or related anti-fungal agents; any acute illness within two weeks of the start of the trial; history of Gilbert's syndrome.

**Dosage:** Each volunteer received ketoconazole 400 mg/day (formulation F12737, batch 99HB340) and placebo (formulation F12019, batch 609445) in random order (one medication in Period A and then the other medication in Period B). A single dose of ZD4522 80 mg (formulation F012568, batch 993151) was given on Trial Day 4 in each period (ZD4522 was given at the same time as the morning dose of ketoconazole/placebo).

**Key assessments:**

**Pharmacokinetic and pharmacodynamic:** Blood samples were taken at specified times during the trial 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),  $t_{1/2}$  and  $t_{max}$  of ZD4522;  $C_{min}$  of ketoconazole and  $C_{max}$ , AUC (0-t), AUC(0-ct),  $t_{1/2}$  and  $t_{max}$  of active and total HMG-CoA reductase inhibitors). If AUC data from both treatment periods was available for 12 or more volunteers then the AUC was analysed, otherwise AUC(0-t) was considered to be the primary end-point. The AUC and  $C_{max}$  values of ZD4522 were analysed using an analysis of variance (ANOVA) model fitting for the effects of volunteer, period and treatment (ketoconazole or placebo). The results of the analysis were presented in terms of geometric least square means (glsmeans), treatment effect (ratio of glsmeans) and 90% confidence interval (CI) for the treatment effect. No clinically relevant interaction was considered to have occurred if the 90% CI for the ratio fell within the interval 0.5 to 2.0.

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

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## RESULTS

**Demography:** Fourteen healthy male Caucasian volunteers entered this trial. Their mean age, height and weight were 24.1 years (range 21 to 31 years), 182.1 cm (range 170 to 189 cm) and 73.5 kg (range 60 to 83 kg), respectively. One volunteer withdrew from the trial during the washout period between Periods A and B due to personal reasons. All volunteers with pharmacokinetic data available were included in the statistical analysis and all volunteers were included in the safety summaries.

**Pharmacokinetic:** The AUC(0-t) of ZD4522 was analysed as the primary end-point since AUC data from both treatment periods was available for fewer than 12 volunteers (available for only 7 patients in the ketoconazole group and 11 patients in the placebo group). The results of the statistical analysis comparing AUC(0-t) and  $C_{max}$  of ZD4522 in the presence and absence of ketoconazole are presented in Table I.

**Table I Statistical analysis of plasma AUC(0-t) and  $C_{max}$  for ZD4522 80 mg in the presence and absence of ketoconazole 200 mg twice-daily (bid)**

Parameter (units)	ZD4522 + ketoconazole		ZD4522 + placebo		Ratio of glsmeans <sup>a</sup>	90% CI for ratio <sup>a</sup>
	glsmean	N	glsmean	N		
AUC(0-t) (ng·h/ml)	310	13	305	14	1.016	0.839 to 1.230
$C_{max}$ (ng/ml)	37.2	13	39.0	14	0.954	0.722 to 1.260

**Data derived from Table T4.1.3**

<sup>a</sup> Ratio and 90% CI are expressed as a ratio of glsmean (ZD4522 + ketoconazole) / 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

Similar exposure to ZD4522, based on AUC(0-t) and  $C_{max}$ , was observed when ZD4522 was dosed with and without ketoconazole. When the AUC(0-t) and  $C_{max}$  of ZD4522 were compared statistically, the 90% CIs were within the pre-determined limits of 0.5 to 2.0. This indicated that there was no relevant clinical interaction between ZD4522 and ketoconazole with respect to AUC(0-t) and  $C_{max}$  of ZD4522. This supports the in vitro metabolism findings that CYP3A4 does not play a major role in the clearance of ZD4522. Comparison of the gmean of individual AUC(0-ct) ratios for ZD4522 and total and active HMG-CoA reductase inhibitors within each treatment period, dosed with and without ketoconazole, suggested that ZD4522 was the major active circulating component, accounting for almost all of the circulating HMG-CoA reductase inhibitors (total circulating reductase inhibitors 86% to 93%). Comparison of the gmean of individual AUC(0-ct) ratios and  $C_{max}$  values for both active and total HMG-CoA reductase inhibitors showed no difference when given with and without ketoconazole. Steady state plasma concentrations of ketoconazole were achieved before dosing with ZD4522 and were maintained during sampling.

**Safety:** Overall, ZD4522 and ketoconazole were well tolerated when given concomitantly. There were no deaths, no serious adverse events and no clinically significant changes in vital signs, ECGs or medical examinations during the trial. The incidence of adverse events in both the ketoconazole and placebo groups did not increase when ZD4522 was co-administered. Overall more volunteers reported adverse events in the ketoconazole group compared to the placebo group, with most events being attributable to the known side-effects of ketoconazole. One volunteer withdrew from the trial due to personal reasons after completing Period A

(placebo treatment). Five volunteers had slightly raised LFTs during the trial and four volunteers had slightly raised CK levels. However, all elevations were small and transient and were not considered to be of clinical concern.