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 Erythromycin, a CYP3A4 Inhibitor, on the Pharmacokinetics of a Single Oral Dose of ZD4522 80 mg in Healthy Male Volunteers (4522IL/0058).

Developmental phase: I

First volunteer recruited: 10 March 2000
Last volunteer completed: 14 April 2000
AstraZeneca approval date: 21 December 2000

Publications: None at the time of writing this report.

OBJECTIVES

The primary objective of this trial was to assess the effect of erythromycin on the pharmacokinetics of a single oral dose of ZD4522 80 mg. The secondary objectives of this trial were to assess the effect of erythromycin 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 addition the safety of all volunteers will be ensured by clinical monitoring.

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 erythromycin 500 mg four times a day or placebo four times a day for seven days. The single dose of ZD4522 80 mg was taken with the first morning dose of erythromycin or placebo on Trial Day 4. In Period B volunteers crossed over to the treatment they had not received in Period A.

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

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, erythromycin and related drugs; any acute illness within two weeks of the start of the trial; history of Gilbert's syndrome.

Dosage: Each volunteer received erythromycin 2 g/day (500 mg qid) (formulation F12729, batch BN001) and placebo (formulation F12132, batch N73249) in random order (one medication in Period A and the other in Period B). A single dose of ZD4522 80 mg (formulation F012568, batch ST74026-001-FA01) was given on Trial Day 4 in each period (ZD4522 was given at the same time as the morning dose of erythromycin/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 erythromycin and C_{max}, AUC (0-t), AUC(0-ct), $t_{1/2}$ and t_{max} of active and total HMG-CoA reductase inhibitor concentrations. Plasma ZD4522, total and active HMG-CoA reductase inhibitors and erythromycin concentration-time data were analysed by non-compartmental pharmacokinetic methods. If AUC data from both treatment periods were available for 12 or more volunteers then the AUC was analysed, otherwise AUC(0-t) was considered to be the primary end-point. The results of the analysis were presented in terms of geometric least squares means (glsmeans), treatment effect (ratio of glsmeans) and 90% confidence intervals (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: Safety and tolerability were assessed during the trial by collection of adverse events, specified laboratory tests (eg, hepatic, muscle and renal), medical examination, periodic vital signs measurements and ECGs. Safety assessment data were summarised.

RESULTS

Demography: Fourteen healthy male Caucasian volunteers entered this trial. Their mean age, height and weight were 32.5 years (range 22 to 44 years), 179.4 cm (range 164 to 190 cm) and 75.9 kg (range 59 to 98 kg), respectively. Two volunteers withdrew from the trial due to adverse events. Volunteer 0001 had some of his Period B pharmacokinetic data excluded from the statistical analyses due to a dosing error, but otherwise all volunteers were included in the statistical analysis.

Pharmacokinetic: The AUC(0-t) of ZD4522 was analysed as the primary end-point since AUC data from both treatment periods was not available for 12 volunteers. The results of the statistical analysis comparing AUC(0-t) and C_{max} of ZD4522 in the presence and absence of erythromycin are presented in Table I.

Table I Statistical analysis of plasma AUC(0-t) and C_{max} for ZD4522 in the presence and absence of erythromycin 500 mg

	ZD4522 + erythromycin		ZD4522 + placebo		Ratio of glsmeans[a]	90% CI[a]
	N	glsmean	N	glsmean		
AUC(0-t) (ng·h/ml)	11	202	14	253	0.80	0.68 to 0.94
C_{max} (ng/ml)	11	23.2	14	33.7	0.69	0.52 to 0.91

Data derived from Table T4.1.3

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

There was a small decrease in ZD4522 plasma concentrations (20% reduction in AUC(0-t)) when ZD4522 80 mg was administered during erythromycin treatment (500 mg four times a day [qid] for seven days) when compared with placebo. However, the 90% CIs for both AUC(0-t) and C_{max} were within the predetermined 0.5 to 2.0 equivalence limits. This indicated that there were no clinically significant interactions between ZD4522 and erythromycin with respect to AUC(0-t) and C_{max} of ZD4522. Comparison of the plasma AUC(0-ct) for ZD4522 and active and total HMG-CoA reductase inhibitors showed that ZD4522 accounted for most of the circulating active HMG-CoA reductase inhibitors and that it was unaffected by erythromycin co-administration. Erythromycin, which is a potent inhibitor of cytochrome P450 3A4 (CYP3A4), did not produce any increase in the plasma concentrations of ZD4522, strongly suggesting that metabolism via CYP3A4 is not an important clearance route for ZD4522. The reduction in ZD4522 concentrations observed during erythromycin treatment was not of a magnitude defined as clinically relevant and would not warrant a dosage adjustment. The decrease observed in ZD4522 plasma concentrations when administered with erythromycin may be a consequence of the profound effect erythromycin has on gastroduodenal motor activity.

Safety: Overall, ZD4522 and erythromycin 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 erythromycin and placebo groups did not increase when ZD4522 was co-administered. Overall, more volunteers reported adverse events in the erythromycin and erythromycin + ZD5422 groups compared with the placebo and placebo + ZD4522 groups, with most events being attributable to the known gastrointestinal side effects of erythromycin. Two volunteers withdrew from the trial whilst receiving erythromycin alone due to severe vomiting. Four volunteers had slightly raised ALT levels: two volunteers had raised ALT values at the 96 hour assessment after placebo + ZD4522 treatment; one volunteer had raised ALT values at the 96 hour assessment after erythromycin + ZD4522 treatment; and one volunteer had raised ALT values during all treatment periods. One volunteer had slightly raised CK levels on Trial Day -1 prior to erythromycin dosing. All elevations were small and transient and were not considered to be of clinical concern.