SUMMARY

ZENECA PHARMACEUTICALS

FINISHED PRODUCT:

ACTIVE INGREDIENT: ZD4522

Trial title (number): A Randomised, Double-Blind, 2-Way Crossover Trial to Assess the Effect of ZD4522 (40 mg) on the Pharmacokinetics of a Single Oral Dose of Digoxin in Healthy Male Volunteers (4522IL/0013)

Developmental phase: I

First volunteer recruited: 31 March 1999
Last volunteer completed: 24 May 1999
Zeneca approval date: 19 January 2000

Publications: None at the time of writing this report.

OBJECTIVES

The objective of this trial was to assess the effect of ZD4522 on the pharmacokinetics of a single dose of digoxin.

METHODS

Design: Double-blind, randomised, 2-way crossover trial conducted at a single centre. The trial consisted of two 12-day trial periods (A and B) during which volunteers were given single daily oral doses of ZD4522 40 mg or placebo. Volunteers were given a single oral dose of 0.5 mg digoxin on Trial Day 8 of each trial period. Following a 4-week washout period, volunteers were crossed over to whichever treatment they did not receive in the first trial period.

Population: Eighteen healthy volunteers. A total sample size of 18 volunteers would have 86% and 90% power to detect a significant pharmacokinetic difference in AUC and C_{max}, respectively, for digoxin in the presence or absence of ZD4522.
Key inclusion criteria: Men aged between 18 and 55 years inclusive; negative screens for serum hepatitis B surface antigen, hepatitis C antibody and a normal screen for ferritin; weight within 20% of desirable weight; no clinically significant abnormalities identified from the medical history, physical examination and ECG as evaluated by the investigator.
Key exclusion criteria: Clinically significant abnormalities in clinical laboratory parameters, specifically total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and creatine kinase (CK); history or presence of gastrointestinal, hepatic or renal disease or other condition known to interfere with 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 to digoxin.
Dosage: Each volunteer was given ZD4522 40 mg (formulation F12420, batch 01240G98) or placebo (formulation F12421, batch 01243I98) once-daily for 12 days in trial period A; in trial period B volunteers were crossed over to whichever treatment they did not receive in period A. A single dose of digoxin 0.5 mg was administered on Trial Day 8 of each trial period at the same time as ZD4522/placebo was given to the volunteers.
Key assessments:
Pharmacokinetics: Blood samples were taken at specified times on Trial Days 8 to 12 and analysed for digoxin to determine the pharmacokinetic variables (AUC, C_{max}, t_{max} and $t_{1/2}$) in the presence and absence of ZD4522. Blood samples were also taken and analysed for ZD4522 to determine the pharmacokinetic variables AUCτ, C_{max} and t_{max}. The log transformed values of AUC and C_{max} of digoxin were analysed using an analysis of variance 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 + digoxin glsmean / placebo + digoxin glsmean) and its 90% confidence interval (CI). The effect of ZD4522 on AUC and C_{max} of digoxin was assessed using the 90% CIs for the treatment ratio. If the 90% CI fell outside the pre-specified interval of 0.74 to 1.35, a pharmacokinetic interaction would be concluded.
Safety: Safety and tolerability were assessed during the trial by collection of adverse events (AEs), specific clinical laboratory tests (eg, hepatic, muscle, and renal), physical examination, periodic vital signs measurements and electrocardiograms (ECGs). Safety assessment data were summarised.

RESULTS
Demography: Eighteen male Caucasians entered this trial. Their mean age, height and weight were 40 years (range 31 to 50 years), 177.3 cm (range 173 to 184 cm), and 79.1 kg (range 60 to 100 kg), respectively. Two volunteers withdrew from the trial; one because of a non-serious adverse event and one because of withdrawal of informed consent. The trial was conducted at a single centre.

Pharmacokinetics: Serum concentrations of digoxin were similar when digoxin was dosed alone or concomitantly with ZD4522. The results of the statistical analysis comparing AUC(0-t) and C_{max} of digoxin in the presence and absence of ZD4522 are shown in Table I. There was insufficient serum digoxin data to define the terminal elimination phase and as a consequence $t_{1/2}$ could not be calculated and only AUC(0-t) was determined.

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

Parameter (units)	ZD4522 + digoxin		Placebo + digoxin		Ratio of glsmeans[a]	90% CI for ratio[a]
	glsmean	n	glsmean	n		
AUC(0-t) (ng·h/ml)	8.14	18	7.80	16	1.04	0.88 to 1.24
C_{max} (ng/ml)	2.22	18	2.12	16	1.04	0.89 to 1.22

Data derived from Table T4.3

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

The geometric mean AUC(0-t) and C_{max} of digoxin were only 4% higher when digoxin was co-administered with ZD4522 compared with when it was given with placebo. The 90% CIs were within the pre-specified interval, therefore, no significant interaction occurred. The time at which maximum serum concentrations of digoxin were observed was also unaffected by the co-administration of ZD4522 (1.00 hour when given with both ZD4522 and placebo). Despite the narrow therapeutic index, the change in serum digoxin concentrations was numerically small and not considered clinically significant. The mean amount of digoxin excreted in urine up to 96 hours after dosing was 40% of administered dose when given with both ZD4522 and placebo and the rate of excretion was also similar.

The pre-dose geometric mean plasma concentrations of ZD4522 on Trial Days 6 and 7 showed that steady state was achieved, however, the plasma concentrations of ZD4522 observed on Trial Day 8, when digoxin was co-administered, were lower than those on Trial Day 7. Geometric mean C_{max} and AUCτ of ZD4522 were 21% and 15% lower, respectively. There was a high degree of variability between individual volunteers for these parameters; Volunteer 0002 had a 50% decrease in C_{max} for ZD4522 on Trial Day 8, however, Volunteers 0001, 0014 and 0015 actually showed slight increases in C_{max} following digoxin dosing. The reason for the differences between Trial Days 7 and 8 is not known and could be due to volunteers being dosed on different days or to an effect of digoxin. This trial was not designed to evaluate the effects of digoxin on the pharmacokinetic parameters of ZD4522 and therefore, no conclusion about this change in ZD4522 concentrations can be made. Renal excretion of ZD4522 was low, with only 1.5 to 10% of the dose being recovered at steady state. Low renal excretion of ZD4522 was expected as it has been observed in previous studies with ZD4522, and was not affected by digoxin.

Safety: The majority of the adverse events reported in this study are not unique to this particular drug or trial. Co-administration of ZD4522 and digoxin was well tolerated. There were no deaths, no serious adverse events and no clinically significant changes in clinical laboratory

parameters, vital signs and medical examination during the trial. No clinically significant myopathy or liver function abnormalities were observed. Overall, the most frequently occurring adverse events were pharyngitis, headache, adverse events pertaining to the digestive system and palpitation. More volunteers reported adverse events when they received ZD4522 plus digoxin than when they received ZD4522 alone (9 and 4 volunteers respectively). Four of these volunteers developed pharyngitis during the period they were receiving ZD4522 plus digoxin. The time of onset of pharyngitis ranged from 6 to 28 days post-dose and therefore, no temporal relationship to trial treatment could be concluded. More volunteers also reported adverse events when they were receiving placebo plus digoxin than when they were given placebo alone (5 and 1 volunteers, respectively). Two volunteers had adverse events that were considered, in the investigator's opinion, to be related to trial medication. Both volunteers complained of palpitations and Volunteer 0006 also developed runs of ventricular bigeminy on Trial Day 8 during trial period A; this volunteer was withdrawn from the trial. The second volunteer (0001) was noted to have unifocal broad complex ventricular ectopics on the real-time ECG on Trial Day 8 during trial period B. The volunteer completed the trial with no further recurrence of the adverse event. Both volunteers were receiving ZD4522 plus digoxin at the time the events occurred. Both events were reported as resolved by the end of the trial and no concomitant treatment was administered to either volunteer. The development of these types of arrhythmias during therapy with digoxin is well recognised. The role of ZD4522, if any, in the development of arrhythmias is not known.