SUMMARY

ZENECA PHARMACEUTICALS

FINISHED PRODUCT:

ACTIVE INGREDIENT: ZD4522

Trial title (number): An Open, Non-Randomised, Parallel-Group, Non-Controlled, Phase I Trial to Assess the Effect of Age and Gender on the Pharmacokinetics of a Single 40 mg Oral Dose of ZD4522 in Healthy Male and Female Volunteers (4522IL/0015)

Developmental phase: I

First volunteer recruited: 7 July 1999
Last volunteer completed: 28 July 1999
Zeneca approval date: 29 November 2000

Publications: None at the time of writing this report.

OBJECTIVES

The primary objective of this trial was to assess the effect of age and gender on the pharmacokinetics of a single 40 mg oral dose of ZD4522 in healthy male and female volunteers. The secondary objective of this trial was to assess the effect of age and gender on the tolerability of a single 40 mg oral dose of ZD4522 in healthy male and female volunteers.

METHODS

Design: Open-label, non-randomised, non-controlled, parallel-group trial conducted at a single centre. The trial consisted of a single oral dose of ZD4522 40 mg with a 96-hour follow-up period.

Population: Healthy male or female volunteers. A total of 32 volunteers were recruited with the expectation that at least 28 would complete the trial. A total sample size of 28 would have 88% power to show that the 90% confidence interval (CI) was between 0.5 and 2.0 for the ratio

(male/female or young/elderly) for AUC(0-t) or C_{max}. This would apply for both the comparison of males with females and the young with the elderly.
Key inclusion criteria: Men or women aged either between 18 to 35 years inclusive or >65 years; no clinically significant abnormalities identified from the medical history, physical examination and ECG as evaluated by the investigator; negative screens for serum hepatitis B surface antigen, hepatitis C antibody, HIV and a normal screen for ferritin.
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 absorption, distribution, metabolism or excretion of drugs.
Dosage: Each volunteer was given one oral dose of ZD4522 40 mg (4 x 10 mg capsules; formulation F12420, batch 01240G98) between 08.00 and 09.15 hours.
Key assessments:
Pharmacokinetics: Blood samples were collected at specified times up to 96 hours following the administration of a single dose of ZD4522, to examine the pharmacokinetic variables (AUC(0-t), C_{max}, t_{max} and $t_{1/2}$) in young and elderly male and female volunteers. The effect of gender and age on the pharmacokinetics of ZD4522 was assessed by constructing 90% confidence intervals for the male/female and young/elderly ratios based on the least squares means from the analysis of variance (ANOVA) of log-transformed AUC(0-t) and C_{max} values, allowing for the effects of age and gender.
Safety: Standard safety assessments included adverse event reports, clinical laboratory data (hepatic biochemistry, CK, renal biochemistry, haematology, urinalysis), vital signs, ECGs and physical examination. Safety data collected during the trial was summarised. Pre-and post-trial safety data was listed.

RESULTS
Demography: Thirty-two volunteers entered this trial; 16 male (8 young and 8 elderly)and 16 female (8 young and 8 elderly) . Sixteen volunteers were in the young age group (18 to 35 years) and 16 were in the elderly age group (>65 years). Thirty-one volunteers were Caucasian and one was of mixed race. The mean age, height and weight of the young volunteers (n=16) were 24.4 years (range 18 to 33 years), 173.4 cm (range 153 to 188 cm), and 66.7 kg (range 55 to 88 kg), respectively. The mean age, height and weight of the elderly volunteers (n=16) were 67.7 years (range 65 to 73 years), 167.3 cm (range 154 to 186 cm), and 71.8 kg (range 58 to 93 kg), respectively. There were no withdrawals during the trial. The trial was conducted at a single centre.
Pharmacokinetics: Geometric mean plasma concentrations of ZD4522 were similar in young and elderly, and male and female volunteers, following a single 40 mg dose. The results of the statistical analysis comparing C_{max} and AUC(0-t) of ZD4522 by age group and gender are shown in Table I.

Table I Statistical comparison of young and elderly volunteers and male and female volunteers for plasma C_{max} and AUC (0-t) of ZD4522 40 mg

Comparison	Young[a]		Elderly[a]		Ratio of glsmeans[b]	90% CI for ratio[b]
Parameter	glsmean	n	glsmean	n		
C_{max} (ng/ml)	20.8	16	18.7	16	1.12	0.83 to 1.51
AUC(0-t) (ng·h/ml)	206	16	194	16	1.06	0.86 to 1.30
	Males[a]		Females[a]		Ratio of glsmeans[c]	90% CI for ratio[c]
	glsmean	n	glsmean	n		
C_{max} (ng/ml)	17.9	16	21.7	16	0.82	0.61 to 1.11
AUC(0-t) (ng·h/ml)	191	16	209	16	0.91	0.74 to 1.12

Data derived from Tables T3.2.4 and T3.2.5

[a] Volunteers are included in 2 categories, 1 age category and 1 gender category

[b] Ratio and 90% CI are expressed as ratio glsmean (young) / glsmean (elderly)

[c] Ratio and 90% CI are expressed as ratio of glsmean (male) / glsmean (female)

C_{max} = maximum plasma concentration; CI = confidence interval;
AUC(0-t) = area under the curve from zero to last quantifiable concentration;
glsmean = least square mean

C_{max} and AUC(0-t) of ZD4522 40 mg were similar in both age groups and in male and female volunteers. Small differences in exposure were noted between the volunteer groups, with exposure in the young being slightly higher than in the elderly and exposure in females being higher than in males. However, since the 90% CIs for C_{max} and AUC(0-t) for both comparisons were within the pre-specified interval of 0.5 to 2.0, these differences are considered unlikely to be of clinical concern and, with respect to these parameters, the pharmacokinetics of ZD4522 were unaffected by age and gender. Maximum plasma concentrations of ZD4522 were achieved at approximately 3 to 5 hours in each volunteer group. Individual t_{max} values ranged from 1 to 5 hours overall, but there were no obvious differences in t_{max} between the young and elderly or male and female volunteers. There were no apparent differences in the elimination rate of ZD4522 between groups, with mean elimination half-lives of approximately 20 hours for all volunteer groups. However, there was high variability for this parameter within each group.

Safety: ZD4522 40 mg was well tolerated by young and elderly male and female volunteers. There were no deaths, no serious adverse events, no withdrawals due to adverse events and no clinically significant changes in clinical laboratory parameters, vital signs or medical examinations.

The number of young and elderly volunteers reporting adverse events was similar, with 8 young volunteers reporting 14 events and 7 elderly volunteers reporting 15 events. More female volunteers reported adverse events during the trial than male volunteers, 69% and 25%, respectively. However, the majority of adverse events (20 out of 22) reported by the female volunteers occurred 3 to 9 days following the single dose of ZD4522 40 mg and, therefore were considered to have no temporal relationship to trial medication.

The most commonly reported adverse event was headache, with 6 volunteers reporting 12 incidences. No clear relationship to trial medication was identified for the occurrences of headache, except for 2 volunteers. In both cases, headaches were resolved within 8 hours of their onset.

Two volunteers (0024 and 0025) reported somnolence during the trial and both events were considered to be related to trial medication. Both incidences were reported as resolved within 3 days of their occurrence.
There were no increases in ALT to >3 x ULN in any volunteer.
Two volunteers reported leg pain (Volunteers 0013 and 0027) and one volunteer reported pelvic pain (Volunteer 0031) during the trial, and, in the opinion of the investigator, these events were related to trial medication. Clinical examination and clinical laboratory tests revealed no signs or symptoms of myalgia. Seven volunteers had transient elevations in CK levels during the trial (ie, levels outside the normal range of 38 to 174 U/L). However, none of the elevations were >10 x ULN and were, therefore, not considered to be clinically significant.
One volunteer (0006), was reported to have non-specific T-wave changes on his ECG tracing at 5, 8 and 12 hours post-dose. There were no other ECG (morphology and/or intervals) changes observed in this or other volunteers during the study.