SUMMARY

ZENECA PHARMACEUTICALS

FINISHED PRODUCT:

ACTIVE INGREDIENT: ZD4522

Trial title (number): A Randomised, Double-blind, Parallel-group, Dose-response Study with the HMG-CoA Reductase Inhibitor ZD4522 in Subjects with Primary Hypercholesterolaemia (4522IL/0023)

Developmental phase: II/III

First subject recruited: 27 April 1999
Last subject completed: 09 December 1999
Zeneca approval date: 28 March 2000

Principal investigator and location (centre number):

Publications: None at the time of writing this report

OBJECTIVES

The primary objective of this trial was to estimate the dose-response relationship between the dose of ZD4522 (40 mg and 80 mg) and the percentage change in low density lipoprotein-cholesterol (LDL-C) from the baseline value with respect to placebo. The secondary objectives of this trial were to: estimate the effects of ZD4522 on high density lipoprotein-cholesterol (HDL-C), triglyceride (TG), total cholesterol (TC), apolipoprotein AI (ApoA-I), apolipoprotein AII (ApoA-II), lipoprotein (a) (Lp(a)), apolipoprotein B-100 (ApoB) and fibrinogen; to assess the pharmacokinetics of oral doses of 40 and 80 mg ZD4522 over a 6-week treatment period and determine if steady state kinetics are maintained over this period; and to assess the tolerability and safety of ZD4522 in comparison with placebo.

METHODS

Design: This was a 16-week, multicentre, randomised, double-blind, parallel-group trial. After a 6-week dietary run-in period, subjects were randomised to treatment with either placebo or

ZD4522 40 mg or 80 mg (in a ratio of 1:1:2) for an additional 6 weeks. Following this, subjects entered into a 4-week follow-up period to ensure that all subjects returned to their pre-trial levels for the safety parameters. The placebo group was included to provide a meaningful comparator for efficacy, safety and tolerance data.

Population: Fourteen randomised subjects in each of the placebo and ZD4522 40 mg groups and 28 subjects in the ZD4522 80 mg group were required for 90% power of detecting a 25% difference between 2 groups in percentage change from baseline in LDL-C levels. Allowing for a 75% screen failure rate, a maximum number of 200 subjects entering the dietary run-in period was required. A ratio of 1:1:2 was used to increase exposure to the ZD4522 80 mg dose.

Key inclusion criteria: Male subjects aged 18 to 70 years or post-menopausal females aged 50 to 70 years; fasting LDL-C levels of >160 mg/dL (4.14 mmol/L) but <240 mg/dL (6.21 mmol/L); fasting TG levels of <300 mg/dL (3.39 mmol/L); body mass index (BMI) of ≤30 kg/m^2; food record rating (FRR) score of ≤15.

Key exclusion criteria: Various concomitant illnesses, including active liver disease or hepatic dysfunction (defined by an ALT, AST or bilirubin concentration of >1.5 times the upper limit of normal [ULN]), active arterial disease, malignancy (unless basal or squamous cell skin carcinoma), uncontrolled hypertension, and uncontrolled hypothyroidism; serum creatine kinase (CK) concentrations of >3 times the ULN; use of concomitant medications known to affect the lipid profile or present a potential safety concern (eg, through drug interaction).

Dosage: Subjects took oral doses of trial medication once daily approximately 3 hours after the evening meal. Doses of treatments were as follows: ZD4522 40 and 80 mg, and placebo. Formulation and batch numbers were as follows: ZD4522 10 mg (F12420, 01242A98 and 01241D98) and placebo (F12421, 01243I98).

Key assessments:

Efficacy: The primary endpoint was percentage change from baseline to Week 6 in LDL-C. LDL-C, HDL-C, TG and TC were assessed at Weeks -6, -2, -1, 0, 1, 2, 4, 6, 8 and 10; the lipoproteins ApoA-I, ApoA-II, ApoB and Lp(a) were assessed at the same timepoints as the lipids; and fibrinogen was assessed at Weeks -2, -1, 2, 4, 6 and 10. Dietary compliance was assessed throughout the trial and evaluated. The primary endpoint was analysed using analysis of variance (ANOVA) on both the per-protocol (main analysis) and intention-to-treat (ITT) populations; linear regression was used to analyse dose-response. Percentage reductions from baseline in other lipids and lipoproteins were secondary endpoints of the trial and were analysed in the same way as the primary endpoint. Lipid ratios (LDL-C/HDL-C, TC/HDL-C, non-HDL-C/HDL-C and ApoB/ApoA-I) were calculated for the per-protocol population only and summarised.

Pharmacokinetics: Plasma concentrations of ZD4522 were measured in samples taken approximately 10 hours after dosing at Weeks 0, 2, 4 and 6.

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

RESULTS

Demography: A total of 198 subjects (recruited from 9 centres) entered into the dietary run-in period, of whom 64 entered into the randomised treatment period (17 subjects were randomised to the placebo group, 16 to the ZD4522 40 mg group and 31 to the ZD4522 80 mg group). Many of the subjects recruited were not included in the randomised treatment period due to not satisfying the randomisation criteria at Week 0. There were 64 subjects in the ITT population and 60 in the per-protocol population. The majority of subjects were aged between 55 and 64 years, and overall mean age was 57.5 years. Mean BMI ranged between 18.4 and 31.1 kg/m^2 across the treatment groups (overall mean BMI was 25.5 kg/m^2). Overall, the treatment groups were comparable for demographic characteristics. In total, 3 subjects withdrew from the randomised treatment period, and the reasons for withdrawal were as follows: adverse event (1 subject) and protocol non-compliance (2 subjects).

Efficacy: The results of the analysis on the percentage change from baseline in LDL-C are shown in Table I.

Table I Mean values (mmol/L and mg/dL) and percentage change from baseline to Week 6 in LDL-C (Friedewald) (per-protocol population)

	Treatment group		
	Placebo	ZD4522 40 mg	ZD4522 80 mg
Baseline: mean (SD)			
mmol/L	4.9 (0.4)	4.8 (0.4)	4.9 (0.4)
mg/dL	191.2 (14.6)	186.4 (15.6)	188.0 (13.7)
Final (Week 6): mean (SD)			
mmol/L	4.9 (0.5)	1.9 (0.4)	1.8 (0.4)
mg/dL	189.6 (19.8)	72.2 (16.4)	70.0 (15.3)
Analysis:			
n	16	15	28
% change (Week 6): lsmean[a] (SE)	-0.4 (2.2)	-61.9 (2.3)	-62.8 (1.7)
Difference from placebo of lsmeans	NA	-61.5	-62.4
Confidence intervals	NA	-67.7, -55.3	-67.8, -57.0
p-value[b]	NA	<0.001[c]	<0.001[c]

[a] lsmean = least square mean.
[b] Compared against placebo using ANOVA and Williams' test.
[c] Statistically significant.
One subject in the ZD4522 40 mg group was not included in the per-protocol population at Week 6 for LDL-C because this subject did not have the Week 6 assessment, therefore, n=59.

Mean values of LDL-C at baseline were similar across all the treatment groups. The percentage change from baseline at Week 6 indicated that ZD4522 40 mg and 80 mg significantly reduced LDL-C values compared with placebo ($p<0.001$, per-protocol analysis).
These results were confirmed in the ITT last observation carried forward (LOCF) analysis. The linear regression analysis was inconclusive (correlation, $R^2=0.003$).
Table II shows mean percentage change from baseline for the main secondary lipid and lipoprotein parameters.

Table II Percentage change from baseline to Week 6 (%) in the main secondary lipid and lipoprotein parameters (per-protocol population)

Lipid parameter	Treatment group		
	Placebo	ZD4522 40 mg	ZD4522 80 mg
HDL-C			
n	16	15	28
lsmean	4.5	10.6	13.7
SE	3.4	3.5	2.5
TC			
n	16	15	28
nlsmean	0.3	-44.9	-45.0
SE	1.8	1.8	1.4
TG			
n	16	15	28
lsmean	-1.2	-26.4	-22.0
SE	7.6	8.0	5.8
ApoB			
n	16	15	28
lsmean	-1.6	-52.5	-54.1
SE	1.9	2.0	1.4
ApoA-I			
n	16	15	28
lsmean	7.2	3.9	9.9
SE	3.6	3.7	2.7
ApoA-II			
n	16	15	28
lsmean	-0.9	-4.7	3.3
SE	2.3	2.3	1.7
Lp(a)			
n	16	15	28
lsmean	5.2	10.2	40.5
SE	13.2	13.8	10.0
Fibrinogen			
n	13	13	27
lsmean	3.1	20.2	10.5
SE	6.1	6.3	4.3

lsmean = least square mean.

The mean baseline values were similar across the treatment groups for each secondary parameter.

For the per-protocol analysis, increases in HDL-C were found across both doses of ZD4522. The percentage change from baseline to Week 6 in HDL-C was statistically significant for the ZD4522 80 mg group ($p=0.037$ compared with placebo).
Reductions in TC, ApoB, and TG were found with both doses of ZD4522 when compared with placebo ($p<0.001$ for TC and ApoB when compared with placebo). For TG, the difference in lsmeans compared with placebo was just statistically significant for the ZD4522 40 mg group ($p<0.050$). Increases in Lp(a) were found for both doses of ZD4522, however, the increase was statistically significant for the ZD4522 80 mg group only ($p=0.042$ compared with placebo).
No dose-related changes were seen for ApoA-I, ApoA-II, or fibrinogen.
Although no formal statistical analyses were performed on the data for lipid ratios, there were favourable trends for both doses of ZD4522 at Week 6 compared with placebo; reductions in all 4 lipid ratios (LDL-C/HDL-C, TC/HDL-C, non-HDL-C/HDL-C and ApoB/ApoA-I) were observed with both doses of ZD4522 compared with placebo.
The results for the ITT population analyses were consistent with the findings of the per-protocol population for each of the secondary endpoints.
The dietary analysis results indicated that the dietary differences between the groups were not sufficiently large to alter the interpretation of the drug effect. Activity levels did not have an impact on the primary endpoint of this trial.

Pharmacokinetics:

The results obtained indicate that steady state was maintained throughout the 6-week dosing period for both the ZD4522 40 mg and 80 mg doses. Also, exposure appeared to be dose-related, with an approximate doubling in plasma concentrations seen for a doubling in dose.

Safety:

ZD4522 was well-tolerated in this trial. During the randomised treatment period, 60.9% of subjects reported adverse events with a similar incidence between groups. Adverse events were mostly mild and transient for both ZD4522 groups and similar to placebo. No subjects withdrew from the study due to an adverse event attributable to ZD4522. Overall incidences of adverse events for principle body sysytems (cardiovascular, respiratory, digestive and musculoskeletal) were broadly similar to placebo for both doses of ZD4522 and did not appear to increase with increasing dose. Adverse events attributable to ZD4522 were constipation, dry mouth, nausea and abdominal pain; the incidence of these events was slightly increased in the ZD4522 80 mg group. This range of adverse events and the relationship to dose was as expected for this class of drug. Serious adverse events were rare - 2 subjects had 3 serious adverse events in the ZD4522 80 mg group (angina, myocardial infarction and gastrointestinal neoplasia). These were considered to be unrelated to trial treatment. There were no deaths reported in the trial.
Overall, no symptom complex consistent with liver disturbances was observed in any subject during the trial. No subject had increases in ALT of >3 times the ULN, and the mean ALT value did not exceed >1 times the ULN in any group. The mean change from baseline in ALT at Week 6 was 13.3 U/L and 9.8 U/L for the ZD4522 40 mg and 80 mg groups, respectively. One subject in the ZD4522 40 mg group had an adverse event of increased gamma glutamyl transferase (γGT) levels, but the event was considered unrelated to trial treatment. For the majority of other hepatic biochemistry parameters, values outside the reference range were noted in all treatment groups, but again there were no increases of clinical significance.

No subject had CK values of >5 or >10 times the ULN. There were no recorded symptoms of myositis. One subject in the ZD4522 40 mg group had an adverse event of increased creatinine phosphokinase levels: the event was considered to be possibly related to trial treatment.
There was a total of 4 subjects who reported myalgia, all during the randomised treatment period. Drug causality was similar across all 3 groups (one subject each in the placebo, ZD4522 40 mg and ZD4522 80 mg groups). All cases of myalgia were mild in intensity and none was associated with a rise in CK.
Other clinical biochemistry parameters and haematology parameters showed little or no trends
Changes from baseline in ECG at Week 10, 4 weeks post last dose of trial treatment, were noted in 8 subjects (1 in the placebo group, 1 in the ZD4522 40 mg group and 6 in the ZD4522 80 mg group); however, none of these was considered to be clinically significant by the investigator.
