SUMMARY

ZENECA PHARMACEUTICALS

FINISHED PRODUCT:

ACTIVE INGREDIENT: ZD4522

Trial title (number): A Randomised, Parallel-Group Dose-Response Study with the HMG-CoA Reductase Inhibitor ZD4522 and Atorvastatin in Subjects with Primary Hypercholesterolaemia (4522IL/0008)

Developmental phase: II/III

First subject recruited: 21 August 1998
Last subject completed: 19 January 1999
Zeneca approval date: 14 January 2000

Principal investigator and location (centre number):

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

OBJECTIVES

The primary objective of this trial was to estimate the dose-response relationship between the dose of ZD4522 and the percentage reduction of low density lipoprotein-cholesterol (LDL-C) (Friedewald) from the baseline value with respect to placebo.

The secondary objectives of this trial were: to estimate the effect of 10 and 80 mg doses of atorvastatin on LDL-C; to estimate the effects of ZD4522 and atorvastatin 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), LDL-C (by β-quantification method), LDL-C/HDL-C, TC/HDL-C, non-HDL-C/HDL-C, ApoB/ApoA-I ratios and fibrinogen levels; to assess the pharmacokinetics of oral doses of 1, 2.5, 5, 10, 20 and 40 mg of ZD4522 over a 6-week treatment period; and to assess the tolerability and safety of ZD4522 in comparison with placebo.

METHODS

Design: 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 ZD4522 (1, 2.5, 5, 10, 20 and 40 mg) or placebo, or atorvastatin (10 and 80 mg; supplied open-labelled) 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 baseline levels. The placebo group was included to provide a meaningful comparator for efficacy, safety and tolerance data. The atorvastatin groups were included to obtain additional data on the starting and high doses of a proven cholesterol-lowering agent in this subject population; the data were to be compared with published data using Bayesian analysis methods, for display purposes only, to model the atorvastatin dose-response curve against the ZD4522 dose-response curve.

Population: Subjects with fasting LDL-C concentrations of >4.14 mmol/L (160 mg/dL) but <6.21 mmol/L (240 mg/dL) were recruited. A total of 14 randomised and evaluable subjects per treatment group, necessitating the recruitment of 250 subjects in this trial, were required for 90% power of detecting a 25% difference between ZD4522 and placebo in percentage change from baseline in LDL-C levels.

Key inclusion criteria: Male subjects aged 18 to 70 years or post-menopausal women aged 50 to 70 years; fasting TG levels of <3.39 mmol/L (300 mg/dL); 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 CK concentrations of >3 times the ULN; usage 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 treatment were as follows: ZD4522 1, 2.5, 5, 10, 20 and 40 mg; placebo; atorvastatin 10 and 80 mg.

Formulation and batch numbers were as follows: ZD4522 1 mg (F12417, CF8002), ZD4522 2.5 mg (F12418, CF8003), ZD4522 5 mg (F12419, CF8004), ZD4522 10 mg (F12420, CF8005), placebo (F12421, CF8008), atorvastatin 10 mg (F12451, 00443018B), and atorvastatin 80 mg (F12452, 0568117).

Key assessments:

Efficacy: LDL-C, HDL-C, TG, and TC were assessed at Weeks -6, -2, -1, 0, 1, 2, 4, 6, 8 and 10; the lipoproteins ApoB, ApoA-I, ApoA-II and Lp(a), and lipid ratios 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 percentage change from baseline to Week 6 in LDL-C, and 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, lipoproteins and lipid subfractions were secondary endpoints of the trial and were analysed in the same way as the primary endpoint. The other secondary endpoint percentage change from baseline in LDL-C in the atorvastatin groups was analysed using Bayesian analysis methods.

Pharmacokinetics: Plasma concentrations of ZD4522 were measured in samples taken approximately 10 hours after dosing at Weeks 2, 4 and 6. In addition, it was assessed whether a pharmacokinetic steady state was maintained over 6 weeks of treatment.
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 396 subjects (recruited from 14 centres) entered into the dietary run-in phase, of whom 142 entered into the randomised treatment phase; the high drop-out rate was because of subjects not meeting the lipid criteria for randomisation. The treatment groups contained between 13 and 18 randomised subjects each. There were 140 subjects in the ITT population and 129 in the per-protocol population. The majority of subjects were aged between 45 and 64 years, with mean ages across the treatment groups of between 53 and 59 years (overall mean age was 55.4 years). Mean BMI ranged between 25 and 26 kg/m^2 across the treatment groups (overall mean BMI was 26 kg/m^2). Overall the treatment groups were comparable for demographic characteristics and baseline lipids. In total, seven subjects withdrew from the randomised treatment phase, and the reasons for withdrawal were as follows: adverse events/concurrent (3 subjects), protocol non-compliance (2 subjects) and informed consent withdrawn (2 subjects).
Efficacy: ZD4522 lowered LDL-C in a dose-dependent manner ($p<0.0001$ compared with placebo, per-protocol analysis). The form of relationship was linear on a log-dose scale (the equation of the regression line is: percentage change from baseline to Week 6 = -35.10 - 7.52*log (dose)). Therefore, the estimate of the effect on LDL-C of doubling the dose of ZD4522 is to increase the percentage reduction from baseline to Week 6 by 5.21%).

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 (%) in LDL-C (Friedewald) (per-protocol population)

	Treatment group								
	Placebo	ZD4522 1 mg	ZD4522 2.5 mg	ZD4522 5 mg	ZD4522 10 mg	ZD4522 20 mg	ZD4522 40 mg	Atorv 10 mg	Atorv 80 mg
Baseline[a]: mean (SD)									
mmol/L	5.1 (0.4)	4.9 (0.4)	4.9 (0.4)	5.0 (0.4)	4.9 (0.4)	4.8 (0.4)	4.8 (0.5)	4.9 (0.2)	5.0 (0.3)
mg/dL	196.8 (15.0)	188.7 (17.0)	188.6 (14.8)	192.8 (15.8)	190.0 (16.2)	183.8 (16.9)	184.2 (19.3)	188.1 (8.0)	192.0 (13.5)
Final (Week 6): mean (SD)									
mmol/L	4.7 (0.6)	3.1 (0.4)	2.8 (0.4)	2.8 (0.4)	2.3 (0.5)	1.9 (0.5)	1.8 (0.4)	2.7 (0.4)	2.1 (0.5)
mg/dL	182.0 (23.3)	119.9 (15.0)	108.8 (14.5)	106.7 (16.6)	90.7 (20.4)	75.2 (19.8)	67.8 (16.4)	104.6 (16.2)	79.7 (19.9)
Analysis:									
n	12	13	13	17	16	13	18	13	10
% change (Week 6): lsmean[b] (SE)	-7.3 (2.5)	-36.2 (2.4)	-42.7 (2.4)	-44.5 (2.1)	-52.4 (2.2)	-58.9 (2.4)	-63.4 (2.1)	-44.2[c] (9.0)	-58.6[c] (9.1)
Difference from placebo of lsmeans	NA	-28.9	-35.4	-37.1	-45.1	-51.6	-56.1	NA	NA
Confidence Intervals									
LCL[d]	NA	-35.7	-42.2	-43.5	-51.6	-58.5	-62.5	NA	NA
UCL[d]	NA	-22.1	-28.6	-30.8	-38.6	-44.6	-49.6	NA	NA
p-value[e]	NA	<0.001[f]	<0.001[f]	<0.001[f]	<0.001[f]	<0.001[f]	<0.001[f]	NA	NA

[a] Baseline is the average of the available readings at -2, -1 and 0 weeks.
[b] lsmean = least square mean.
[c] The % change values for atorvastatin are not from the fitted model (atorvastatin is not in the model), and SD is presented instead of SE.
[d] LCL = lower 95% confidence interval limit; UCL = upper 95% confidence interval limit.
[e] p-values are based on the Williams' test.
[f] Statistically significant compared to placebo.

Mean values of LDL-C at baseline were similar across all treatment groups. There was a highly statistically significant difference in percentage change from baseline to Week 6 in LDL-C, for each dose of ZD4522 compared with placebo ($p<0.001$). These results were confirmed in the ITT last observation carried forward (LOCF) analysis. The mean percentage reductions were comparable to those seen with atorvastatin in the dose ranges studied.

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						Atorvastatin	
	(n=13)	1 mg (n=15)	2.5 mg (n=15)	5 mg (n=18)	10 mg (n=17)	20 mg (n=17)	40 mg (n=18)	10 mg (n=15)	80 mg (n=13)
TC									
n	12	13	13	17	16	13	18	13	10
lsmean	-5.0	-25.3	-30.7	-32.7	-36.6	-42.1	-46.4	-32.0[a]	-46.1[a]
SE	2.0	1.9	1.9	1.7	1.8	2.0	1.7	7.6	6.9
LDL-C[b]									
n	12	10	13	15	14	11	16	11	7
lsmean	3.8	-29.5	-33.6	-35.3	-45.3	-52.7	-59.2	-35.9[a]	-49.4[a]
SE	3.1	3.4	3.0	2.8	2.9	3.3	2.7	11.4	8.3
TG									
n	12	13	13	17	16	13	18	13	10
lsmean	-1.0	-19.1	-11.1	-35.0	-10.3	-23.5	-28.7	-13.6[a]	-30.7[a]
SE	6.6	6.4	6.4	5.6	5.8	6.4	5.5	17.2	20.7
HDL-C									
n	12	13	13	17	16	13	18	13	10
lsmean	2.5	9.3	8.5	13.3	13.6	9.3	9.5	6.8[a]	-3.2[a]
SE	3.1	3.0	3.0	2.6	2.7	2.9	2.5	10.3	14.3
ApoB									
n	12	13	13	16	16	11	18	13	10
lsmean	-2.6	-29.0	-34.6	-37.5	-42.0	-49.2	-54.8	-36.4[a]	-50.2[a]
SE	2.4	2.3	2.3	2.1	2.1	2.5	2.0	11.1	6.1

[a] The % change values for atorvastatin are not from the fitted model (atorvastatin is not in the model), and SD is presented instead of SE.
[b] By β-quantification method.

For the per protocol analysis, statistically significant reductions in TC, LDL-C (β-quantified) and ApoB were found across all doses of ZD4522 ($p<0.001$ compared with placebo), and the reductions were similar to atorvastatin. Reductions in TG levels were found with all doses of ZD4522 compared with placebo; however, the percentage change from baseline to Week 6 in TG was only statistically significant for the ZD4522 5 and 40 mg groups ($p=0.001$ and $p=0.009$, respectively); the reductions were similar to those seen with atorvastatin. Increases in HDL-C were found with all doses of ZD4522 compared with placebo (the percentage change from baseline to Week 6 in HDL-C was only statistically significant in the ZD4522 5 and 10 mg groups [$p=0.040$ and $p=0.035$, respectively]); an increase in HDL-C was observed with atorvastatin 10 mg and a decrease in HDL-C was observed with atorvastatin 80 mg. The type of subject population in this trial was not expected to demonstrate the maximal possible effect of ZD4522 on TGs and HDL-C, and the trial was not powered to show these effects.
For ApoA-I, ApoA-II, Lp(a) and fibrinogen, no statistically significant differences compared with placebo were found. All conclusions based on the per-protocol population were supported by the ITT LOCF analysis, verifying that the effect of subject withdrawals prior to Week 6 was

minimal. There was a trend for increasing doses of ZD4522 to reduce the values of all 4 lipid ratios at Week 6.
The LDL-C data were also analysed using Bayesian techniques to perform a meta-analysis incorporating historic data from atorvastatin trials. The analysis produced good line fits for both atorvastatin and ZD4522 and further indicated that only one-half of the dose of ZD4522 was required to achieve the same efficacy (as assessed by the percentage change in LDL-C from baseline) as atorvastatin.
Diet and activity levels did not have an impact on the primary endpoint of this trial.
Pharmacokinetics: Despite the limited collection of pharmacokinetic samples, the mean plasma concentrations at approximately 10 hours post-dose increased with increasing dose. In addition, the data indicated that a steady state appeared to be maintained between Weeks 2 and 6.
Safety: The incidence of treatment-emergent adverse events ranged from 41% to 67% across all treatment groups. There was no increase in the incidence of treatment-emergent adverse events with increasing doses of ZD4522. ZD4522 was well tolerated in this trial. During the randomised treatment phase, 75 out of 140 subjects (53.6%) reported 173 treatment-emergent adverse events. Serious adverse events, and adverse events leading to withdrawal were rare. Only one subject, in the ZD4522 5 mg group, had a serious adverse event of sepsis, but this was unrelated to the trial medication, and only 3 subjects were withdrawn due to adverse events (1 subject each in the ZD4522 20 mg, atorvastatin 10 mg and atorvastatin 80 mg groups). The incidence of adverse events was similar across treatment groups. No subject died during the trial. Overall, the commonly reported adverse events in the ZD4522 groups were headache, pharyngitis, nausea and diarrhoea.
No adverse events were reported that were indicative of liver injury.
Any increases in ALT were not dose-related for ZD4522, and no subjects had increases in ALT of >3 times the ULN, and the mean ALT value did not exceed >1 times the ULN in any group. There were no relevant changes in any other liver markers. 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 ≥3 times the ULN.
There was a total of 8 subjects who reported myalgia (1 subject during the dietary run-in period and 7 subjects during the randomised treatment period). Myalgia was reported as a treatment-emergent, drug-related adverse event in 2 subjects in the ZD4522 groups (5 mg and 20 mg groups) and 2 subjects in the atorvastatin groups (10 mg and 80 mg groups) and as non-drug-related in subjects in the ZD4522 1 mg, 2.5 mg, and 40 mg groups; there was only 1 case of severe myalgia accompanied by a small but clinically insignificant rise in circulating CK concentrations, which occurred in Subject 0003/0377 in the atorvastatin 80 mg group.
For CK, increases in mean values at Week 0 to Week 6 were noted in all treatment groups, except the ZD4522 1 mg group. No subjects had CK values of ≥10 times the ULN, and a total of 5 (3.6%) subjects presented with CK results of ≥3 times the ULN during the trial, but these increases were not considered to be of clinical significance. There were no reports of associated myalgia or any other symptoms of myositis for any of these subjects.
Other clinical biochemistry parameters and haematology parameters showed little or no trends. There were no clinically significant changes in vital signs or ECG traces in subjects receiving ZD4522.