SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT:

ACTIVE INGREDIENT: ZD4522

Trial title (number): A 24-Week, Randomised, Double-blind, Multicentre, Multinational Trial to Evaluate the Efficacy and Safety of ZD4522 and Atorvastatin in the Treatment of Subjects with Heterozygous Familial Hypercholesterolaemia (4522IL/0030).

Developmental phase: III

First subject recruited: 27 July 1999
Last subject completed: 6 June 2000
AstraZeneca approval date: 9 February 2001

Principal investigator(s) and location (centre number):

Publications: None at the time of writing this report.

OBJECTIVES

The primary objective was to compare the efficacy of ZD4522 (force-titrated to 80 mg) with that of atorvastatin (force-titrated to 80 mg) in reducing low-density lipoprotein cholesterol (LDL-C) levels in subjects with heterozygous familial hypercholesterolaemia (FH) at Week 18 (18 weeks of treatment).

The secondary objectives were to compare the efficacy of ZD4522 with that of atorvastatin in relation to the following: reducing LDL-C levels at Weeks 2, 6 and 12; in modifying other lipids and lipoprotein fractions at Week 2, 6, 12 and 18; in reducing LDL-C levels to within relevant national and international guidelines at Week 6, 12 and 18; in modifying the inflammatory marker C-reactive protein (CRP) at Week 18. A further secondary objective was to determine the safety of ZD4522.

METHODS

Design: This was a 24-week, randomised, double-blind, parallel-group, forced-titration, multicentre, multinational trial. After a 6-week dietary lead-in period, subjects were randomised to treatment with either ZD4522 20 mg daily, or atorvastatin 20 mg daily for 6 weeks. Randomisation was weighted such that more patients received ZD4522 than atorvastatin. Following this initial treatment period, all subjects with an LDL-C level >1.3 mmol/L (>50 mg/dL) were permitted to force-titrate at 6-week intervals as follows: from ZD4522 20 to 40 to 80 mg, and from atorvastatin 20 to 40 to 80 mg (maximum dose at 18 weeks of treatment).

Population: A total of 265 (200 in the ZD4522 group, 65 in the atorvastatin group) evaluable subjects with documented heterozygous FH, derived from approximately 1240 entered subjects, were required to enable 80% power in detecting a 6% difference between groups in the percentage change from baseline in LDL-C levels.

Key inclusion criteria: Men or women aged ≥18 years with heterozygous FH; discontinuation of all cholesterol-lowering drugs and dietary supplements; fasting LDL-C level ≥5.69 and <12.93 mmol/L (≥220 and <500 mg/dL); fasting triglyceride (TG) level ≤4.52 mmol/L (≤400 mg/dL); an Eating Pattern Assessment Tool (EPAT) score of ≤28 to demonstrate dietary compliance.

Key exclusion criteria: Various concomitant illnesses, including active liver disease or hepatic dysfunction (defined by an alanine aminotransferase [ALT], aspartate aminotransferase [AST] or bilirubin concentration ≥1.5 x the upper limit of normal [ULN]), active arterial disease, history of malignancy within the previous 10 years (unless basal or squamous cell skin carcinoma), uncontrolled hypertension, and uncontrolled hypothyroidism; serum creatine kinase (CK) concentration >3 x ULN; usage of concomitant medications known to affect the lipid profile or present a potential safety concern (e.g. through drug interaction); women pregnant, breast-feeding or at risk of pregnancy.

Dosage: Subjects took oral doses of trial treatment once daily, approximately 3 hours after the evening meal. Doses of treatments were as follows: ZD4522 20, 40, and 80 mg, atorvastatin 20, 40, and 80 mg. Subjects had their doses titrated up at 6-week intervals in a sequential manner, if not contra-indicated by an LDL-C level ≤1.3 mmol/L (≤50 mg/dL).

Formulation and batch numbers were as follows: ZD4522 20 mg (F12522; 99-3086, 99-3108); ZD4522 40 mg (F12566, 99-3159, 99-3087, 99-3110); atorvastatin 20 mg (F12558, 99-0466, 99-3048); atorvastatin 40 mg (F12560, 99-3049); the 80 mg dose was administered as 2x40 mg (the trial was *not* blinded with respect to dose).

Key assessments:

Efficacy: Fasting LDL-C, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and TG were assessed at Weeks 0, 2, 6, 12 and 18; fasting apolipoprotein B (ApoB) and apolipoprotein A-I (ApoA-I) were assessed at Weeks 0 and 18; C-reactive protein (CRP) was assessed at Weeks 0 and 18. Dietary compliance throughout the trial was assessed and evaluated.

The primary endpoint was the percentage change from baseline to Week 18 in LDL-C levels, and was analysed using analysis of variance (ANOVA) on last observations carried forward (LOCF) from an intention-to-treat (ITT) population; the initial ANOVA model included terms for treatment, centre, and centre-by-treatment interaction. Additional analyses at Week 18 using observed data from ITT and per-protocol (PP) populations were used to confirm the robustness

of the main ITT analysis.
Secondary endpoints (analysed using ANOVA) were: percentage changes from baseline to Weeks 2, 6, and 12 (observed) in LDL-C and from baseline to Weeks 2, 6, 12 and Week 18 (LOCF and observed) in the other lipids (TC, HDL-C and TG); and percentage change from baseline to Week 18 (LOCF) in apolipoproteins (ApoA-I and ApoB). The main analysis was at Week 18 using ITT LOCF data with supportive analyses using Week 18 ITT and PP observed data. The other secondary endpoints of the percentage of subjects in the ITT population, who achieved targets for LDL-C levels specified by the National Cholesterol Education Program (NCEP) or the European Atherosclerosis Society (EAS), and the percentage change from baseline in the inflammatory marker CRP, were summarised only.
Subgroup and exploratory analyses were performed on LDL-C and HDL-C data, based on pre-defined demographic groupings.
Safety: Standard safety assessments included adverse event reports, clinical laboratory data (hepatic biochemistry, CK, renal biochemistry, haematology, urinalysis), vital signs, electrocardiograms (ECGs) and physical examination. Ophthalmological examinations were performed only in South Africa sites. All data were summarised.

RESULTS
Demography: A total of 999 subjects were recruited into 58 centres. Fewer drop outs than anticipated during the dietary lead-in period resulted in over recruitment of eligible subjects: 623 in total (436 randomised to ZD4522 20/40/80 mg and 187 randomised to atorvastatin 20/40/80 mg). The majority (88%) of the 376 drop outs were screen failures, defined by a failure to meet inclusion/exclusion criteria for randomisation. Demographic characteristics of the 623 randomised subjects were generally well balanced between treatment groups. The majority of subjects were Caucasians with a mean age of 48.0 years and mean Body Mass Index (BMI) of 27.13 kg/m^2. The first subject was recruited into the trial on 27 July 1999 and the last subject completed the trial on 6 June 2000. A total of 34 of the randomised subjects were withdrawn, 22 of these as a result of adverse events. There were 622 subjects in the identical ITT and safety populations (1 subject was randomised to ZD4522 20/40/80 mg but did not receive treatment), 589 of whom completed the trial. There were 436 subjects in the PP population at Week 18.

Efficacy: A summary of the key efficacy findings is presented in Tables I and II.

Table I Summary of changes of efficacy parameters at Week 18 (ITT population)

Efficacy endpoint	ZD4522 20/40/80 mg	Atorvastatin 20/40/80 mg
lsmean of percentage change from baseline to Week 18 (LOCF) in lipids and lipid ratios		
LDL-C	-57.88[a,c]	-50.41
TC	-46.35[a]	-42.13
HDL-C	12.36[a]	2.91
TG	-27.82[ns]	-31.60
LDL-C/HDL-C	-61.69[a]	-51.16
TC/HDL-C	-51.44[a]	-43.17
Non-HDL-C/HDL-C	-59.40[a]	-49.86
ApoB	-50.21[a]	-44.44
ApoA-I	5.86[a]	-2.33
ApoB/ApoA-I	-52.03[a]	-42.46
Percentage subjects reaching NCEP or EAS targets for LDL-C levels at Week 18[b] (LOCF)		
NCEP, all subjects	60.5	46.0
NCEP, subjects in high-risk category	23.9	3.2
EAS, all subjects	47.4	24.1
EAS, subjects in high-risk category	47.5	24.2
Median percentage change from baseline to Week 18 in inflammatory marker (Observed data)		
CRP	-34.00	-33.33

[a] $p<0.001$ in favour of ZD4522 20/40/80 mg; [ns] = not significant versus atorvastatin 20/40/80 mg ($p>0.050$).
[b] Statistical analysis was not performed for NCEP and EAS targets.
[c] Primary efficacy endpoint.
lsmean = Least squares mean.

Table II Summary of changes of lipids and lipid ratios at Weeks 2, 6 and 12 (Observed data on ITT population)

Efficacy endpoint	ZD4522 20/40/80 mg			Atorvastatin 20/40/80 mg		
	Week			Week		
	2	6	12	2	6	12
lsmean of percentage change from baseline in lipids and lipid ratios						
LDL-C	-36.81[a]	-47.15[a]	-55.42[a]	-29.73	-37.93	-47.37
TC	-29.31[a]	–37.48[a]	-44.33[a]	-24.30	-31.14	-39.15
HDL-C	7.31[a]	11.78[a]	10.74[a]	4.36	5.30	2.81
TG	-16.56[ns]	-23.01[ns]	-25.86 [ns]	-16.12	-22.12	-25.64
LDL-C/HDL-C	nc	-52.10[a]	-59.12[a]	nc	-40.67	-48.38
TC/HDL-C	nc	-43.46[a]	-49.10[a]	nc	-34.26	-40.46
Non-HDL-C/HDL-C	nc	-50.21[a]	-56.73[a]	nc	-39.58	-46.75

[a] $p<0.01$ in favour of ZD4522 20/40/80 mg; [ns] = not significant versus atorvastatin 20/40/80 mg.
nc = not calculated.
lsmean = Least squares mean.

ZD4522 20/40/80 mg resulted in a significantly ($p<0.001$ in comparison between treatment arms) greater percentage reduction in LDL-C levels than did atorvastatin 20/40/80 mg at all time points (LOCF data at Week 18 and observed data at Weeks 2, 6, 12). The difference between treatments was also considered to be clinically significant at all time points (> the pre-defined 6%). TC and lipid ratios (LDL-C/HDL-C, TC/HDL-C, non-HDL-C/HDL-C) investigated in the trial were significantly reduced, and HDL-C was significantly increased, more by ZD4522 20/40/80 mg than by atorvastatin 20/40/80 mg at all time points. ApoB and the ratio ApoB/ApoA-I were significantly reduced, and ApoA-I was significantly increased more by ZD4522 20/40/80 mg than by atorvastatin 20/40/80 mg (LOCF data at Week 18). There were no significant differences in reduction of TG levels between ZD4522 20/40/80 mg and atorvastatin 20/40/80 mg at any time point, with exception of values for observed ITT data at Week 18 in favour of atorvastatin. A greater percentage of subjects achieved NCEP and EAS target levels in the ZD4522 20/40/80 mg group than did those in the atorvastatin 20/40/80 mg group at Weeks 6, 12 and 18, with the greatest difference between treatments observed for the NCEP high-risk group. Analysis of percentage change in CRP showed no apparent differences between treatment groups, the data being extremely variable. Results from the analyses of Week 18 observed data from the PP and ITT populations generally supported results from the main efficacy analyses (ITT LOCF data at Week 18). Exploratory analyses (ANCOVA) demonstrated that age, baseline HDL-C and baseline TG each had a significant effect on the percentage LDL-C reduction from baseline.

Safety: ZD4522 20/40/80 mg was generally well tolerated and the types and incidences of treatment-emergent adverse events were similar to those of the atorvastatin 20/40/80 mg group. There was no apparent increasing incidence of adverse events with time/increasing dose over the dose-titration period. Overall, the treatment-emergent adverse events suggested no change to the adverse event profile of ZD4522 from that reported in previous trials. There was one death (sudden death, confirmed by autopsy to be due to myocardial infarction), which occurred in the atorvastatin 20/40/80 mg group. The incidence of subjects experiencing serious adverse events was low (1.6%) in both treatment groups: 7 subjects in the ZD4522 20/40/80 mg group and 3 subjects (including the sudden death) in the atorvastatin 20/40/80 mg group. The incidence of subjects experiencing adverse events leading to withdrawal was similar in both treatment groups: 3.7% (16) in the ZD4522 20/40/80 mg group and 3.2% (6) in the atorvastatin 20/40/80 mg group. The incidence of clinically relevant increases in ALT (>3xULN) was 2.3% (10) in the ZD4522 20/40/80 mg group and 1.1% (2 subjects) in the atorvastatin 20/40/80 mg group; in all except 1 subject in the ZD4522 20/40.80 mg group the clinically relevant increase in ALT was reported as an adverse event, “SGPT increased”. The adverse event increased SGPT was reported in 3.9% (17) and 3.2% (6) of subjects in the ZD4522 20/40/80 mg and atorvastatin 20/40/80 mg groups, respectively. There were no reports of symptom patterns suggestive of liver injury in any subject during the trial. There were no clinically relevant rises in CK (>10xULN) during the randomised forced-titration treatment period. The incidence of myalgia in both treatment groups was 5.3% (23 and 10 subjects in the ZD4522 20/40/80 mg and atorvastatin 20/40/80 mg groups, respectively). Other clinical biochemistry; haematology; and urinalysis data; and data from other safety assessments (vital signs, physical examination and ECGs) were all generally unremarkable with no apparent treatment-related trends or patterns or clinically important differences between treatments. Ophthalmological assessment data

indicated no safety concerns and there were no obvious or clinically meaningful differences between treatment groups.