SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT:

ACTIVE INGREDIENT: ZD4522

Trial title (number): A 12-Week, Randomised, Double-blind, Multicentre Trial to Evaluate the Efficacy and Safety of ZD4522 (5 and 10 mg), Pravastatin (20 mg), and Simvastatin (20 mg) in the Treatment of Subjects with Hypercholesterolaemia (4522IL/0027).

Clinical phase: III

First subject recruited: 14 June 1999
Last subject completed: 11 April 2000
AstraZeneca approval date: 01 December 2000

Principal investigator and location (centre number):

Publications: None at the time of writing this report.

OBJECTIVES

The primary objective was to compare the efficacy of ZD4522 at 5 mg and 10 mg doses with the efficacy of the comparators pravastatin (20 mg) and simvastatin (20 mg) in reducing low-density lipoprotein cholesterol (LDL-C) levels in subjects with hypercholesterolaemia. The secondary objectives were to compare the efficacy of ZD4522 at 5 mg and 10 mg doses with that of pravastatin (20 mg) and simvastatin (20 mg) in modifying other lipids and lipoprotein fractions; in reducing LDL-C levels to within relevant national and international guidelines; and to determine the safety of ZD4522.

METHODS

Design: This was a 12-week, randomised, double-blind, 4-group, parallel group, multicentre trial. After a 6-week dietary lead-in period, subjects were randomised to treatment with either ZD4522 (5 or 10 mg), pravastatin (20 mg), or simvastatin (20 mg) for 12 weeks.

Population: A total of 100 randomised and evaluable subjects with hypercholesterolaemia, derived from an estimated 1200 recruited subjects, was to be recruited per treatment group for 80% power of detecting a 6% difference between groups in % change from baseline in LDL-C levels.

Key inclusion criteria: Men or women aged ≥18 years; discontinuation of all cholesterol-lowering drugs and dietary supplements; fasting LDL-C levels between 4.14 and <6.50 mmol/L (160 and <250 mg/dL); fasting triglyceride (TG) levels <4.52 mmol/L (400 mg/dL); and 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 (unless basal or squamous cell skin carcinoma), uncontrolled hypertension, and uncontrolled hypothyroidism; serum creatine kinase [CK] concentration >3 x ULN; and 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 encapsulated trial treatment once daily, approximately 3 hours after the evening meal. Doses of treatments were as follows: ZD4522 5mg, ZD4522 10 mg, pravastatin 20 mg, or simvastatin 20 mg. The same dose of trial treatment was taken for 12 weeks. Formulation and batch, numbers were as follows:
ZD4522 5 mg (F12570, 99-3162, 99-0510, 99-3034, 99-3085, 99-3095); ZD4522 10 mg (F12572, 99-3047, 99-3088, 99-3104, 99-3145); pravastatin 20 mg (F12556, 99-3026); simvastatin 20 mg (F12562, 99-0472, 99-3027).

Key assessments:

Efficacy: Fasting LDL-C, high-density lipoprotein cholesterol (HDL-C), TG and total cholesterol (TC) were assessed during the dietary lead-in and Weeks 0, 2, 6, 10, and 12; fasting apolipoprotein B (ApoB), apolipoprotein A-I (ApoA-I) and lipoprotein (a) (Lp(a)) were assessed at Weeks 0 and 12. Dietary compliance was assessed and evaluated throughout the trial.
The primary end-point of the trial was the % change from baseline in LDL-C levels at Week 12, 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. Statistical testing was done separately for the comparison between each ZD4522 group and pravastatin, and each ZD4522 group and simvastatin. Additional analyses using observed data from ITT, and per-protocol (PP) populations were used to confirm the robustness of the main ITT analysis.
Secondary end-points included the % reductions from baseline in the other lipids; these data were analysed using ANOVA. Other secondary end-points were the % of subjects in the ITT population who achieved EAS (European Atherosclerosis Society) and NCEP (National Cholesterol Education Program) targets for LDL-C levels at Week 12; these data were

summarised only. Subgroup and exploratory analyses were performed on LDL-C and HDL-C data, based on certain 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. All data were summarised.

RESULTS

Demography: A total of 1329 subjects was recruited from 69 centres; and of these, 502 were eligible for randomisation following the dietary lead-in period. Of the 502 subjects randomised to treatment, 120 received ZD4522 5 mg, 115 received ZD4522 10 mg, 137 received pravastatin and 130 received simvastatin. Demographic characteristics were generally well-balanced among the treatment groups. Subjects were between 20 and 84 years of age (mean age ranged from 57 to 60 years of age) with a mean BMI of 27 kg/m^2. The proportion of males and females was similar in the ZD4522 5 mg and simvastatin groups (49.2% and 50%, respectively) but there were slightly more females than males in the ZD4522 10 mg and pravastatin groups (57.4% and 54%, respectively). Subjects were predominantly Caucasian. There were 827 screen failures/withdrawals during the dietary lead-in period and 28 subjects withdrew during the randomised treatment period. The most common reason for withdrawal during the randomised treatment period was adverse events (2 subjects in the ZD4522 5 mg group, 6 in the ZD4522 10 mg group, 3 in the pravastatin group and 1 in the simvastatin group). There were 502 subjects in the safety population, 495 in the ITT population and 388 in the PP population.
Efficacy: A summary of the key efficacy findings is presented in Table I.

Table I Summary of key efficacy findings (LOCF on ITT population)

Efficacy end-point	ZD4522 5 mg	ZD4522 10 mg	Pravastatin 20 mg	Simvastatin 20 mg
lsmean of percentage change from baseline at Week 12 in lipids and lipid ratios				
LDL-C	-41.9[a, c]	-48.6[a, b]	-27.5	-36.8
TC	-29.8[a, c]	-34.2[a, b]	-19.8	-26.3
HDL-C	6.2[ns]	6.8[ns]	4.4	3.9
TG	-11.7[ns]	-18.2[ns]	-12.6	-13.6
LDL-C/HDL-C	-44.6[a, c]	-51.4[a, b]	-29.2	-38.6
TC/HDL-C	-33.2[a, c]	-37.8[a, b]	-22.1	-28.4
Non-HDL-C/HDL-C	-40.7[a, c]	-47.2[a, b]	-27.3	-35.4
ApoB	-33.5[a, d]	-38.6[a, b]	-21.1	-29.4
ApoA-I	6.7[ns]	5.0[ns]	3.8	4.4
ApoB/ApoA-I	-36.7[a, c]	-40.7[a, b]	-23.1	-31.5
Lp(a)	5.8[ns]	-5.0[ns]	3.0	8.9
% subjects reaching NCEP or EAS targets for LDL-C levels at Week 12				
NCEP, overall	71.4	86.5	52.9	64.3
NCEP, high risk	41.9	66.7	7.1	19.4
EAS, overall	63.0	82.9	19.9	50.4
EAS, high risk	62.0	79.5	17.5	49.5

[a] $p<0.001$ versus pravastatin 20 mg; [b] $p<0.001$ versus simvastatin 20 mg; [c] $p\leq0.01$ versus simvastatin 20 mg; [d] $p<0.05$ versus simvastatin 20 mg; [ns] Not significant.
Statistical analysis was not performed for NCEP and EAS targets.

ZD4522 at both doses resulted in statistically significantly greater reductions in LDL-C levels compared with pravastatin and simvastatin. In all comparisons of ZD4522, with the exception of ZD4522 5 mg and simvastatin, the difference in LDL-C was greater than 6%. This level was set by AstraZeneca as reflecting a level of clinical significance, and a level that was equivalent to the effect obtained by a doubling of dose of other statins. ZD4522 5 mg and 10 mg produced statistically significantly greater reductions in TC and ApoB compared with pravastatin and simvastatin. Both doses of ZD4522 produced numerically greater increases in HDL-C and ApoA-I compared with pravastatin and simvastatin. TG levels decreased similarly in all groups. In addition, both doses of ZD4522 resulted in significantly greater reductions in the 4 lipid ratios (LDL-C/HDL-C, TC/HDL-C, non-HDL-C/HDL-C and ApoB/ApoA-I) than pravastatin and simvastatin. There was no statistically significant difference in Lp(a) effect between either dose of ZD4522, pravastatin or simvastatin. ZD4522 at both doses resulted in more subjects reaching NCEP and EAS target guidelines for all categories and most notably in the high-risk categories.
Safety: ZD4522 was well tolerated at the 5 mg and 10 mg doses. The incidence of adverse events was similar between the treatment groups (adverse events ranged from 43% to 49%). The adverse event profile of ZD4522 was similar to pravastatin and simvastatin, and there were no unexpected adverse events in the ZD4522 groups. Whole body and digestive system adverse events were most commonly reported - the incidence between the groups was similar. Adverse events leading to withdrawal from the trial were reported in 12 subjects (2 in the ZD4522 5 mg group, 6 in the ZD4522 10 mg group, 3 in the pravastatin group and 1 in the simvastatin group). Five serious adverse events were reported by 4 subjects in the ZD4522 10 mg group. Of these, one subject died due to cerebral haemorrhage on the day of randomisation, but trial medication had not been taken. While it is noted that there were more adverse events leading to withdrawal in the ZD4522 10 mg group, and serious adverse events occurred only in the ZD4522 10 mg group, no particular pattern was noted in the body system affected or time to onset. In addition, none of the serious adverse events were considered to be related to trial medication. Furthermore, some of these events were to be expected in an ageing high-risk population. This indicates that it is unlikely that the increased incidence in these adverse events is related to ZD4522 10 mg or that there was a dose-response relationship in the between the 5 mg and 10 mg doses of ZD4522. ALT profiles over time were stable with no trends or signals noted. The number of subjects with elevations in ALT of >1 x ULN were similar across the treatment groups. Four subjects had an increase in ALT of >3 x ULN - 2 in each of the 5 mg and 10 mg ZD4522 groups. Three of these cases resolved on continued treatment with ZD4522 (ie, when subjects entered the long-term open-label safety trial - Trial ZD4522IL/0034) and 1 subject was lost to follow-up. There was no evidence of muscle toxicity as no subjects in the ZD4522 groups had elevations in CK of >10 x ULN. Eight subjects had myalgia (2 in the ZD4522 5 mg group, 3 in the ZD4522 10 mg group, 2 in the pravastatin group and 1 in the simvastatin group). Associated CK elevations were seen in only 3 subjects - 1 each in the ZD4522 10 mg, pravastatin and simvastatin groups. For the subjects receiving ZD4522 10 mg and pravastatin, the elevations in CK were <2 x ULN, and for the subject receiving simvastatin, the elevation was >10 x ULN. Changes in ECG from baseline were noted for 6 subjects in the ZD4522 groups and 1 subject each in the pravastatin and simvastatin groups. The nature of the changes seen was to be expected in this high-risk population, suggesting that the increased incidence seen in the ZD4522 groups was unlikely to be related to the treatment.