SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT:

ACTIVE INGREDIENT: ZD4522

Trial title (number): A 12-Week, Randomized, Double-blind, Placebo-controlled, Multicenter Trial to Evaluate the Efficacy and Safety of ZD4522 5 mg and 10 mg and Atorvastatin 10 mg in the Treatment of Subjects with Hypercholesterolemia (4522IL/0024).

Developmental phase: III

First subject recruited: 19 April 1999
Last subject completed: 17 February 2000
AstraZeneca approval date: 24 August 2000

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

Publications: None at the time of writing this report.

OBJECTIVES

The primary objective was to compare the efficacy of ZD4522 5 mg and 10 mg with that of atorvastatin 10 mg and placebo in reducing low-density lipoprotein cholesterol (LDL-C) levels in subjects with hypercholesterolemia. The secondary objectives were to compare the efficacy of ZD4522 5 mg and 10 mg with that of atorvastatin 10 mg and placebo in modifying other lipids and lipoprotein fractions and 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, randomized, double-blind, placebo-controlled, multicenter trial. After a 6-week dietary lead-in period, subjects were randomized to treatment with either ZD4522 (5 or 10 mg), atorvastatin 10 mg, or placebo for 12 weeks.

Population: A total of 100 randomized and evaluable subjects with hypercholesterolemia, derived from an estimated 1200 recruited subjects, were required 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 (between 160 and <250 mg/dL); fasting triglyceride (TG) levels <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 times 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 × 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 treatment once daily approximately 3 hours after the evening meal. Doses of treatments were as follows: ZD4522 5 mg, ZD4522 10 mg, atorvastatin 10 mg, and placebo. 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, 99-3033, 99-3034, 99-3085, 99-3095); ZD4522 10 mg (F12572; 99-3046, 99-3088, 99-3096, 99-3104, 99-3145); atorvastatin 10 mg (F12513; 99-3024); placebo (F12545; 98-3177).
Key assessments:
Efficacy: Fasting LDL-C, high-density lipoprotein cholesterol (HDL-C), TG, and total cholesterol (TC) were assessed at 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 throughout the trial was assessed and evaluated. The primary endpoint was the % change from baseline to Week 12 in LDL-C levels, and was analyzed 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, center, and center-by-treatment interaction. Additional analyses using observed data from ITT and per-protocol (PP) populations were used to confirm the robustness of the main ITT analysis. Percentage changes from baseline in the other lipids and lipoproteins were secondary endpoints of the trial and were analyzed using ANOVA. The other secondary endpoints of % of subjects in the ITT population who achieved targets for LDL-C levels specified by the NCEP (National Cholesterol Education Program) or the EAS (European Atherosclerosis Society) were summarized 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, hematology, urinalysis), vital signs, electrocardiograms [ECGs], and physical examination. All data were summarized.

RESULTS
Demography: A total of 1888 subjects were recruited from 52 centers; and of these, 519 were eligible for randomization following the dietary lead-in period. Of the 519 subjects randomized to treatment, 132 were given placebo, 129 were given ZD4522 5 mg, 130 were given ZD4522 10 mg, and 128 were given atorvastatin 10 mg; 3 subjects were not given any trial medication and were not included in the safety or ITT populations. Demographic characteristics were

generally well balanced among the treatment groups. The majority of the subjects were Caucasians between 18 and 65 years of age, with a mean body mass index (BMI) of 29 kg/m^2. The first subject entered the trial on April 19, 1999 and the last subject completed the trial on February 17, 2000. There were 1369 screen failures and withdrawals in the dietary lead-in period and 36 subjects withdrew during the randomized treatment period. Most of the subjects who were not randomized after the dietary lead-in period were screening failures, defined as the failure to meet inclusion/exclusion criteria. The most common reason for withdrawal during randomized treatment was adverse events. There were 516 subjects in the safety population, 516 in the ITT population and 380 in the PP population for the primary endpoint (change in LDL-C at Week 12).

Efficacy: A summary of the key efficacy findings is presented in Table I.

Table I Summary of key efficacy findings (ITT LOCF analysis)

Efficacy endpoint	Placebo	ZD4522 5 mg	ZD4522 10 mg	Atorvastatin 10 mg
lsmean of % change from baseline to Week 12 in lipids and lipid ratios				
LDL-C	0.03	–40.43 [c, e]	–42.85 [c, f]	–35.12
TC	0.23	–27.91 [c, d]	–29.70 [c, f]	–25.31
HDL-C	3.84	12.51 [c, e]	11.65 [c, e]	7.99
TG	–1.00	–16.56 [c, nss]	–18.57 [c, nss]	–18.75
LDL-C/HDL-C	–3.05	–46.26 [c, f]	–48.37 [c, f]	–39.46
TC/HDL-C	–2.81	–35.19 [c, e]	–36.64 [c, f]	–30.44
Non-HDL-C/HDL-C	–3.34	–43.19 [c, e]	–44.83 [c, f]	–37.35
ApoB	4.39	–31.25 [c, e]	–32.99 [c, f]	–26.48
ApoA-I	3.11	7.21 [b, e]	6.57 [a, d]	3.32
ApoB/ApoA-I	2.07	–35.11 [c, f]	–36.54 [c, f]	–28.26
Lp(a)	7.33	2.02 [ns, nss]	4.27 [ns, nss]	8.20
% subjects reaching NCEP or EAS targets for LDL-C levels at Week 12				
NCEP, overall	12.9	83.5	84.4	73.2
NCEP, high risk	0	42.1	47.4	18.8
EAS, overall	3.0	59.4	75.2	52.8
EAS, high risk	2.9	53.7	72.3	51.6

[a] $p \leq 0.05$, [b] $p \leq 0.01$, [c] $p \leq 0.001$, [ns] = not significant compared with placebo.
[d] $p \leq 0.05$, [e] $p \leq 0.01$, [f] $p \leq 0.001$, [nss] = not significant compared with atorvastatin.
Statistical analysis was not performed for NCEP and EAS targets.

ZD4522 at both doses resulted in significantly greater reductions in LDL-C levels than did atorvastatin 10 mg. From baseline to Week 12, LDL-C was reduced by 42.85% in the ZD4522 10-mg group and 35.12% in the atorvastatin 10-mg group. The difference in % reduction of LDL-C between ZD4522 10 mg and atorvastatin 10 mg was significant ($p<0.001$). A greater percentage of subjects in the ZD4522 groups achieved NCEP and EAS target levels than in the atorvastatin 10-mg group, with the greatest difference seen for the NCEP high-risk group. Both ZD4522 doses resulted in significantly greater decreases in TC and significantly greater

increases in HDL-C than did atorvastatin 10 mg. There were no significant differences in TG reduction between ZD4522 and atorvastatin. Both ZD4522 doses resulted in significantly greater decreases in ApoB and increases in ApoA-I than atorvastatin 10 mg. In addition, both doses of ZD4522 resulted in significantly greater reductions in the LDL-C/HDL-C, TC/HDL-C, non-HDL-C/HDL-C and ApoB/ApoA-I ratios than did atorvastatin 10 mg. There was no significant difference in Lp(a) effect between either ZD4522 dose and atorvastatin or placebo. Both ZD4522 doses significantly reduced LDL-C, TC, TG, and ApoB and increased HDL-C and ApoA-I in comparison to placebo. Both ZD4522 5 mg and 10 mg significantly decreased all tested ratios in comparison to placebo: LDL-C/HDL-C, TC/HDL-C, non-HDL-C/HDL-C and ApoB/ApoA-I.

Safety: ZD4522 was well tolerated at the 5-mg and 10-mg doses. The types and incidences of treatment-emergent adverse events in the ZD4522 groups were generally similar to those in the placebo group and in the atorvastatin 10-mg group. Adverse events leading to trial withdrawal were reported in 21 subjects (7 placebo, 6 ZD4522 5 mg, 4 ZD4522 10 mg, 4 atorvastatin 10 mg); 13 subjects reported serious adverse events during the randomized treatment period (5 placebo, 3 ZD4522 5 mg, 5 atorvastatin 10 mg). There was 1 death reported in this trial: a subject in the placebo group committed suicide. Sixteen subjects had myalgia (1 placebo, 6 ZD4522 5 mg, 4 ZD4522 10 mg, 5 atorvastatin 10 mg). Two subjects had a single instance of ALT $>3 \times$ ULN (1 ZD4522 10 mg and 1 atorvastatin 10 mg). No subject had a CK level $>10 \times$ ULN.