SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT:

ACTIVE INGREDIENT: **ZD4522**

Trial title (number): A 12-Week Randomized, Open-label, Multicenter Trial to Evaluate the Efficacy, Safety, and Tolerability of ZD4522 (80 mg) and the Combination of ZD4522 (80 mg) and Cholestyramine (16 g) in the Treatment of Subjects with Severe Hypercholesterolemia (4522IL/0031).

Clinical phase: III	**First subject recruited:**	27 October 1999
	Last subject completed:	6 September 2000
	AstraZeneca approval date:	23 March 2001

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 80 mg once daily with the combination ZD4522 80 mg once daily and cholestyramine (QUESTRAN™ Light, Bristol Laboratories, Bristol-Myers Squibb) 2 packets twice daily (ie, 16 g total) in reducing low-density lipoprotein cholesterol (LDL-C) at Week 6 (compared to baseline at Week –6). The secondary objectives were (1) to assess the percentage change from baseline (Week –6) to Week 0 (randomization) in LDL-C and the percentage from baseline (Week –6) to Week 0 and to Week 6 in total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), other lipid and lipoprotein fractions, and in the inflammatory markers C-reactive protein (CRP), interleukin-6 (IL–6), and E-selectin; and (2) to determine the safety and tolerability of treatment with ZD4522 and the combination of ZD4522 and cholestyramine by evaluating the incidence and severity of adverse events and abnormal laboratory values and by assessing the preservation of adrenal function using ACTH stimulation testing at selected sites. The intent was to compare randomized treatments with respect to the secondary endpoints.

METHODS

Design: This was an open-label, multicenter, randomized, force-titration, 2-group comparator trial. After a 6-week dietary lead-in phase (Weeks –12 to –6), all subjects received ZD4522 40 mg once daily for 6 weeks (pre-randomized phase, Weeks –6 to 0). Subjects were subsequently randomized to treatment with either (1) ZD4522 80 mg once daily or (2) ZD4522 80 mg once daily + cholestyramine 16 g (2 packets twice daily) for 6 weeks (Weeks 0 to 6). Main endpoints were assessed at the end of this period.

Population: A total of 98 randomized and evaluable subjects (49 per group) with severe hypercholesterolemia, derived from an estimated 310 recruited subjects, were required for a 90% power of detecting a 10% difference between groups in % change from baseline 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 from 190 to 400 mg/dL (4.91 to 10.3 mmol/L), fasting TG <400 mg/dL (4.52 mmol/L), 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 × the upper limit of normal (ULN); active arterial disease; history of malignancy (unless basal or squamous cell skin carcinoma, or disease free for >10 years); uncontrolled hypertension or hypothyroidism; history of homozygous familial hypercholesterolemia or known type III hyperlipoproteinemia; serum creatine kinase (CK) concentration >3 × ULN; use of concomitant medications known to affect the lipid profile or that present a potential safety concern (eg, through possible drug interactions).

Dosage: Subjects took oral doses of ZD4522 once daily approximately 3 hours after the evening meal, and cholestyramine twice daily with meals. Doses were as follows: ZD4522 40 mg once daily (Weeks –6 to 0); ZD4522 80 mg once daily or ZD4522 80 mg once daily + cholestyramine 2 packets (8 g) twice daily, for a total of 16 g/day (Weeks 0 to 6). Formulation and batch numbers were as follows: ZD4522 40 mg (F12566, batch numbers 99-3159, 99-3087, 99-3110); ZD4522 80 mg (F12568, batch numbers 99-3152, 00-0096, 00-0152, 99-3151); cholestyramine packets (F12574, batch number GO9975A). Subjects could decrease the cholestyramine dose to 1 packet twice daily (8 g/day) per protocol for reasons of tolerability.

Key assessments:

Key evaluations were conducted at the end of the randomized treatment phase (Week 6). Evaluations were also made at baseline (Week –6) and at randomization (Week 0).

Efficacy: Fasting LDL-C, HDL-C, TG, TC, apolipoprotein B (ApoB), ApoA-I, CRP, IL-6, and E-selectin were assessed at Weeks –6, 0, and 6. Dietary compliance throughout the trial was assessed and evaluated. The primary endpoint was the % change from baseline (Week –6) to Week 6 in LDL-C levels in the 2 randomized treatment groups, analyzed using analysis of variance (ANOVA) on last observations carried forward (LOCF) in the intent-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 analysis. Percentage changes from baseline (Week –6) to Week 6 in other lipids and lipoproteins in the 2 randomized treatment groups were secondary endpoints and were analyzed using ANOVA.

Subgroup and exploratory analyses were performed on LDL-C and HDL-C data for predefined demographic groupings.
Safety: Standard safety assessments included adverse event reports, clinical laboratory data (hepatic biochemistry, CK, renal biochemistry, hematology, urinalysis), adrenocorticotrophic hormone (ACTH) stimulation tests, vital signs, electrocardiograms (ECGs), and physical examinations. All data were summarized by treatment.

RESULTS
Demography: This trial was conducted at 17 centers in the USA from 27 October 1999 to 6 September 2000. A total of 372 subjects were enrolled into the 6-week dietary lead-in phase of this trial, 153 received ZD4522 40 mg once daily during the pre-randomization period (Week –6 to Week 0), and 147 were randomized to 6 weeks of treatment (Week 0 to Week 6) with ZD4522 80 mg once daily (n = 71) or to ZD4522 80 mg once daily + cholestyramine 2 packets twice daily (n = 76). A total of 219 subjects did not meet inclusion/exclusion criteria at the end of the dietary lead-in period (Week –6); and 12 withdrew from treatment (Weeks –6 to 6) for reasons of adverse events, withdrawal of informed consent, lost to follow-up, protocol non-compliance and LDL-C ≤50 mg/dL at randomization (Week 0). Subjects in the ZD4522 80-mg and ZD4522 80-mg + cholestyramine groups were a mean of 54 and 55 years of age, 61% and 53% male, 93% and 92% Caucasian, and had a mean body mass index of 28 and 28 kg/m^2, respectively. The 2 randomized groups were balanced with respect to demographic and background variables. The all treated, ITT and PP populations contained 147, 144 and 86 subjects, respectively.
Efficacy: A summary of the key efficacy findings is presented in Table I.

Table I Summary of key efficacy findings[a]

Efficacy endpoint	Pre-randomized to Week 0	Randomized treatment, Week 0 to Week 6		
	ZD4522 40 mg[b] N = 153	ZD4522 80 mg[b] N = 71	ZD4522 80 mg + cholestyramine[b] N = 76	p-value[c]
% change from baseline (Week –6) to Week 6 in lipids and lipid ratios				
	Mean (SD)	**lsmean (SE)**	**lsmean (SE)**	
LDL-C	–52.2 (13.0)	–56.35 (1.82)	–60.52 (1.75)	0.079
TC	–40.7 (9.6)	–43.31 (1.52)	–45.82 (1.47)	0.204
HDL-C	12.9 (12.5)	11.28 (2.06)	10.29 (1.98)	0.710
TG	–30.1 (18.6)	–23.31 (2.92)	–26.04 (2.80)	0.470
LDL-C/HDL-C	–57.3 (12.3)	–60.20 (1.86)	–63.54 (1.79)	0.168
TC/HDL-C	–47.0 (10.0)	–48.49 (1.70)	–49.81 (1.63)	0.548
NonHDL-C/HDL-C	–54.9 (11.4)	–57.02 (1.96)	–58.73 (1.88)	0.498
ApoB	–43.6 (11.6)	–46.91 (1.91)	–47.72 (1.83)	0.746
ApoA-I	9.0 (14.3)	8.31 (2.04)	9.97 (1.95)	0.532
ApoB/ApoA-I	–47.5 (13.0)	–50.42 (2.06)	–51.38 (1.97)	0.719
Median % change from baseline (Week –6) to Week 6 in inflammatory markers				
C-reactive protein	NA	–42.22	–48.00	NA
Interleukin-6	NA	6.44	11.93	NA
E-selectin	NA	–3.25	–2.45	NA

Data derived from Tables T10 to T22

[a] The main analyses (change from Week –6 to Week 6) is on the LOCF from the ITT population; summary statistics on the pre-randomized period (Week –6 to Week 0) are on observed data from the all treated population. Summary statistics for both the change from Week –6 to Week 0 (pre-randomized) and the change from Week –6 to Week 6 (randomized) are on observed data from the all treated population.

[b] All subjects were treated with ZD4522 40 mg from baseline (Week –6) to Week 0 (pre-randomized treatment phase); following randomization, subjects were treated with their randomized treatment from Week 0 to Week 6.

[c] p-value obtained from pairwise t-tests using least square means and mean square error from the ANOVA model.

lsmean = Least squares mean; SD = Standard deviation; SE = Standard error.

A numerically greater mean % decrease from baseline (Week –6) to Week 6 in LDL-C levels was observed with ZD4522 80 mg + cholestyramine than with ZD4522 80 mg (–60.52% vs. –56.35%, respectively), but the difference between treatments did not reach statistical significance. In addition, numerically greater mean % decreases in TC and TG were observed with ZD4522 80 mg + cholestyramine, but the differences between treatments were not significant. Both randomized treatments resulted in similar mean increases in HDL-C and ApoA-I and decreases in ApoB. Lipid ratios and apolipoprotein ratios were substantially decreased in both treatment groups and not different between groups. Substantial and clinically meaningful decreases from baseline in LDL-C, TC and TG and an increase in HDL-C were obtained during the 6-week pre-randomized treatment phase with ZD4522 40 mg, which were in most cases further improved with the 80-mg dose. Changes in inflammatory markers were highly variable, and no conclusions can be drawn.

Safety: Treatment with ZD4522 was well tolerated at both the 40-mg and 80-mg doses. ZD4522 80 mg + cholestyramine was less well tolerated, primarily due to digestive system adverse events. Subjects randomized to ZD4522 80 mg + cholestyramine had a higher incidence of constipation, dyspepsia and abdomen enlarged than did those on ZD4522 80 mg. These frequent adverse events were expected due to the known tolerability problems of cholestyramine. Nine subjects reduced the cholestyramine dose as per protocol, and compliance with cholestyramine among other subjects was poor. Other adverse events were few and were usually mild to moderate and considered not related to treatment. No deaths occurred during the trial, and none of the 3 serious adverse events were considered related to treatment. Only 1 patient had a clinically meaningful elevation in CK ($\leq 10.3 \times$ ULN), which was resolving on treatment; 1 patient had abnormal CK values ($\leq 1.8 \times$ ULN), including at baseline, and reported myalgia during the treatment period. A single subject had a meaningful increase in ALT during treatment with ZD4522 40 mg, which resolved upon discontinuation of treatment. No clinically meaningful changes in other laboratory values, ECG, vital signs, or physical examination were observed. There was no evidence of impairment of adrenal cortical reserve after 12 weeks of treatment with ZD4522. No new safety issues emerged with co-administration of ZD4522 and cholestyramine.