SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT:

ACTIVE INGREDIENT: ZD4522

Trial title (number): A Randomized, Double-blind, Multicenter Trial to Compare the Short-term and Long-term Efficacy and Safety of ZD4522 5 and 10 mg, Simvastatin 20 mg, and Pravastatin 20 mg in the Treatment of Subjects with Hypercholesterolemia (4522IL/0028).

Developmental phase: III

First subject recruited: 20 April 1999
Last subject completed: 09 October 2000
AstraZeneca approval date: 30 March 2001

Principal investigator and location (center number):

Publications: None at the time of writing this report.

OBJECTIVES

The primary objective of this trial was to compare the efficacy of treatment with ZD4522 5 mg and 10 mg with the efficacy of treatment with pravastatin 20 mg and simvastatin 20 mg in the reduction of low-density lipoprotein cholesterol (LDL-C) in subjects with hypercholesterolemia following 12 weeks of treatment.

The secondary objectives of this trial were:

- to compare the efficacy of treatment with ZD4522 5 mg and 10 mg with the efficacy of treatment with pravastatin 20 mg and simvastatin 20 mg in modifying other lipids and lipoprotein fractions at 12 weeks of treatment
- following a 40-week dose titration period, to compare the efficacy of treatment with ZD4522 (up to 80 mg) with the efficacy of treatment with pravastatin (up to 40 mg) and simvastatin (up to 80 mg) and in modifying other lipids and lipoprotein fractions in subjects with hypercholesterolemia
- to compare the efficacy of treatment with ZD4522 with the efficacy of treatment with pravastatin and simvastatin in achieving relevant national and international guidelines in subjects with hypercholesterolemia at 12 and 52 weeks of treatment
- to compare the titration schedules of ZD4522, pravastatin, and simvastatin

- to determine the safety of ZD4522 by evaluating the incidence and severity of adverse events and abnormal laboratory parameters

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METHODS

Design: This was a 52-week, randomized, double-blind, parallel-group, comparator-controlled, multicenter trial conducted with 4 groups in 3 periods. After a 6-week dietary lead-in period, subjects were randomized to fixed doses of either ZD4522 5 mg or 10 mg, or pravastatin 20 mg, or simvastatin 20 mg for 12 weeks (fixed-dose treatment period). After the 12-week fixed-dose treatment period, subjects were allowed to be titrated to a new dose of their original trial medication to maintain LDL-C levels within the National Cholesterol Education Program (NCEP) guidelines (titrated-dose treatment period). The titrated-dose treatment period lasted 40 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 percentage 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 ≥160 and <250 mg/dL (≥4.14 and <6.50 mmol/L); fasting triglyceride (TG) levels <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 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; serum creatinine >2.5 mg/dL (>220 μmol/L); 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 during the 12-week fixed-dose treatment period were as follows: ZD4522 5 mg, ZD4522 10 mg, pravastatin 20 mg, and simvastatin 20 mg per day. Doses of treatments during the 40-week titrated-dose period were, for the ZD4522 5-mg treatment group, ZD4522 5, 10, 20, 40, or 80 mg per day; for the ZD4522 10-mg treatment group, ZD4522 10, 20, 40, or 80 mg per day; for the pravastatin 20-mg treatment group, pravastatin 20 or 40 mg per day; for the simvastatin 20-mg treatment group, simvastatin 20, 40, or 80 mg per day.

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; 00-0005, 00-0044, 99-3046, 99-3047, 99-3088, 99-3096, 99-3104, 99-3145); ZD4522 20 mg (F12522; 99-3086, 99-3108, 99-3146, 00-0045); ZD4522 40 mg (F12566; 99-3159, 00-0063, 99-3110); ZD4522 80 mg (F12568; 00-0152); pravastatin 20 mg (F12556; 99-0514, 99-3026); simvastatin 20 mg (F12562; 99-0472, 99-3027); simvastatin 80 mg (F12564; 99-0477, 99-3050); 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 -6, -2, -1, 0, 2, 6, 10, 12, 20, 28, 36, 44, 50, and 52; fasting apolipoprotein B (ApoB), apolipoprotein A-I (ApoA-I), and lipoprotein (a) (Lp(a)) were assessed at Weeks 0 and 52. Dietary compliance throughout the trial was assessed and evaluated. The primary end-point was the percentage 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 end-points of the trial and were analyzed using ANOVA. The other secondary end-points of percentage of subjects in the ITT population who achieved targets for LDL-C levels specified by the NCEP or the EAS (European Atherosclerosis Society), and the titration schedules of ZD4522, pravastatin, and simvastatin 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 477 subjects were recruited from 43 centers and randomized to treatment; 123 were randomized to ZD4522 5 mg, 116 were randomized to ZD4522 10 mg, 118 were randomized to pravastatin 20 mg, and 120 were randomized to simvastatin 20 mg. Demographic characteristics were generally well balanced among the treatment groups. The majority of subjects in each treatment group were female, Caucasian, and between 18 and 64 years of age. The most common reason for withdrawal during randomized treatment was adverse events. The most common protocol deviation in all treatment groups was non-compliance with trial medication. There were 475 subjects in the safety population, 472 in the ITT population, and 341 (at Week 12) 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 and observed on ITT population)

Efficacy end-point	ZD4522 5 mg	ZD4522 10 mg	Pravastatin 20 mg	Simvastatin 20 mg
Week 12 (LOCF)				
lsmean of % change from baseline in lipids and lipid ratios				
LDL-C	-39.13 [a, f]	-47.37 [a, d]	-26.54	-34.56
TC	-27.96 [a, e]	-33.41 [a, d]	-18.53	-23.77
HDL-C	8.19 [ns, nss]	11.90 [c, nss]	8.29	8.83
TG	-17.56 [ns, f]	-21.54 [b, d]	-11.37	-10.15
LDL-C/HDL-C	-43.16 [a, f]	-52.47 [a, d]	-31.72	-39.36
TC/HDL-C	-32.81 [a, f]	-39.99 [a, d]	-24.26	-29.35
Non-HDL-C/HDL-C	-40.04 [a, f]	-48.91 [a, d]	-29.68	-36.08
ApoB	-31.14 [a, e]	-37.27 [a, d]	-20.28	-26.68
ApoA-I	4.24 [ns, nss]	5.86 [ns, nss]	4.64	5.15
ApoB/ApoA-I	-32.95 [a, nss]	-40.16 [a, d]	-23.18	-29.60
Lp(a)	-3.12 [ns, nss]	12.02 [ns, nss]	10.79	5.85
% subjects reaching NCEP and EAS targets for LDL-C levels				
NCEP, overall	80.2	89.6	53.4	68.9
NCEP, high risk	47.6	63.2	8.7	30.0
EAS, overall	62.0	77.4	11.2	45.8
EAS, high risk	66.3	75.9	7.9	45.3
Week 52 (observed) – Treatment shown represents the initial dose at randomization and was to be titrated after 12 weeks if the NCEP target for LDL-C was not reached.				
Lsmean of % change from baseline in lipids and lipid ratios				
LDL-C	-41.59 [a, nss]	-47.97 [a, d]	-31.61	-37.87
TC	-30.07 [a, f]	-34.20 [a, d]	-22.75	-26.98
HDL-C	4.49 [ns, nss]	7.56 [ns, nss]	4.48	6.20
TG	-15.75 [ns, nss]	-18.05 [c, nss]	-9.30	-14.06
LDL-C/HDL-C	-43.33 [a, nss]	-51.06 [a, d]	-34.07	-40.81
TC/HDL-C	-32.27 [a, nss]	-38.18 [a, d]	-25.56	-30.45
Non-HDL-C/HDL-C	-39.44 [a, nss]	-46.69 [a, d]	-31.22	-37.34
ApoB	-34.55 [a, f]	-38.67 [a, d]	-25.06	-30.83
ApoA-I	6.37 [ns, nss]	5.99 [ns, nss]	6.86	6.97
ApoB/ApoA-I	-38.17 [a, nss]	-41.53 [a, d]	-29.44	-34.80
Lp(a)	-10.65 [ns, nss]	-5.90 [ns, nss]	-15.56	-12.85
% subjects reaching NCEP targets for LDL-C levels				
NCEP, overall	88.1	87.5	60.0	72.5
NCEP, high risk	84.2	71.4	5.9	29.6

[a] $p \leq 0.001$ compared with pravastatin 20 mg; [b] $p \leq 0.01$ compared with pravastatin 20 mg; [c] $p \leq 0.05$ compared with pravastatin 20 mg; [ns] = Not significant compared with pravastatin 20 mg.
[d] $p \leq 0.001$ compared with simvastatin 20 mg; [e] $p \leq 0.01$ compared with simvastatin 20 mg; [f] $p \leq 0.05$ compared with simvastatin 20 mg; [nss] = Not significant compared with simvastatin 20 mg.
Statistical analysis was not performed for NCEP and EAS targets.
LOCF = Last observation carried forward.

At Week 12, ZD4522 5 mg and ZD4522 10 mg both resulted in statistically significantly greater reductions in LDL-C levels than did pravastatin 20 mg and simvastatin 20 mg. From baseline to Week 12, LDL-C was reduced by 39.13% in the ZD4522 5-mg group and 47.37% in the ZD4522 10-mg group compared with 26.54% in the pravastatin 20-mg group and 34.56% in the simvastatin 20-mg group. At Week 52, statistically significantly greater reductions in LDL-C levels for the ZD4522 groups also were seen, except for the ZD4522 5-mg group compared with the simvastatin 20-mg group. The mean percentage of subjects in the ZD4522 groups achieving NCEP and EAS target levels was higher in the ZD4522 groups than in the pravastatin and simvastatin groups. This difference was especially evident in the high-risk subjects. In addition, more subjects in the ZD4522 5-mg and ZD4522 10-mg groups achieved NCEP targets for LDL-C with fewer upward titration steps than in either the pravastatin 20-mg group or the simvastatin 20-mg group. At Week 12, ZD4522 5 mg and ZD4522 10 mg produced statistically significant decreases in TC and ApoB compared with pravastatin 20 mg and simvastatin 20 mg. At Week 52, statistically significantly greater decreases in TC and ApoB for the ZD4522 groups also were seen compared with the pravastatin and simvastatin groups. Increases in HDL-C and ApoA-I were seen in both ZD4522 groups at Weeks 12 and 52, but the differences were not statistically significant when compared with pravastatin and simvastatin, except for HDL-C at Week 12 for ZD4522 10 mg compared with pravastatin 20 mg. Statistically significant decreases were seen in TG levels for both the ZD4522 groups at Week 12 compared with pravastatin and simvastatin, except for ZD4522 5 mg compared with pravastatin 20 mg, but significant decreases were not seen at Week 52, except for the ZD4522 10-mg group compared with the pravastatin 20-mg group. Both ZD4522 5 mg and ZD4522 10 mg resulted in statistically significant greater reductions in the lipid ratios LDL-C/HDL-C, TC/HDL-C, and non-HDL-C/HDL-C at Week 12 when compared with pravastatin 20 mg and simvastatin 20 mg; the lipid ratio for ApoB/ApoA-I was also statistically significantly reduced except for ZD4522 5 mg compared with simvastatin 20 mg. The same pattern was observed for lipid ratios at Week 52.

Safety: Overall, ZD4522 was well tolerated. The overall incidence of treatment-emergent adverse events over the 52 weeks of treatment was similar for all treatment groups (range, 79.5% to 86.2%), as were the incidence of adverse events leading to withdrawal (range, 7.5% to 9.8%) and the incidence of serious adverse events (range, 5.1% to 10.0%). Adverse events leading to trial withdrawal were reported in 42 subjects (12 ZD4522 5-mg group, 10 ZD4522 10-mg group, 11 pravastatin 20-mg group, and 9 simvastatin 20-mg group). Adverse events were as expected for statins, with drug-related adverse events affecting the gastrointestinal system predominantly. Thirty-eight subjects had serious adverse events during the randomized treatment period (11 ZD4522 5-mg group, 9 ZD4522 10-mg group, 6 pravastatin 20-mg group, and 12 simvastatin 20-mg group); only 2 events were considered to be related to treatment and both occurred in a subject in the simvastatin 20-mg group. There was 1 death reported in this trial: a subject in the pravastatin 20-mg group died as a result of accidental injury. Three subjects receiving ZD4522 had a single CK level >10 x ULN (1 ZD4522 5-mg group, 2 ZD4522 10-mg group) but none of these subjects was reported to have myositis. Thirty subjects had myalgia (11 ZD4522 5-mg group, 7 ZD4522 10-mg group, 2 pravastatin 20-mg group, and 10 simvastatin 20-mg group). Nine subjects had an of ALT >3 x ULN (3 ZD4522 5-mg group, 1 ZD4522 10-mg group, 2 pravastatin 20-mg group, and 3 simvastatin 20-mg group); all cases were transient or resolved

with continued treatment. The number of subjects with adverse events considered by the investigator to be related to treatment was similar in the 4 treatment groups: 27 (22.0%) in the ZD4522 5-mg group, 26 (22.6%) in the ZD4522 10-mg group, 22 (18.8%) in the pravastatin 20-mg group, and 33 (27.5%) in the simvastatin 20-mg group. Clinically significant changes from screening ECGs were observed for 7 subjects: 1 in the ZD4522 10-mg group and 3 each in the pravastatin 20-mg and simvastatin 20-mg groups. The subject who received ZD4522 had a normal baseline ECG, except for left axis deviation, and at Week 52 had left axis deviation plus T-wave inversion in the precordial leads. The clinical significance of this change is unknown.