SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT:

ACTIVE INGREDIENT: ZD4522

Trial title (number): A 24-week, Randomized, Double-blind, Multicenter Trial to Evaluate the Efficacy and Safety of Starting and Maximum Doses of ZD4522 and Atorvastatin in the Treatment of High Risk Hypercholesterolemic Subjects (4522IL/0025).

Developmental phase: III

First subject recruited: 28 July 1999
Last subject completed: 16 November 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 of this trial was to compare the efficacy of ZD4522 80 mg with atorvastatin 80 mg in the reduction of low-density lipoprotein cholesterol (LDL-C) in high-risk hypercholesterolemic subjects following 24 weeks of treatment.

The secondary objectives of this trial were:

- to compare the efficacy of treatment with ZD4522 with that of atorvastatin in reducing LDL-C following 12 and 18 weeks of treatment;
- to compare the efficacy of treatment with ZD4522 with that of atorvastatin in modifying other lipids and lipoprotein fractions and inflammatory markers at 12, 18, and 24 weeks;
- to compare the efficacy of treatment with ZD4522 and atorvastatin in reducing LDL-C concentrations to within relevant national and international guidelines at 12, 18, and 24 weeks;
- to compare the number and type of major medical events;
- to determine the safety of ZD4522 by evaluating the incidence and severity of adverse events and abnormal laboratory values.

METHODS

Design: This was a multicenter, randomized, double-blind, 3 parallel-group, forced-titration, comparator trial. After a 6-week dietary lead-in period, subjects were randomized to treatment with a starting dose of either ZD4522 (5 mg or 10 mg) or atorvastatin for 12 weeks. At Week 12, subjects had their doses increased to intermediate dose for 6 weeks. At Week 18, subjects had their doses increased to maximum dose for 6 weeks.

Population: A total of 288 randomized and evaluable high-risk subjects (2:1 ratio of ZD4522 80 mg versus atorvastatin 80 mg) were required to have 90% power for the primary objective, derived from an estimated 900 recruited subjects.

Key inclusion criteria: Men or women aged ≥18 years with Type IIa or IIb hypercholesterolemia and documented atherosclerosis (ie, a history of peripheral vascular disease [PVD], coronary artery disease, or cerebrovascular disease), or Type 2 diabetes mellitus; discontinuation of all cholesterol-lowering drugs and lipid-lowering dietary supplements; fasting LDL-C levels between 160 and <250 mg/dL (between 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; use 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 either ZD4522 or atorvastatin once daily approximately 3 hours after the evening meal. Doses of treatments were as follows during the first 12 weeks: ZD4522 5 mg, ZD4522 10 mg, or atorvastatin 10 mg. For subjects who completed the 12-week fixed-dose period, drug doses were increased at Week 12 from ZD4522 5 mg to 20 mg, from ZD4522 10 mg to 40 mg, and from atorvastatin 10 mg to 40 mg. At Week 18, drug doses were again increased; the increases were from ZD4522 20 mg to 80 mg, from ZD4522 40 mg to 80 mg, and from atorvastatin 40 mg to 80 mg. Subjects whose LDL-C was ≤50 mg/dL (≤1.29 mmol/L) at the Week 12 or Week 18 visit remained at the dose level they had been receiving.

Formulation and batch numbers of trial medications were as follows: ZD4522 5 mg tablets (F12570; 99-3162, 99-0510, 99-3034, 99-3085, 99-3095), ZD4522 10 mg tablets (F12572; 00-0005, 00-0044, 99-3046, 99-3088, 99-3096, 99-3104, 99-3145), ZD4522 20 mg tablets (F12522; 00-0045, 99-3086, 99-3108, 99-3146, 00-0182), ZD4522 40 mg tablets (F12566; 99-3159, 00-0166, 00-0063, 99-3087, 99-3110), atorvastatin 10 mg tablets (F12513; 99-0486, 99-3024), atorvastatin 40 mg tablets (F12560; 99-0513, 99-3049).

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, 12, 18, and 24; fasting Apolipoprotein B (ApoB), and Apolipoprotein A-I (ApoA-I) were assessed at Weeks 0, 12, 18, and 24. Dietary compliance throughout the trial was assessed and evaluated. The primary endpoint was the % change from baseline at Week 24 in LDL-C levels. Data from both ZD4522 groups were

combined and compared with atorvastatin. The endpoint was analyzed using analysis of variance (ANOVA) on last observations carried forward (LOCF) data 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 and nonparametric analyses were used to confirm the robustness of the main ITT analysis. Percentage changes from baseline to Weeks 12 and 18 in LDL-C and to Weeks 12, 18, and 24 in the other lipids and lipoproteins were secondary endpoints of the trial and were analyzed using ANOVA. For the Week 12 and 18 endpoints, data for each ZD4522 group were compared individually with atorvastatin. The percentages 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) at Weeks 12, 18, and 24 were analyzed by logistic regression. The other secondary endpoints were summarized only: % change in specified inflammatory markers and incidence of major medical events. 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, creatine kinase [CK], renal biochemistry, other biochemistry, hematology, urinalysis), vital signs, electrocardiograms (ECGs), and physical examination. All data were summarized.

RESULTS

Demography:

A total of 1233 subjects were recruited from 68 centers; of these, 383 subjects from 57 centers were eligible for randomization following the dietary lead-in period. Of the 383 subjects randomized to treatment, 127 were randomized to ZD4522 5/20/80 mg, 128 were randomized to ZD4522 10/40/80 mg, and 128 were randomized to atorvastatin 10/40/80 mg; 1 atorvastatin subject returned all trial medication dispensed and was not included in the safety or ITT populations. All subjects were high-risk subjects with hypercholesterolemia (Type IIa and IIb). Demographic characteristics were generally well balanced among the treatment groups. The majority of the subjects were Caucasians (91%) and between 18 and 64 years of age (57%). Mean age was 62 years, with 43% of subjects 65 years or older, and mean body mass index (BMI) was 29 kg/m^2. The first subject entered the trial on 28 July 1999 and the last subject completed the trial on 16 November 2000. The most common reasons for withdrawal during randomized treatment were withdrawal of informed consent and adverse events. There were 382 subjects in the safety population, 382 in the ITT population, and 220 in the PP population for the primary endpoint (% change from baseline at Week 24 in LDL-C).

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

Table I Summary of key efficacy findings

Efficacy endpoint	Combined ZD4522 5/20/80 mg and ZD 10/40/80 mg	Atorvastatin 10/40/80 mg
lsmean of % change from baseline at Week 24 in lipids and lipid ratios (ITT, LOCF)		
LDL-C	-59.56[c]	-52.03
TC	-43.24[b]	-39.51
HDL-C	8.05[c]	0.94
TG	-24.59[ns]	-27.05
LDL-C/HDL-C	-61.83[c]	-51.68
TC/HDL-C	-46.61[c]	-39.32
Non-HDL-C/HDL-C	-56.19[c]	-47.30
ApoB	-47.21[b]	-42.82
ApoA-I	5.84[b]	1.59
ApoB/ApoA-I	-49.56[c]	-42.69
% subjects reaching NCEP or EAS targets for LDL-C levels at Week 24 (ITT, LOCF)		
NCEP	84.3[a]	74.0
EAS	89.8[ns]	86.6

	ZD4522 5/20/80 mg	ZD 10/40/80 mg	Atorvastatin 10/40/80 mg
Median % change from baseline at Week 24 in inflammatory markers (observed data)			
C-reactive protein	-41.46	-41.05	-38.79
IL-6	15.14	-2.88	-1.28
E-selectin	-5.72	-2.36	-1.60
% subjects with major medical events during the 24-week period (observed data)			
Emergency department visits	3.1	3.1	3.9
Hospitalizations	3.9	4.7	4.7
Acute myocardial infarctions	0.8	0.8	0.8
Cardiovascular procedures	3.1	3.1	3.9

[a] $p<0.05$, [b] $p<0.01$, [c] $p<0.001$, [ns] = not significant compared with atorvastatin 10/40/80 mg.
Statistical analysis was not performed for inflammatory markers or for major medical events.
NCEP target for high-risk subjects is 2.59 mmol/L (≤100 mg/dL). EAS target for all subjects is <3.00 mmol/L (<116 mg/dL).

At the end of a 24-week treatment period, ZD4522 80 mg (combined ZD4522 treatment groups) was superior to atorvastatin 80 mg in lowering LDL-C ($p<0.001$) for these high-risk subjects. ZD4522 80 mg resulted in an LDL-C reduction of 60%. The 7.5% greater reduction in LDL-C with ZD4522 80 mg was clinically meaningful and exceeded the 5-7% LDL-C reduction typically achieved by doubling the dose of a statin. ZD4522 80 mg was significantly more effective ($p<0.01$) than atorvastatin 80 mg in reducing TC, the tested lipid ratios (LDL-C/HDL-C, TC/HDL-C, and non-HDL-C/HDL-C), ApoB, and ApoB/ApoA-I. ZD4522 80 mg was significantly more effective ($p<0.01$) than atorvastatin 80 mg in increasing HDL-C and ApoA-I. Reductions in TG were similar for ZD4522 80 mg and atorvastatin 80 mg.

At starting doses (assessed at Week 12) ZD4522 10 mg was significantly more effective than atorvastatin 10 mg in altering lipid and lipoprotein levels (LDL-C, TC, HDL-C, LDL-C/HDL-C, TC/HDL-C, non-HDL-C/HDL-C, ApoB, ApoB/ApoA-I, NCEP, EAS, $p<0.001$; ApoA-I, $p<0.05$). ZD4522 5 mg was generally more effective than atorvastatin 10 mg, but the differences were not always statistically significant. At intermediate doses (assessed at Week 18) ZD4522 40 mg was also significantly more effective than atorvastatin 40 mg in altering lipid and lipoprotein levels (LDL-C, TC, HDL-C, LDL-C/HDL-C, TC/HDL-C, non-HDL-C/HDL-C, ApoB, ApoA-I, ApoB/ApoA-I, NCEP, EAS, $p<0.001$). ZD4522 20 mg was generally more effective than atorvastatin 40 mg, but the difference versus atorvastatin was not always statistically significant. Reductions in TG were similar for ZD4522 and atorvastatin.

The percentage of subjects reaching the NCEP target at Week 24 was significantly greater ($p<0.05$) with ZD4522 80 mg than with atorvastatin 80 mg. A higher percentage of ZD4522 80 mg subjects reached the EAS target compared with atorvastatin group, but the difference was not statistically significant. Assessments at earlier time points showed that more subjects in the ZD4522 groups reached the NCEP target and the EAS target compared with the subjects in the atorvastatin dose group, with the greatest difference between ZD4522 and atorvastatin seen at Week 2. At Week 2, the percentage of subjects reaching the NCEP target in the ZD4522 10 mg group (50.8%) was nearly 4 times that in the atorvastatin 10 mg group (13.4%), the percentage in the ZD4522 5 mg group (22.8%) was nearly twice that in the atorvastatin 10 mg group, and the differences between each ZD4522 group and atorvastatin were statistically significant ($p<0.05$).

Changes in inflammatory markers were highly variable, but median CRP values decreased in all treatment groups during the course of the trial.

The major medical events chosen for assessment (emergency department visits, hospitalizations, etc.) were so infrequent over the 24-week period that no definitive conclusions could be drawn.

Safety:

ZD4522 was generally well tolerated in the high-risk subjects of this trial. The types and incidences of treatment-emergent adverse events for the ZD4522 groups were generally similar to those for the atorvastatin group. Treatment-emergent adverse events leading to trial withdrawal were reported for 18 subjects (5 ZD4522 5/20/80 mg, 7 ZD4522 10/40/80 mg, 6 atorvastatin 10/40/80 mg); 27 subjects experienced serious adverse events during the randomized treatment period (12 ZD4522 5/20/80 mg, 8 ZD4522 10/40/80 mg, and 7 atorvastatin 10/40/80 mg). One ZD4522 10/40/80 mg subject died of pneumonia that was considered unrelated to trial medication. Six subjects had CK >10 x ULN. Of these 6 subjects, 1 subject receiving ZD4522 80 mg was hospitalized because of marked CK elevations and an

increase in serum creatinine to 2.1 mg/dL and 2 subjects receiving ZD4522 80 mg had an asymptomatic CK elevation >10 x ULN. Nine subjects had ALT >3 x ULN. Of these 9 subjects, 1 subject receiving atorvastatin 80 mg and 1 subject receiving ZD4522 80 mg had an unexplained ALT elevation on their final trial visit. All other subjects with CK >10 x ULN or ALT >3 x ULN had their elevations resolved despite continuing treatment or had elevations explainable by causes other than trial medication.