SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT:

ACTIVE INGREDIENT: ZD4522

Trial title (number): A 6-week, Randomized, Double-blind, Multicenter Trial to Evaluate the Safety and Efficacy of ZD4522 (5, 10, 20, 40, and 80 mg) and Atorvastatin (10, 20, 40, and 80 mg) Across Their Respective Dose Ranges in the Treatment of Subjects with Hypercholesterolemia (4522IL/0033).

Developmental phase: III

First subject recruited: 27 October 1999
Last subject completed: 16 June 2000
AstraZeneca approval date: 06 December 2000

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 (5, 10, 20, 40, and 80 mg) with the efficacy of atorvastatin (10, 20, 40 and 80 mg) in the reduction of low-density lipoprotein cholesterol (LDL-C) at 6 weeks in subjects with hypercholesterolemia.
The secondary objectives of the trial were to compare the efficacy of treatment with ZD4522 with that of atorvastatin in modifying other lipids and lipoprotein fractions; to compare the efficacy of treatment with ZD4522 with that of atorvastatin in reducing LDL-C concentrations at Weeks 1, 2, and 4; and to determine the safety of treatment with ZD4522 by evaluating the incidence and severity of adverse events and abnormal laboratory values.

METHODS

Design: This was a 6-week, randomized, double-blind, parallel-group, multicenter, comparator trial. After a 6-week dietary lead-in period, subjects were randomized to treatment with either ZD4522 (5, 10, 20, 40, and 80 mg) or atorvastatin (10, 20, 40, and 80 mg) for 6 weeks.
Population: A total of 35 randomized and evaluable subjects with hypercholesterolemia per treatment group (9 groups; 315 subjects total), derived from an estimated 875 recruited subjects, were required for 95% power to estimate a parallel dose-response relationship in LDL-C

lowering and 80% power to estimate a 6% difference in LDL-C lowering between treatment groups using a linear regression model.

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) level <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

Dosage: Subjects were given oral doses of either ZD4522 or atorvastatin once daily approximately 3 hours after the evening meal. The same dose of trial treatment was given for 6 weeks. Formulation and lot numbers were as follows: ZD4522 5 mg (F12570; 99-3162, 99-0510, 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 40 mg (F12566; 99-3159, 99-3087, 99-3110), atorvastatin 10 mg (F12513, 99-0486, 99-3024), atorvastatin 40 mg (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, 1, 2, 4, and 6; fasting Apolipoprotein B (ApoB) and Apolipoprotein A-I (ApoA-I) were assessed at Week 6. Dietary compliance throughout the trial was assessed and evaluated. The primary endpoint was the percentage change from baseline at Week 6 in LDL-C levels, and was analyzed using regression analysis across the entire dose range (ANCOVA model). Analyses were done on last observations carried forward (LOCF) from an intention-to-treat (ITT) population; the initial model included terms for baseline value, log(dose), treatment-by-log(dose) interaction, 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 at Week 6 in the other lipids and lipoproteins were secondary endpoints of the trial and were analyzed in the same manner as LDL-C, using regression analysis (ANCOVA model). As there was no evidence of a linear parallel dose-response relationship for HDL-C, TG, and ApoA-I, dose-by-dose comparisons on percentage change from baseline were performed using analysis of variance (ANOVA).

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 978 subjects were recruited from 41 centers; of these, 374 were eligible for randomization following the dietary lead-in period. Of the 374 subjects randomized to treatment, 209 were given ZD4522 and 165 were given atorvastatin. All subjects took at least 1 dose of trial medication. Demographic characteristics were generally well balanced among the 9 treatment groups. The majority of the subjects were Caucasians between 18 and 64 years of age; mean body mass index was 28 kg/m^2. There were 604 screen failures and withdrawals in the dietary lead-in period; most of the 604 subjects failed to meet inclusion/exclusion criteria for

randomization. A total of 17 subjects withdrew during the randomized treatment period; the most common reason for withdrawal was adverse events. There were 374 subjects in the safety population, 372 in the ITT population, and 285 in the PP population for the primary endpoint (% change in LDL-C at Week 6).

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

ZD4522 (5 mg - 80 mg) was superior to atorvastatin (10 mg - 80 mg) at lowering LDL-C across the entire dose range; the difference of 8.4% at Week 6 was clinically meaningful and statistically significant ($p<0.001$). ZD4522 resulted in LDL-C reductions over a 6-week period ranging from 42% (5 mg) to 62% (80 mg). ZD4522 was also statistically significantly ($p<0.001$) better than atorvastatin in reducing TC, the tested lipid ratios (LDL-C/HDL-C, TC/HDL-C, non-HDL-C/HDL-C, and ApoB/ApoA-I), and ApoB across the entire dose range at Week 6. ZD4522 was statistically significantly ($p<0.01$) better than atorvastatin in increasing HDL-C at 40 mg and 80 mg; ZD4522's effect at the lower doses was also greater than atorvastatin's, but the differences were not statistically significant. Reductions in TG were similar for ZD4522 and atorvastatin, except at the 80-mg dose, where atorvastatin produced a statistically significantly ($p<0.05$) greater decrease compared with ZD4522. Both ZD4522 and atorvastatin produced increases in ApoA-I at all doses tested, with ZD4522 producing statistically significantly ($p<0.05$) greater increases at 80 mg compared with atorvastatin.

Table I Summary of key efficacy findings

Efficacy endpoint	Dose					
Treatment	5 mg	10 mg	20 mg	40 mg	80 mg	Difference across dose range (SE)
lsmeans of % change from baseline at Week 6 in lipids, lipoproteins, and ratios						
LDL-C[a]						
ZD4522	-41.53	-46.62	-51.72	-56.81	-61.91	-8.42 (1.38)[c]
Atorvastatin	NA	-38.21	-43.30	-48.40	-53.49	
TC[a]						
ZD4522	-29.38	-33.29	-37.20	-41.11	-45.02	-4.86 (1.08)[c]
Atorvastatin	NA	-28.43	-32.34	-36.25	-40.16	
HDL-C[b]						
ZD4522	7.36	6.01[ns]	9.14[ns]	12.28[c]	9.58[d]	NA
Atorvastatin	NA	5.01	7.58	4.09	2.12	
TG[b]						
ZD4522	-23.11	-22.09[ns]	-18.36[ns]	-25.70[ns]	-19.70	NA
Atorvastatin	NA	-17.54	-25.60	-27.22	-34.54[e]	
LDL-C/HDL-C[a]						
ZD4522	-45.60	-50.31	-55.02	-59.72	-64.43	-9.51 (1.48)[c]
Atorvastatin	NA	-40.80	-45.50	-50.21	-54.92	
TC/HDL-C[a]						
ZD4522	-34.64	-38.23	-41.83	-45.42	-49.01	-6.94 (1.21)[c]
Atorvastatin	NA	-31.29	-34.88	-38.48	-42.07	
Non-HDL-C/HDL-C[a]						
ZD4522	-42.36	-46.72	-51.08	-55.45	-59.81	-8.37 (1.50)[c]
Atorvastatin	NA	-38.35	-42.71	-47.07	-51.44	
ApoB[a]						
ZD4522	-34.62	-38.84	-43.06	-47.28	-51.51	-6.25 (1.21)[c]
Atorvastatin	NA	-32.59	-36.82	-41.04	-45.26	
ApoA-I[b]						
ZD4522	6.08	5.17[ns]	8.47[ns]	6.18[ns]	9.17[e]	NA
Atorvastatin	NA	5.27	3.56	1.50	3.08	
ApoB/ApoA-I[a]						
ZD4522	-39.05	-42.99	-46.93	-50.86	-54.80	-8.15 (1.29)[c]
Atorvastatin	NA	-34.84	-38.78	-42.72	-46.65	

[a] Lsmeans and p-value obtained from regression analysis across the entire dose range.
[b] Lsmeans and p-values obtained from dose-by-dose comparisons using ANOVA.
[c] $p<0.001$ versus atorvastatin; [d] $p<0.01$ versus atorvastatin; [e] $p<0.05$ versus atorvastatin.
ns = not statistically significant; NA = Not applicable; SE = Standard error.

Safety: ZD4522 was well tolerated at all doses. The types and incidences of treatment-emergent adverse events in the ZD4522 groups were similar to those in the atorvastatin groups. There was no consistent pattern suggesting a relationship between dose and incidence of adverse events. There were no deaths reported in this trial. Adverse events leading to trial withdrawal were reported for 9 subjects (5 ZD4522 and 4 atorvastatin); 3 subjects reported serious adverse events during the randomized treatment period (2 ZD4522and 1 atorvastatin). Nine subjects had myalgia (4 ZD4522 and 5 atorvastatin). Three subjects had a single instance of ALT >3 x ULN (1 ZD4522 and 2 atorvastatin). No subject had a CK level >10 x ULN.