SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT:

ACTIVE INGREDIENT: ZD4522

Trial title (number): A Randomised, Double-blind, Multinational, Multicentre Trial to Compare the Short-term and Long-term Efficacy and Safety of ZD4522 and Atorvastatin in the Treatment of Subjects with Hypercholesterolaemia (4522IL/0026).

Clinical phase: III

First subject recruited: 28 April 1999
Last subject completed: 31 October 2000
AstraZeneca approval date: 14 March 2001

Principal investigator and location (centre number):

Publications: None at the time of writing this report.

OBJECTIVES

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

The secondary objectives of the trial were as follows:

- To compare the efficacy of treatment with ZD4522 (5 and 10 mg fixed dose and also over the titration period) with that of atorvastatin (10 mg fixed dose and also over the titration period) in: the reduction of LDL-C levels in subjects with hypercholesterolaemia following 52 weeks of treatment; in modifying other lipids and lipoprotein fractions; and in reducing LDL-C concentrations to within relevant national and international guidelines.

- To compare the titration schedule of ZD4522 5 mg and 10 mg groups with that of the atorvastatin 10 mg group.
- To determine the safety of ZD4522 by evaluating the incidence and severity of adverse events and abnormal laboratory values.

In order to fulfil these objectives, data were summarised at Weeks 2, 6, 10, 12, 20, 28, 36, 44, 50 and 52, and statistical analyses were carried out on Week 2, 6, 10, 12 and 52 data. After the initial 12-week fixed-dose treatment period, subjects could receive an increasing titration of their randomised dose for the next 40 weeks in order to meet NCEP guidelines for LDL-C levels. NCEP targets were analysed up to week 52, but EAS targets were only assessed up to Week 12.

METHODS

Design: This was a randomised, double-blind, multinational, multicentre, parallel-group, 3-group trial. After a 6-week dietary lead-in period, subjects were randomised to treatment with fixed doses of either ZD4522 (5 or 10 mg) or atorvastatin (10 mg); subjects were given their randomised dose once daily for 12 weeks. After the initial 12-week treatment period, subjects remained on their randomised treatment, which was then titrated upwards as needed over the course of the next 40 weeks so that subjects could achieve NCEP guidelines (titration doses for ZD4522: 5, 10, 20, 40, and 80 mg; titration doses for atorvastatin: 10, 20, 40, and 80 mg).
Population: A total of 100 randomised and evaluable subjects with hypercholesterolaemia, derived from approximately 900 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 with Type IIa or IIb hypercholesterolaemia; discontinuation of all cholesterol-lowering drugs and dietary supplements; fasting LDL-C levels between 4.14 and <6.50 mmol/L (160 and <250 mg/dL); fasting triglyceride (TG) levels <4.52 mmol/L (400 mg/dL); and 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; and usage of concomitant medications known to affect the lipid profile or present a potential safety concern (eg, through drug interaction).
Dosage: After a 6-week dietary lead-in period, subjects took oral doses of encapsulated trial treatment once-daily, approximately 3 hours after the evening meal. Doses of treatments were as follows: ZD4522 5 mg, ZD4522 10 mg, and atorvastatin 10 mg. The same dose of trial treatment was taken for 12 weeks. After this initial 12-week treatment period, subjects could have their randomised dosages increased in a sequential manner to the following dosages if their LDL-C levels had not reached the NCEP target level: ZD4522 10, 20, 40 and 80 mg; ZD4522 20, 40 and 80 mg; atorvastatin: 20, 40 and 80 mg. Formulation and batch numbers were as follows: ZD4522 5 mg (F12570; 99-3034, 99-3085, 99-3095, 99-3162, 99-0510); ZD4522

10 mg (F12572; 99-3047, 99-3088, 99-3096, 99-3104, 99-3145, 00-0005, 00-0044); ZD4522 20 mg (F12522; 99-3086, 99-3108, 99-3146, 00-0045); ZD4522 40 mg (F12566; 99-3087, 99-3109, 99-3159); atorvastatin 10 mg (F12513; 99-3024, 99-0486); atorvastatin 20 mg (F12558; 99-3048, 99-0466); atorvastatin 40 mg (F12560; 99-0513, 99-3084).

Key assessments:

Efficacy: Fasting LDL-C, high-density lipoprotein cholesterol (HDL-C), TG and TC were assessed at Weeks 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, 12 and 52. Dietary compliance was assessed and evaluated throughout the trial.

The primary endpoint was the percentage change from baseline to Week 12 in LDL-C levels, and this was analysed using an 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, centre, and centre-by-treatment interaction. Additional analyses using observed data from ITT and per-protocol (PP) populations were used to address the objectives for timepoints other than Week 12 and to confirm the robustness of the main ITT analysis. Percentage changes from baseline in the other lipids and lipoprotiens were secondary endpoints of the trial and were analysed using ANOVA. Other secondary endpoints included the following: the percentage of subjects in the ITT population who achieved EAS (European Atherosclerosis Guidelines) and NCEP (National Cholesterol Education Programme) targets for LDL-C levels at Week 12, and also the percentage of subjects in the ITT population who achieved NCEP targets for LDL-C at Week 52 (these data were summarised only); the number of titration steps (these data were summarised); and the percentage of subjects on each of the possible titrated-doses at Week 52 (these data were summarised). Subgroup and exploratory analyses were performed on LDL-C and HDL-C data, based on certain demographic groupings.

Safety: Standard safety assessments included adverse event reports, clinical laboratory data (hepatic biochemistry, CK, renal biochemistry, haematology, urinalysis), vital signs, electrocardiograms (ECGs), and ophthalmological and physical examination. All data were summarised.

RESULTS

Demography: Due to a higher than expected rate of screening failures and drop-outs during the dietary lead-in period, a total of 1521 subjects were recruited from 45 centres in order to provide 412 subjects who were eligible for randomisation. A total of 138 subjects were subsequently randomised to ZD4522 5 mg, 134 to ZD4522 10 mg and 140 to atorvastatin 10 mg. Demographic characteristics were generally well balanced among the treatment groups. The majority of the subjects were Caucasians, with a mean age of 57.4 years and a mean body mass index (BMI) of 26.48 kg/m^2. The first subject entered the screening period of the trial on 28 April 1999 and the last subject completed the trial on 31 October 2000. Sixty-nine subjects withdrew during the trial (17 in the ZD4522 5 mg group, 27 in the ZD4522 10 mg group and 25 in the atorvastatin 10 mg group). The most common reason for withdrawal during randomised treatment was adverse events. There were 408 subjects in the safety population, 406 in the ITT population and 262 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 (LOCF and observed data[a] on ITT population)

Efficacy endpoint	ZD4522 5 mg group[b]	ZD4522 10 mg group[b]	Atorvastatin 10 mg group[b]
Week 12 (LOCF)			
lsmean of percentage change from baseline in lipids and lipid ratios			
LDL-C	-45.58[e]	-50.08[e]	-39.48
TC	-31.89[e]	-35.25[e]	-28.10
HDL-C	6.21[ns]	8.04[ns]	6.23
TG	-15.06[ns]	-19.11[ns]	-16.21
LDL-C/HDL-C	-47.92[e]	-53.38[e]	-42.39
TC/HDL-C	-35.28[d]	-39.57[e]	-31.83
Non-HDL-C/HDL-C	-44.17[d]	-49.72[e]	-39.65
ApoB	-35.23[c]	-39.72[e]	-32.18
ApoA-I	5.90[ns]	8.61[ns]	5.74
ApoB/ApoA-I	-37.82[ns]	-43.84[e]	-35.46
Lp(a)	8.54[ns]	0.94[ns]	0.86
percentage subjects reaching NCEP and EAS targets for LDL-C levels			
NCEP, overall	85.9	89.4	73.4
NCEP, high risk	62.2	77.5	27.3
EAS, overall	74.8	86.4	55.4
EAS, high risk	71.0	85.9	50.5
Week 52 (observed) - treatment shown represents the initial dose at randomisation and was to be titrated after 12 weeks if the NCEP target for LDL-C was not reached.			
lsmean of percentage change from baseline in lipids and lipid ratios			
LDL-C	-47.12[c]	-53.20[e]	-44.34
TC	-34.42[ns]	-38.32[e]	-32.83
HDL-C	1.88[ns]	3.48[c]	-0.58
TG	-19.62[ns]	-21.39[ns]	-18.69
LDL-C/HDL-C	-47.52[d]	-54.26[e]	-43.34
TC/HDL-C	-35.06[c]	-39.93[e]	-31.84
Non-HDL-C/HDL-C	-43.80[d]	-49.85[e]	-39.57
ApoB	-38.68[ns]	-43.39[e]	-37.56
ApoA-I	3.88[ns]	4.44[ns]	1.72
ApoB/ApoA-I	-40.26[ns]	-44.99[e]	-38.11
Lp(a)	-16.39[ns]	-16.17[ns]	-18.15
percentage subjects reaching NCEP targets for LDL-C levels			
NCEP, overall	88.4	98.1	87.1
NCEP, high risk	64.7	96.8	60.7

[a] Week 12 - LOCF data; Week 52 - observed data.
[b] Dose could be titrated up to 80 mg after the initial 12-week treatment period (see methods section).
[c] $p \leq 0.05$ for ZD4522 vs atorvastatin, [d] $p \leq 0.01$ for ZD4522 vs atorvastatin, [e] $p \leq 0.001$ for ZD4522 vs atoravastatin
[ns] = not significant versus atorvastatin.
Lsmean = least squares mean
Statistical analysis was not performed for NCEP and EAS targets.

At Week 12 both doses of ZD4522 resulted in significantly greater reductions in LDL-C levels compared with atorvastatin 10 mg. The difference in percentage reduction between ZD4522 and atorvastatin was considered clinically significant for both the ZD4522 5 mg and ZD4522 10 mg groups since the difference exceeded 6% (6% was the difference on which the trial was powered). In addition to changes in LDL-C, ZD4522 was also seen to be statistically superior to atorvastatin at Week 12 in reducing TC and ApoB levels and also in reducing the ratios of LDL-C/HDL-C, TC/HDL-C and non-HDL-C/HDL-C. The ZD4522 10 mg group also significantly reduced ApoB/ApoA-I levels compared with atorvastatin. All three treatment groups showed an increase in HDL-C and ApoA-I values and a reduction in TG levels, but there were no statistically significant differences in the changes between the two ZD4522 groups and atorvastatin. There was no significant difference in Lp(a) effect across the treatment groups. A greater percentage of subjects in the ZD4522 groups achieved NCEP and EAS target levels at Week 12 than in the atorvastatin 10 mg group, with the greatest difference being seen in the NCEP high-risk group.

At Week 52 similar results were seen for the ZD4522 10 mg group, with clinically and statistically significant differences being seen in LDL-C values compared with atorvastatin. The difference between the ZD4522 5 mg group and atorvastatin was only statistically significant. For the other lipid parameters, similar patterns were seen to that observed at Week 12, although the ZD4522 5 mg group did not maintain a statistically significant difference to atorvastatin for TC and ApoB.

Analysis of the titration data showed that 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 the atorvastatin 10 mg group.

Safety: ZD4522 was well tolerated, with the types and incidences of treatment-emergent adverse events in the ZD4522 groups being generally similar to those in the atorvastatin group. Adverse events leading to trial withdrawal were reported in 28 (6.9%) subjects (8 subjects (5.9%) in the ZD4522 5 mg group, 8 subjects (6.1%) in the ZD4522 10 mg group, 12 subjects (8.6%) in the atorvastatin 10 mg group); 25 subjects (6.1%) reported serious adverse events during the randomised treatment period (4 subjects (2.9%) in the ZD4522 5 mg group, 12 subjects (9.1%) in the ZD4522 10 mg group, 9 subjects (6.4%) in the atorvastatin 10 mg group). There were 2 deaths reported during this trial (both in the ZD4522 10 mg group): one subject died from an aortic aneurysm and the other from a myocardial infarction. Both events were considered unrelated to the study drug treatment by the investigator. Twenty-three subjects (5.6%) had myalgia (12 subjects (8.8%) in the ZD4522 5 mg group, 6 subjects (4.5%) in the ZD4522 10 mg group, 5 subjects (3.6%) in the atorvastatin 10 mg group). Five subjects had ALT >3 x ULN (2 subjects in the ZD4522 10 mg group and 3 subjects in the atorvastatin 10 mg group). Four cases were classed as resolving and one was classed as persisting. In two subjects in the atorvastatin group, the changes in ALT were reported as adverse events, with one case being regarded as a serious adverse event. One subject in the ZD4522 5 mg group and one subject in the ZD4522 10 mg group had a CK level >10 x ULN but both cases were classed as transient and no associated adverse events were reported. Ophthalmological data gave no safety concerns.