SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT:

ACTIVE INGREDIENT: Rosuvastatin

Trial title (number): An 18-week, randomised, double-blind, multicentre, placebo-controlled trial to evaluate the efficacy and safety of rosuvastatin (5 and 10 mg) in the treatment of hypercholesterolaemic postmenopausal women receiving hormone replacement therapy (4522IL/0032).

Clinical phase: III

First subject recruited: 01 November 1999
Last subject completed: 11 January 2001
AstraZeneca approval date: 24 August 2001

Principal investigators and location:

Publications: None at the time of writing this report.

OBJECTIVES

The primary objective of this trial was to compare the efficacy of treatment with 5 and 10 mg of rosuvastatin with that of placebo in modifying levels of LDL-C in hypercholesterolaemic postmenopausal women receiving HRT. The secondary objectives were to compare the efficacy of treatment with rosuvastatin (5 and 10 mg) with that of placebo in modifying TC, TG and other lipid and lipoprotein fractions; and to determine the safety of rosuvastatin in combination with HRT by evaluating the incidence and severity of adverse events, electrocardiogram (ECG) and abnormal laboratory values.

METHODS

Design: This was an 18-week, randomised, fixed-dose, double-blind, 3-group, placebo-controlled, parallel-group, multicentre trial. After a 6-week dietary lead-in period,

subjects were randomised to treatment with either rosuvastatin (5 or 10 mg) or placebo; subjects were given their randomised dose once daily for 12 weeks.

Population: A total of 135 randomised and evaluable postmenopausal women with hypercholesterolaemia, who were taking HRT, were derived from 689 screened subjects. Seven subjects were required per treatment group to have at least 80% power of detecting a 25% change from baseline in LDL-C levels in a pairwise comparison between treatment groups; however, a greater number of subjects was randomised to acquire more safety data.

Key inclusion criteria: Postmenopausal women taking HRT; discontinuation of all cholesterol-lowering drugs and dietary supplements; fasting LDL-C levels between 3.36 and <6.50 mmol/L (130 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: Subjects whose current HRT was begun or changed within the last 3 months of entering the trial, 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; fasting serum glucose > 9.99 mmol/L (180 mg/dL); serum creatinine > 220 μmol/L (2.5 mg/dL); serum creatine kinase [CK] concentration >3 x ULN; usage of concomitant medications known to affect the lipid profile or present a potential safety concern (eg, through drug interaction); history of serious or hypersensitivity reactions to other HMG-CoA reductase inhibitors.

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. Subjects were randomised to one of the following treatments: rosuvastatin 5 mg, rosuvastatin 10 mg, and matching placebo. The same dose of trial treatment was taken for 12 weeks. Formulation and batch, numbers were as follows: rosuvastatin 5 mg (F12513; batch number 2000001877 [UK and US]); rosuvastatin 10 mg (F12570; batch numbers 993104A, 993145B, 2000002090, 2000002702 [UK], 2000002702, 2000008252, 2000008293 [US]); placebo (F12545; batch numbers 983188B [UK], 983177A [US]).

Key assessments:

Efficacy: Fasting LDL-C, high-density lipoprotein cholesterol (HDL-C), TG and total cholesterol (TC) were assessed during the dietary lead-in and at Weeks 0, 2, 6, 10, and 12; fasting apolipoprotein B (ApoB) and apolipoprotein A-I (ApoA-I) were assessed at Weeks 0 and 12. Dietary compliance was assessed and evaluated throughout the trial.

The primary endpoint of the trial was the % change from baseline in LDL-C levels at Week 12, and was analysed using analysis of covariance (ANCOVA) on last observations carried forward (LOCF) from an intention-to-treat (ITT) population; the initial ANCOVA model included terms for treatment, centre, and centre-by-treatment interaction. Statistical testing was done separately for the comparison between each rosuvastatin group and placebo. Additional analyses using observed data from ITT, and per-protocol (PP) populations were used to confirm the robustness of the main ITT analysis.

Secondary endpoints included the % change from baseline in the other lipids and lipoproteins;

these data were analysed using analysis of variance (ANOVA). Subgroup and exploratory ANCOVA analyses were performed on LDL-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 physical examination. All data were summarised.

RESULTS

Demography: A total of 689 subjects entered the dietary lead-in period; of these, 135 subjects from 31 centres within the United Kingdom and North America were randomised to treatment. Of those randomised, 46 were given placebo, 45 were given rosuvastatin 5 mg and 44 were given rosuvastatin 10 mg. Demographic characteristics were generally well balanced among the treatment groups. The majority of the subjects were Caucasians under the age of 65. The first subject entered the trial on 1 November 1999 and the last subject completed the trial on 22 January 2001. There were 554 screen failures (did not meet essential randomisation criteria) or withdrawals in the dietary lead-in period, while 11 subjects withdrew during the randomised treatment period. There were 135 subjects in the safety and ITT populations and 98 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 on ITT population)

Efficacy endpoint	rosuvastatin 10 mg	rosuvastatin 5 mg	Placebo
lsmean of % change from baseline to Week 12 in lipids and lipid ratios			
LDL-C	–49.30[c]	–37.62[c]	–1.24[c]
TC	–31.33[c]	–24.96[c]	0.82[c]
HDL-C	7.86[c]	10.98[c]	–0.53[c]
TG	–8.94[c]	–12.62[c]	10.54[c]
LDL-C/HDL-C	–51.95[c]	–43.81[c]	0.04[c]
TC/HDL-C	–35.44[c]	–31.77[c]	1.84[c]
Non-HDL-C/HDL-C	–45.55[c]	–40.18[c]	2.43[c]
ApoB	–37.82[c]	–32.51[c]	0.44[c]
ApoA-I	8.19[a]	9.43[b]	3.86[c]
ApoB/ApoA-I	–41.64[c]	–40.14[c]	–2.18[c]

[a] $p<0.05$, [b]$p<0.01$, [c]$p<0.001$, [ns] = not significant compared with placebo.

Rosuvastatin at both doses resulted in significantly greater reductions and % reductions in LDL-C levels than did placebo. At Week 12 (LOCF), LDL-C was reduced by 49% in the rosuvastatin 10 mg group and 38% in the rosuvastatin 5 mg group. The difference in % reduction of LDL-C between both rosuvastatin 10 mg and 5 mg compared with placebo was significant ($p<0.001$). Both rosuvastatin doses significantly reduced LDL-C, TC, TG, and ApoB and increased HDL-C and ApoA-I in comparison with placebo at both 6 (observed data) and 12 (observed and LOCF) Weeks. Both rosuvastatin 5 mg and 10 mg significantly decreased all tested lipid ratios at Weeks 6 and 12 in comparison to placebo: LDL-C/HDL-C, TC/HDL-C, non-HDL-C/HDL-C and ApoB/ApoA-I. The PP analysis generally supported the ITT findings.

The subgroup analyses on LDL-C levels by age, race and baseline LDL-C, HDL-C and TG levels did not show any significant interaction with treatment.
Safety: Rosuvastatin was well tolerated at the 5 mg and 10 mg doses. The types and incidences of treatment-emergent adverse events in the rosuvastatin groups were generally similar in all 3 treatment groups. Adverse events leading to withdrawal from trial treatment were reported in 11 subjects: 1 (2.3%) rosuvastatin 10 mg, 7 (15.6%) rosuvastatin 5 mg, 3 (6.5%) placebo. Only one subject (rosuvastatin 10 mg) reported a serious adverse event (abdominal pain) during the randomised treatment period, but this was not considered to be treatment related. There were no deaths. No subjects had ALT >3 x ULN or CK >10 x ULN. Data from other laboratory parameters, ECG and vital signs indicated no treatment or dose-related trends or patterns.