SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT:

ACTIVE INGREDIENT: ZD4522

Trial title (number): A 12-Week, Multicenter, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy and Safety of ZD4522 5 to 80 mg in the Treatment of Subjects with Hypertriglyceridemia (4522IL/0035).

Developmental phase: III

First patient recruited: 6 December 1999
Last patient completed: 23 August 2000
AstraZeneca approval date: 15 January 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 5 to 80 mg with placebo in hypertriglyceridemic patients (Type IIb or IV) in reducing total triglyceride (TG) concentrations at Week 6.

- The secondary objectives of this trial were:
- to compare the efficacy of ZD4522 5 to 80 mg with placebo in modifying low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and other lipid and lipoprotein fractions at Week 6
- to compare the efficacy of ZD4522 5 to 80 mg with placebo in modifying total TG concentrations at Weeks 2 and 4
- to compare the effects of treatment with ZD4522 and placebo on the following inflammatory markers: activated factor XII, C-reactive protein (CRP), interleukin-6 (IL-6), and E-selectin
- to provide pharmacokinetic data from western patients which can be compared with pharmacokinetic data from similar studies performed in Japanese patients in Japan

- 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 12-week, randomized, double-blind, fixed-dose, parallel-group, placebo-controlled, multicenter trial designed to compare the efficacy and safety of ZD4522 5 to 80 mg in the treatment with patients with hypertriglyceridemia (Fredrickson type IIb or IV). After a 6-week dietary lead-in period, patients were randomized to a 6-week, fixed-dose treatment period in 1 of 6 treatment groups.

Population: A total of 23 randomized and evaluable patients with hypertriglyceridemia (Fredrickson type IIb or IV), derived from an estimated 385 recruited patients, were required per treatment group for 90% power of detecting a 30% difference between groups in % change from baseline in TG levels.

Key inclusion criteria: To enter the dietary lead-in period, men or women aged ≥18 years with hypertriglyceridemia (Fredrickson type IIb or IV); discontinuation of all cholesterol-lowering drugs and dietary supplements; for patients not on lipid lowering therapy, fasting TG levels of ≥300 and <800 mg/dL (≥3.39 and <9.03 mmol/L). To enter the treatment period, fasting TG within above ranges, Eating Pattern Assessment Tool (EPAT) Section 1 scores of ≤28 at Week –2.

Key exclusion criteria: Active liver disease or hepatic dysfunction (defined by an ALT, AST or bilirubin concentration ≥1.5 times the upper limit of normal [ULN]); active arterial disease; history of malignancy (unless basal or squamous cell skin carcinoma); uncontrolled hypertension; uncontrolled hypothyroidism; serum CK concentration >3 x ULN; serum creatinine >2.5 mg/dL (>220 **m**mol/L); usage of concomitant medications known to affect the lipid profile or present a potential safety concern (eg, through drug interaction).

Dosage: Patients took oral doses of trial treatment once daily approximately 3 hours after the evening meal. Doses of treatments were as follows: ZD4522 5, 10, 20, 40, or 80 mg, or placebo. The same dose of trial treatment was taken for 6 weeks.

Formulation, lot numbers, and batch numbers were as follows: for ZD4522 5 mg; F12570; batch numbers 99-3162, 99-0510, 99-0510, 99-3085, 99-3095; ZD4522 10 mg; F12572; batch numbers 00-0005, 00-0044, 99-3096, 99-3104, 99-3145; for ZD4522 20 mg F12522; batch numbers 99-3086, 99-3108, 99-3146; for ZD4522 40 mg F12566; batch numbers 99-3159, 00-0063, 99-3087, 99-3110; for ZD4522 80 mg F12568; batch numbers 99-3152, 00-0096, 00-0174; for matching placebo F12545; batch numbers 98-3177, 99-3151.

Key assessments:

Efficacy: Fasting TG, total cholesterol (TC), LDL-C, and HDL-C were assessed to Weeks 2, 4, and 6; fasting HDL-TG, HDL2, HDL3, LDL-TG, very low-density lipoprotein cholesterol (VLDL-C), VLDL-TG, ApoB, LDL-ApoB, VLDL-ApoB, ApoA-I, ApoA-II, ApoC-III, ApoC-III:B, ApoC-III:Non-B, and lipoprotein (a) (Lp(a)) were assessed at Weeks 4 and 6; inflammatory markers (activated factor XII, C-reactive protein, interleukin-6, and E-selectin) were assessed at Week 6. The primary endpoint was the % change from baseline to Week 6 in TG levels, and was analyzed using analysis of variance (ANOVA) on the last observations carried forward (LOCF) data set from the intent-to-treat (ITT) population; the initial ANOVA model included terms for treatment, center, and center-by-treatment interaction. Additional

analyses using the observed cases data set from the ITT and per-protocol (PP) populations were also performed at Weeks 2, 4, and 6. Percentage changes from baseline in the other lipids and lipoproteins were secondary endpoints of the trial and were analyzed using a similar approach to that of the primary endpoint. The other secondary endpoints of inflammatory markers were summarized only. Subgroup and exploratory analyses were performed on TG and HDL-C data, based on pre-defined demographic groupings.
Pharmacokinetics: Plasma concentrations of ZD4522 were summarized at Weeks 0, 2, 4, and 6.
Safety: Standard safety assessments included adverse event reports, clinical laboratory data (including hematology, hepatic biochemistry, CK, renal biochemistry, urinalysis), vital signs and weight, ECGs and physical examination. All data were summarized.

RESULTS
Demography: Of 467 patients recruited from 31 centers, a total of 156 patients were randomized to treatment; 26 patients were randomized to placebo, 26 to ZD4522 5 mg, 23 to ZD4522 10 mg, 28 to ZD4522 20 mg, 26 to ZD4522 40 mg, and 27 to ZD4522 80 mg. There were 155 patients in the safety population, 153 patients in the ITT population, and 117 patients in the per-protocol population. One patient in the ZD4522 5-mg treatment group did not take trial medication, and 1 patient in each of the ZD4522 20-mg and 40-mg treatment groups had missing baseline or post-baseline efficacy assessments. Nine patients were withdrawn from the trial during the randomized treatment period, 4 because of adverse events, 4 who withdrew consent, and 1 who was lost to follow-up. Demography and baseline characteristics were similar between treatment groups. Mean ages ranged from 53.0 years to 58.4 years between treatment groups. Most patients in each treatment group were males (54% to 71%), and most patients were Caucasian (81% to 100%). Mean body mass indices ranged from 29.5 to 30.6 between treatment groups. The first patient was enrolled 6 December 1999 and the last visit of the last patient was 23 August 2000.
Efficacy: A summary of the key efficacy findings is presented in Table I.

Table I Summary of key efficacy findings

Efficacy endpoint	Lsmean of % change from baseline to Week 6					
	Placebo	ZD4522 5 mg	ZD4522 10 mg	ZD4522 20 mg	ZD4522 40 mg	ZD4522 80 mg
Lipids and lipid ratios						
TG	2.9	–18.1[a]	–37.0[a]	–36.8[a]	–40.0[a]	–39.5[a]
VLDL-TG	6.0	–10.8	–35.4[a]	–39.7[a]	–42.7[a]	–48.9[a]
LDL-TG	23.8	–5.7	–15.4	–4.5	–10.6	–16.5[a]
HDL-TG	–3.9	–3.7	–17.2	–18.8	–27.2[a]	–7.2
LDL-C	6.2	–27.5[a]	–40.1[a]	–33.6[a]	–39.0[a]	–45.2[a]
TC	2.5	–22.5[a]	–37.6[a]	–34.0[a]	–37.9[a]	–42.3[a]
HDL-C	–2.0	4.0	6.1[a]	18.3[a]	14.9[a]	10.0[a]
HDL2	16.6	24.3	7.4	25.2	17.9	26.4
HDL3	–2.8	2.0	10.4	22.6[a]	19.5[a]	4.8
VLDL-C	5.5	–22.6[a]	–44.8[a]	–47.2[a]	–51.6[a]	–54.4[a]
LDL-C/HDL-C	10.8	–29.2[a]	–43.7[a]	–43.1[a]	–46.1[a]	–50.4[a]
TC/HDL-C	4.9	–24.1[a]	–41.2[a]	–43.2[a]	–45.3[a]	–47.6[a]
Non-HDL-C/HDL-C	5.7	–28.3[a]	–48.3[a]	–50.1[a]	–52.8[a]	–55.2[a]
ApoB	1.9	–21.4[a]	–35.9[a]	–33.0[a]	–37.1[a]	–44.0[a]
LDL-ApoB	1.0	–23.7[a]	–36.3[a]	–35.1[a]	–31.2[a]	–33.3[a]
VLDL-ApoB	22.9	–13.6	–23.2[a]	–31.3[a]	–36.7[a]	–28.5[a]
ApoA-I	1.2	0.9	1.5	6.7	6.0	3.0
ApoA-II	–1.4	2.1	–2.2	3.1	1.9	–2.6
ApoB/ApoA-I	1.7	–20.2[a]	–36.2[a]	–35.8[a]	–40.3[a]	–44.9[a]
ApoC-III	2.6	–13.6[a]	–30.0[a]	–22.3[a]	–26.4[a]	–23.0[a]
ApoC-III:B	16.4	3.2	–11.5[a]	–16.2[a]	–22.8[a]	–23.7[a]
ApoC-III:Non-B	4.9	–13.4	–31.5[a]	–24.1[a]	–24.3[a]	–23.5[a]
Lp(a)	–8.6	29.1[a]	12.5	9.0	30.0[a]	1.1
Inflammatory markers[b]						
Activated factor XII	–0.2	1.2	–0.5	1.9	–0.6	–2.2
C-reactive protein	13.7	53.4	36.3	–6.0	–46.0	–30.2
Interleukin-6	0.3	–1.8	35.0	16.2	1.2	22.6
E-selectin	3.0	3.3	–9.2	–5.0	–2.7	–2.1

[a] $p<0.05$ versus placebo.
[b] Hypothesis testing not performed for inflammatory markers.

In hypertriglyceridemic patients (Fredrickson type IIb or IV), ZD4522 produced statistically significant reductions in total TG relative to placebo at all doses studied beginning at Week 2, a 21% to 43% reduction in total TG from baseline, a reduction in TG within VLDL, LDL, and HDL, and an improvement in the atherogenic profile with respect to LDL-C, HDL-C, TC,

LDL-C/HDL-C, TC/HDL-C, Non-HDL-C/HDL-C, ApoB/ApoA-I, VLDL-C, ApoB, and ApoC-III. ZD4522 10 mg to 80 mg produced reductions in total TG levels of at least 30% (the predefined difference) relative to placebo. There was weak evidence of a dose response in total TG reduction.

Pharmacokinetics: Visual inspection of the plasma concentration data suggested that a pharmacokinetic steady state was maintained at all dose levels over the 6-week dosing period. The increase in plasma concentration of ZD4522 with increasingly administered dose was consistent with dose proportionality.

Safety: In hypertriglyceridemic patients (Fredrickson type IIb or IV), ZD4522 was generally well tolerated at all doses studied; the incidence of adverse events did not appear to be dose related generally, although some adverse events occurred more frequently in the 80-mg treatment group (myalgia, diarrhea, increased ALT, increased AST). Elevation of CK >10 times the upper limit of normal (ULN) was experienced in 3 patients (1 asymptomatic in the 40-mg treatment group and 2 associated with moderate, drug-related myalgia in the 80-mg treatment group). Two cases of severe, drug-related CK elevations were ongoing (1 worsening, 1 resolving; both resolved after discontinuation of trial medication); 1 mild, unrelated case was resolving (returned to within the normal range at Week 6). Elevations in ALT >3 ULN were experienced in 3 patients (2 of whom also experienced drug-related CK elevations), all in the 80-mg treatment group; all resolved upon discontinuation of trial medication.