# SUMMARY

**ASTRAZENECA PHARMACEUTICALS**

**FINISHED PRODUCT:**

**ACTIVE INGREDIENT:** ZD4522

**Trial title (number):** A 24-Week Randomized Multicenter Trial to Evaluate the Efficacy and Safety of ZD4522 10 to 40 mg and Extended-release Niacin 0.5 to 2 g Monotherapy, as well as Selected Combinations of ZD4522 and Extended-release Niacin, in the Treatment of Subjects with Type IIb or IV Hyperlipidemia (4522IL/0029).

**Developmental phase:** III

**First patient recruited:** 4 October 1999
**Last patient completed:** 27 October 2000
**AstraZeneca approval date:** 14 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 40 mg in reducing low-density lipoprotein cholesterol (LDL-C) at Week 24 with each of the following:

- extended-release niacin (NIASPAN™, Kos Pharmaceuticals, Inc.) 2 g
- the combination of ZD4522 40 mg and extended-release niacin 1 g
- the combination of ZD4522 10 mg and extended-release niacin 2 g

The secondary objectives of this trial were:

- to compare the efficacy of ZD4522, extended-release niacin, and the selected combinations in reducing LDL-C at Weeks 12 and 18
- to compare the efficacy of ZD4522, extended-release niacin, and the selected combinations in modifying total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), and other lipid and lipoprotein fractions at Weeks 12, 18, and 24

- to determine the safety of treatment with ZD4522, extended-release niacin, and the selected combinations by evaluating the incidence and severity of adverse events and abnormal laboratory values

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**METHODS**

**Design:** This was a 24-week, randomized, open-label, forced-titration, parallel-group, multicenter trial designed to compare the efficacy and safety of ZD4522 40 mg with extended-release niacin 2 g monotherapy, as well as with combination therapy of ZD4522 and extended-release niacin in the treatment with patients with type IIb or type IV hyperlipidemia. Patients were randomized to treatment groups in a ratio of 2:3:3:3. After a 6-week dietary lead-in period, patients were randomized to a 24-week treatment period in 1 of 4 treatment groups.

**Population:** A total of 40 randomized and evaluable patients with hyperlipidemia (Fredrickson type IIb or IV), derived from an estimated 720 recruited patients, were required per treatment group for 80% power of detecting a 10% difference in percent change from baseline in LDL-C levels.

**Key inclusion criteria:** To enter the dietary lead-in period, men or women aged ≥18 years with Fredrickson type IIb or IV hyperlipidemia; discontinuation of all cholesterol-lowering drugs and dietary supplements; for patients not on lipid lowering therapy, fasting TC levels ≥200 mg/dL (≥5.17 mmol/L) and fasting TG levels of ≥200 and ≤800 mg/dL (≥2.26 and ≤9.03 mmol/L). To enter the treatment period, fasting TC and TG within above ranges, fasting HDL-C levels <45 mg/dL (<1.16 mmol/L) and apolipoprotein B (ApoB) levels ≥110 mg/dL, 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 alanine aminotransferase [ALT], aspartate aminotransferase [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 or a disease free interval of at least 10 years); uncontrolled hypertension; uncontrolled hypothyroidism; serum creatine kinase [CK] concentration >3 x ULN; serum creatinine >1.8 mg/dL (>158 μmol/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 ZD4522 once daily approximately 3 hours after the evening meal, and oral doses of extended-release niacin once daily at bedtime, with water, after a low-fat snack. Doses of treatments for patients in Group A were ZD4522 10 mg for Weeks 0 to 12, 20 mg for Weeks 12 to 18, and 40 mg from Weeks 18 to 24; in Group B, extended-release niacin 0.5 g for Weeks 0 to 4, 1 g for Weeks 4 to 12, 1.5 g from Weeks 12 to 18, and 2 g from Weeks 18 to 24; in Group C, extended-release niacin 0.5 g for Weeks 0 to 4, extended-release niacin 1 g from Weeks 4 to 6, extended-release niacin 1 g with ZD4522 10 mg from Weeks 6 to 12, extended-release niacin 1 g with ZD4522 20 mg from Weeks 12 to 18, and extended-release niacin 1 g with ZD4522 40 mg from Weeks 18 to 24; and Group D, extended-release niacin 0.5 g from Weeks 0 to 4, extended-release niacin 1 g from Weeks 4 to 6, extended-release niacin 1 g with ZD4522 10 mg from Weeks 6 to 12, extended-release niacin 1.5 g with ZD4522 10 mg from Weeks 12 to 18, and extended-release niacin 2 g with ZD4522 10 mg from Weeks 18 to 24. Patients were not to be titrated to the next level of trial medication if LDL-C levels did not exceed 50 mg/dL (1.29 mmol/L). Formulation and batch numbers were as follows: for

ZD4522 10 mg; F12572; batch numbers 00-0005, 00-0044, 99-3046, 99-3047, 99-3088, 99-3096, 99-3104, 99-3145; for ZD4522 20 mg F12522; batch numbers 00-0045, 99-3086, 99-3108, 99-3146; for ZD4522 40 mg F12566; batch numbers 99-3159, 00-0063, 00-0166, 99-3087, 99-3110; for extended-release niacin F12576; batch number 100002A.

**Key assessments:**

**Efficacy:** Fasting LDL-C, TC, TG, LDL-TG, VLDL-C, VLDL-TG, HDL-C, HDL-TG, HDL2, HDL3, ApoA-I, ApoA-II, ApoB, LDL-ApoB, VLDL-ApoB, ApoC-III (total, C-III:B, C-III:non-B), and Lp(a) were assessed at baseline and at Weeks 12, 18, and 24; and activated factor XII at Week 24. The primary endpoint was the percent change from baseline in LDL-C levels at Week 24, and was analyzed using 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, 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 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 endpoint of % change from baseline in activated factor XII at Week 24 in the ITT population was summarized descriptively only. Subgroup and exploratory analyses were performed on % change from baseline in LDL-C at Week 24 based on pre-defined demographic groupings and selected baseline lipid levels.

**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.

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**RESULTS**

**Demography:** Of 774 patients recruited from 39 centers, a total of 270 patients were randomized to treatment; 46 patients were randomized to ZD4522 40 mg, 72 to extended-release niacin 2 g, 72 to ZD4522 40 mg + niacin 1 g, and 80 to ZD4522 10 mg + niacin 2 g. There were 270 patients in the safety population, 265 patients in the ITT population, and 210 patients in the per-protocol population. Of 54 patients withdrawn from the trial during the randomized treatment period, 31 withdrew because of adverse events, and 18 withdrew consent; only 3 of these 54 patients were randomized to ZD4522 40 mg monotherapy. Demography and baseline characteristics were similar between treatment groups. Mean ages ranged from 54.2 years to 58.6 years between treatment groups. Most patients in each treatment group were males (69% to 76%), and most patients were Caucasian (91% to 99%). Mean body mass indices ranged from 29.8 to 31.4 between treatment groups. From 13% to 18% of patients had diabetes mellitus at entry. The first patient was enrolled 4 October 1999 and the last visit of the last patient was 27 October 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 at Week 24 | | | |
|---|---|---|---|---|
| | ZD4522 10/20/40 mg | Niacin 0.5/1/1.5/2 g | ZD4522 10/20/40 mg with niacin 0.5/1 g | ZD4522 10 mg with niacin 0.5/1/1.5/2 g |
| **Lipids and lipid ratios[a]** | | | | |
| LDL-C | –47.5 | –0.1[b] | –42.4 | –35.5[b] |
| TC | –40.7 | –7.2[b] | –37.5 | –29.1[b] |
| HDL-C | 10.6 | 12.3 | 16.7 | 23.7[b] |
| HDL-TG | –11.1 | –4.9 | –8.9 | –15.1 |
| HDL2 | 9.3 | 14.9 | 20.3 | 40.6[b] |
| HDL3 | 22.2 | 15.5 | 24.0 | 21.4 |
| TG | –32.6 | –20.9 | –38.6 | –33.9 |
| LDL-TG | –23.4 | 36.7[b] | –30.2 | –7.8 |
| VLDL-TG | –43.5 | –23.1 | –43.6 | –35.4 |
| VLDL-C | –51.0 | –22.0[b] | –46.6 | –38.4 |
| LDL-C/HDL-C | –52.5 | –11.7[b] | –49.1 | –45.5 |
| TC/HDL-C | –45.3 | –16.1[b] | –45.3 | –39.2 |
| Non-HDL-C/HDL-C | –52.4 | –18.8[b] | –52.9 | –45.8 |
| ApoB | –42.4 | –8.9[b] | –41.7 | –33.7[b] |
| LDL-ApoB | –32.9 | 0.4[b] | –34.2 | –27.4 |
| VLDL-ApoB | –62.2 | –48.1 | –36.0 | –19.4 |
| ApoA-I | 4.7 | 7.0 | 6.2 | 10.6[b] |
| ApoA-II | –2.4 | –4.2 | –5.7 | 0.5 |
| ApoB/ApoA-I | –44.5 | –14.5[b] | –44.3 | –38.9 |
| ApoC-III | –19.8 | –6.4 | –20.5 | –18.4 |
| ApoC-III:B | –25.9 | –9.2 | –23.6 | –20.4 |
| ApoC-III:Non-B | 13.8 | 17.7 | –9.7 | 2.7 |
| Lp(a) | 6.5 | –19.8[b] | –17.5[b] | –20.2[b] |
| **Activated factor XII[c]** | | | | |
| Activated factor XII | 2.7 | –2.5 | 3.6 | 1.0 |

[a] Main analysis of LOCF from the ITT population.
[b] $p<0.017$ versus ZD4522 40 mg.
[c] Observed data from the ITT population. Hypothesis testing not performed for activated factor XII.

In patients with Fredrickson's type IIb or IV hyperlipidemia, ZD4522 40 mg produced a 47.5% reduction from baseline in LDL-C by Week 24 versus 0.1% with niacin 2 g and 42.4% and 35.5% with combination therapy with ZD4522 40 mg + niacin 1 g and with ZD4522 10 mg + niacin 2 g, respectively. For patients randomized to ZD4522, either as monotherapy or as combination therapy, most of the reductions in LDL-C occurred by Week 12, when patients in these 3 treatment groups had been administered ZD4522 10 mg, nominally, for

at least 6 weeks. For patients randomized to extended-release niacin 2 g, LDL-C was not reduced at Weeks 12 or 18, when nominal doses of niacin were 1 g and 1.5 g at the Week 12 and 18 assessments, respectively. ZD4522 40 mg had statistically significantly more favorable effects on the atherogenic lipid profile (LDL-C, TC, VLDL-C, LDL-C/HDL-C, TC/HDL-C, Non-HDL-C/HDL-C, ApoB, LDL-ApoB, ApoB/ApoA-I) than extended-release niacin 2 g at Week 24. For patients randomized to ZD4522, either as monotherapy or as combination therapy, most of the improvement in the atherogenic profile occurred by Week 12, when patients had been administered ZD4522 10 mg, nominally, for at least 6 weeks. ZD4522 40 mg had statistically significantly more favorable effects on the atherogenic lipid profile (LDL-C, TC, ApoB, VLDL-ApoB) than combination therapy with ZD4522 10 mg + niacin 2 g. ZD4522 40 mg produced TG reductions to levels comparable to niacin or the selected ZD4522 + niacin combinations. Niacin, when given alone or in combination with ZD4522, reduced Lp(a) relative to ZD4522 40 mg monotherapy at Week 24. Extended-release niacin did not increase the reduction of LDL-C observed with ZD4522. Combination therapy of ZD4522 10 mg + niacin 2 g was more effective in increasing HDL-C, HDL2, and ApoA-I than ZD4522 40 mg monotherapy.

**Safety:** In patients with Fredrickson's type IIb or IV hyperlipidemia, ZD4522 40 mg was generally well tolerated with no clinically significant elevations in ALT or CK; extended-release niacin, when administered alone or in combination with ZD4522, demonstrated a safety profile similar to that expected for this agent. The most common adverse events occurring in at least 10% of patients randomized to the ZD4522 40 mg treatment group were pain, diarrhea, myalgia, and pharyngitis. The most common adverse events occurring in at least 10% of patients randomized to the extended-release niacin 2 g treatment group were vasodilatation (flushing), pruritus (itching), rash, and pharyngitis. The most common adverse events occurring in at least 10% of patients randomized to either group treated with combination therapies of ZD4522 and extended-release niacin were vasodilatation (flushing), pruritus (itching), rash, paresthesia, and pharyngitis. No clinically significant elevations in ALT were observed in patients treated with extended-release niacin, however, 1 subject receiving niacin monotherapy had an asymptomatic CK elevation >10 ULN at Week 4 that was slightly elevated at Week 12 with continuing therapy. One of 46 patients in the ZD4522 40 mg treatment group withdrew because of an adverse event versus 10 of 65 patients in the extended-release niacin 2 g treatment group. The incidence of patient withdrawal because of adverse events in treatment groups with combined therapies of ZD4522 and extended-release niacin were comparable to the extended-release niacin 2 g treatment group. The proportion of serious adverse events was comparable between treatment groups.