# SUMMARY

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**ASTRAZENECA PHARMACEUTICALS**

**FINISHED PRODUCT:**

**ACTIVE INGREDIENT:** ZD4522

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Trial title (number): A 24-Week, Randomised, Multicentre Trial to Evaluate the Efficacy and Safety of ZD4522 and Fenofibrate, Alone and in Various Combinations, in the Treatment of Type IIb and IV Hyperlipidaemia Associated with Type 2 Diabetes Mellitus (4522IL/0036).

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**Clinical phase:** III

**First subject recruited:** 28 September 1999
**Last subject completed:** 25 October 2000
**AstraZeneca approval date:** 6 March 2001

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**Principal investigator(s) and location (centre number):**

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**Publications:** None at the time of writing this report.

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**OBJECTIVES**

The primary objective was to compare the efficacy of ZD4522 10/20/40 mg daily in reducing total triglyceride (TG) concentrations at Week 24 with each of the following comparator treatments: (1) fenofibrate 67 mg od/bd/tds; and (2) ZD4522 10 mg daily + fenofibrate 67 mg od/bd/tds.

The secondary objectives included comparison of ZD4522 10/20/40 mg daily with fenofibrate 67 mg od/bd/tds for reduction in TG at Week 24, assessment of other lipids and lipoproteins at Week 24, assessments of TG, other lipids and lipoproteins at Weeks 12 and 18, comparison of ZD4522 5 mg or 10 mg with placebo at Week 6, and safety.

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**METHODS**

**Design:** This was a randomised, 4-group, multinational, multicentre trial. After a 6-week dietary lead-in period, subjects were randomised to 1 of 4 treatment groups: ZD4522 5 mg; ZD4522 10 mg; or placebo (2 treatment arms). Each group was given a fixed dose once daily for 6 weeks under double-blind conditions. The subsequent 18-week period of the trial was an open-label, forced-titration phase, in which all subjects with an LDL-C value which had not fallen below 1.3 mmol/L (50 mg/dL) were force-titrated as follows: the first placebo group received a forced titration of ZD4522 (6 week periods, each at doses of 10, 20, and 40 mg); the second placebo group received a forced titration of fenofibrate 67 mg (6 week periods, each at a frequency of od, bd, and tds); and subjects previously randomised to receive ZD4522 5 mg or ZD4522 10 mg continued to receive their randomised dose in combination with a forced titration of fenofibrate 67 mg (6 week periods, each at a frequency of od, bd, and tds).

**Population:** A total of 44 randomised and evaluable Type 2 diabetic subjects with Type IIb or Type IV hyperlipidaemia, derived from an estimated 735 recruited subjects, were required per treatment group (for 80% power of detecting a 20% difference between groups in % change from baseline in TG levels in a pairwise comparison between treatment groups, using a 2-sided t-test).

**Key inclusion criteria:** Diabetic men or women aged ≥18 years; discontinuation of all cholesterol-lowering drugs and dietary supplements; fasting TG levels ≥2.26 mmol/L (≥200 mg/dL) and ≤9.03 mmol/L (≤800 mg/dL); fasting TC concentrations of ≥5.17 mmol/L (≥200 mg/dL); glycated haemoglobin of <10% at Visit 1 (fasting blood glucose was to be <11.10 mmol/L [<200 mg/dL] throughout the trial); and an Eating Pattern Assessment Tool (EPAT) score of ≤28 to demonstrate dietary compliance.

**Key exclusion criteria:** Type 1 diabetes mellitus; 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 >10 x ULN; and usage of concomitant medications known to affect the lipid profile or present a potential safety concern (e.g. through drug interaction).

**Dosage:** Subjects took oral doses of trial treatment once daily, approximately 3 hours after the evening meal. Formulation and batch numbers were as follows: ZD4522 5 mg (F12570, ST74023-001-FB01, ST74023-001-FB02, ST74023-001-FB03, ST74023-001-FB05, ST74023-001-FB06), ZD4522 10 mg (F12572, ST74024-001-FA03, ST74024-001-FA05, ST74024-001-FA06, ST74024-001-FA07, ST74024-001-FA08), ZD4522 20 mg (F12522, ST73066-001-FB04, ST73066-001-FB05), ZD4522 40 mg (F12566, ST74025-001-FA04), fenofibrate 67 mg (F12575, 016), and placebo to ZD4522 (F12545, ST73074-001-FB01).

**Key assessments:**

**Efficacy:** Fasting TG, TC, LDL-C, LDL-TG, VLDL-C, VLDL-TG, HDL-C, HDL-TG, HDL2, HDL3, ApoA-I, ApoA-II, ApoB, LDL-ApoB, VLDL-ApoB, Total ApoC-III, ApoC-III:non-B, ApoC-III:B, Lp(a), non-HDL-C/HDL-C, TC/HDL-C, LDL-C/HDL-C, and ApoB/ApoA-I were assessed during the dietary lead-in and at Weeks 0, 6, 12, 18, and 24. Activated factor XII, C-reactive protein (CRP), interleukin-6 (IL-6), and fibrinogen were assessed at Weeks 0 and 24. Dietary compliance was assessed and evaluated at regular intervals throughout the trial.

The primary efficacy endpoint of this trial, was the % change from baseline to Week 24 in TG. In this analysis, data from the ZD4522 10/20/40 mg group were compared with data from each of the following 2 groups: fenofibrate od/bd/tds; and ZD4522 10 mg + fenofibrate od/bd/tds; although a secondary endpoint, the same comparison was made between ZD4522 10/20/40 mg and ZD4522 5 mg + fenofibrate od/bd/tds. These comparisons were made 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, centre, and centre-by-treatment interaction. Statistical testing was done separately for each comparison. Additional analyses using observed data from ITT, and per-protocol (PP) populations were used to confirm the robustness of the main ITT analysis.

For the secondary endpoints, 3 types of comparison were made. The first comparison focussed on the groups examined in the primary analysis described above, and the analyses of the primary efficacy endpoint were repeated on the % changes in baseline to Week 24 for all the other lipids and ratios. The second comparison focussed on data generated at Weeks 12 and 18 for TG and all lipids and ratios examined in the first comparison. The third comparison focused on data generated at Week 6 (i.e. at the end of the fixed-dose phase) for all lipids and lipid ratios. In this comparison, data from the 2 placebo groups were combined and compared with data from each of the ZD4522 5 mg and ZD4522 10 mg groups. All secondary end-points with % change from baseline in lipid concentration were analysed using ANOVA. Subgroup and exploratory analyses were performed on TG 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.

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**RESULTS**

**Demography:** A total of 764 subjects entered the dietary lead-in period; of these, 216 diabetic subjects from 47 centres were randomised to treatment. In the fixed-dose phase of randomised treatment, two groups of 53 and 49 subjects received placebo, 60 received ZD4522 5 mg, and 54 received ZD4522 10 mg. In the forced titration phase, 53 subjects received ZD4522 10/20/40 mg, 49 received fenofibrate od/bd/tds, 60 received ZD4522 5 mg + fenofibrate od/bd/tds and 54 received ZD4522 10 mg + fenofibrate od/bd/tds. There were 216 subjects in the safety population, 213 in the ITT population and 98 in the PP population for the primary endpoint (change in TG at Week 24). Demographic characteristics were generally well balanced among the treatment groups; the mean body mass index was 31 $kg/m^2$ and the majority of the subjects were Caucasians between 18 and 64 years of age. The first subject entered the trial on 28/09/1999 and the last subject completed the trial on 25/10/2000. Twenty-nine subjects withdrew during the randomised treatment period, the most common reason being adverse events.

**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 end-point | Placebo/ZD4522 10/20/40 mg | Placebo/Feno od/bd/tds | ZD4522 5 mg + Feno od/bd/tds | ZD4522 10 mg + Feno od/bd/tds |
|---|---|---|---|---|
| **lsmean of % change from baseline to Week 24 in key lipids and lipid ratios** | | | | |
| TG | -30.25 | -33.55 | -40.88 | -47.11[a] |
| LDL-C | -46.69 | 0.70[a] | -34.06[a] | -42.16 |
| TC | -36.58 | -7.49[a] | -30.97 | -36.26 |
| HDL-C | 6.42 | 9.24 | 10.79 | 11.72 |
| LDL-C/HDL-C | -48.86 | -6.30[a] | -38.76[a] | -46.80 |
| TC/HDL-C | -39.22 | -13.90[a] | -36.20 | -41.89 |
| non-HDL-C/HDL-C | -47.33 | -16.64[a] | -43.51 | -50.39 |
| VLDL-C | -43.56 | -30.09 | -46.81 | -44.16 |
| VLDL-TG | -31.93 | -14.68 | -32.46 | -41.53 |
| ApoA-I | 2.71 | 5.02 | 4.72 | 5.41 |
| ApoB | -41.38 | -7.55[a] | -34.98 | -40.21 |
| ApoB/ApoA-I | -41.89 | -11.26[a] | -37.15 | -42.70 |
| Lp(a) | 67.30 | 41.50 | 22.86 | 39.22 |

[a] $p \leq 0.017$ versus ZD4522 10/20/40 mg. A threshold for statistical significance of $p \leq 0.017$ was used at Weeks 12, 18 and 24 in order to control for multiple comparisons
Feno = fenofibrate; lsmean = Least squares mean; NA = results not available due to inadequate samples

ZD4522 10/20/40 mg produced reductions in TG at Week 24 which were similar to those for fenofibrate od/bd/tds (analysis of LOCF from the ITT population). ZD4522 10 mg + fenofibrate od/bd/tds resulted in a significantly greater reduction in TG by Week 24 compared to ZD4522 10/20/40 mg ($p = 0.001$). At Week 24, ZD4522 10/20/40 mg produced significantly greater decreases in LDL-C and TC compared to fenofibrate od/bd/tds ($p<0.001$), and the reductions were similar to those seen for both ZD4522 + fenofibrate od/bd/tds combinations. Changes in HDL-C and VLDL-C at Week 24 were similar in all treatment groups. At Week 24, ZD4522 10/20/40 mg resulted in significantly greater decreases in the atherogenic ratios LDL-C/HDL-C, TC/HDL-C and non-HDL-C/HDL-C than did fenofibrate od/bd/tds ($p<0.001$). At Week 24, the reductions in these ratios were similar for ZD4522 10/20/40 mg and ZD4522 10 mg + fenofibrate od/bd/tds. At Week 6, ZD4522 5 mg and 10 mg produced significantly greater reductions in TG, LDL-C, TC, VLDL-C, and atherogenic ratios, and increases in HDL-C and ApoB, compared with placebo ($p<0.001$).

**Safety:** The number of subjects experiencing at least one adverse event was lowest in the ZD4522 5 mg + fenofibrate group and highest in the ZD4522 10 mg + fenofibrate group. Ten subjects withdrew from the trial due to adverse events (3 in the ZD4522 10/20/40 mg group, 1 in the fenofibrate od/bd/tds group, 5 in the ZD4522 5 mg + fenofibrate od/bd/tds group and 1 in the ZD4522 10 mg + fenofibrate od/bd/tds group; there were 3, 2, 3 and 1 subjects, respectively, with serious adverse events in each of these groups. Two deaths were reported in the trial; one in the ZD4522 10/20/40 mg group due to post-operative complications following CABG surgery, while the other was reported in a subject in the ZD4522 5 mg + fenofibrate od/bd/tds group who had septicaemic shock following intestinal obstruction. Both subjects had been withdrawn from the trial prior to death. Seven subjects had elevated ALT >3 x ULN, one (2%) on fenofibrate

od/bd/tds, 3 (5%) on ZD4522 5 mg + fenofibrate od/bd/tds and 3(6%) on ZD4522 10 mg + fenofibrate od/bd/tds. There were 6 cases of myalgia. Only 1 case of myalgia, which was non-serious and reported in a subject receiving ZD4522 5 mg + fenofibrate od/bd/tds, led to withdrawal from the trial. There were no clinically meaningful elevations in CK following treatment with ZD4522 or fenofibrate, alone or in combination. Changes in other clinical biochemistry parameters, vital signs, and physical examination were small and showed no treatment-related trends. There were 6 (3%) subjects with clinically relevant ECG changes from baseline. There appeared to be no treatment-related pattern or trends and the overall incidence and nature of these ECG changes is not unexpected given the indication and medical history of the subjects in this trial.