# SUMMARY

**ASTRAZENECA**

**FINISHED PRODUCT:**

**ACTIVE INGREDIENT:** ZD4522

**Trial title (number):** A 30-Week, Forced-titration and Randomised, Crossover, Multicentre, Multinational Trial to Evaluate the Efficacy and Safety of ZD4522 and Atorvastatin in Subjects with Homozygous Familial Hypercholesterolaemia (4522IL/0054): Report of the First 18 Weeks of Treatment (Open label ZD4522 20/40/80 mg, Forced-titration Period)

**Clinical phase:** III

**First subject recruited:** 19 April 2000
**Last subject completed:** 04 December 2000
(last subject visit for the forced-titration period)
**AstraZeneca approval date:** 30 March 2001

**Principal investigators and locations:**

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

**OBJECTIVES**

The primary objective was to assess the efficacy of ZD4522 in the reduction of low-density lipoprotein cholesterol (LDL-C) levels in subjects with homozygous familial hypercholesterolaemia after 18 weeks of open label treatment with ZD4522.

The secondary objectives of the forced-titration period of the trial were as follows:

- to assess the efficacy of ZD4522 in the reduction of LDL-C levels in subjects with homozygous familial hypercholesterolaemia at Weeks 6 and 12;

- to examine the relationship between LDL-C receptor status and response to statins;
- to determine the safety and tolerability of ZD4522 by evaluating the incidence and severity of adverse events and abnormal laboratory values.

Additional secondary objectives of interest were assessment of the effects of ZD4522 on other lipids and lipid ratios at Weeks 6, 12, and 18; and lipoprotein fractions and lipoprotein ratio, and inflammatory markers at Week 18.

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**METHODS**

**Design:** This was a multinational, multicentre trial with an open label dose titration period and a randomised treatment, double blind, 2-group, crossover, comparative period. After a 4-week dietary lead-in period, subjects entered the first phase of the trial, which was the open label forced-titration titration period. Over the next 18 weeks, subjects received a forced-titration of ZD4522, which was increased at 6-week intervals (ie, from 20 mg, to 40 mg, to 80 mg). After 18 weeks of forced-titration treatment, subjects immediately proceeded to the randomised crossover period of the trial where they received either ZD4522 80 mg or atorvastatin 80 mg for the next 6 weeks. **This summary covers only the first 18 weeks of treatment (open label, forced-titration period).**

**Population:** The primary endpoint is non-comparative in the forced-titration period of the trial. The sample size of the subject population was determined by the availability of subjects through the participating centres; 40 to 60 recruited subjects with homozygous familial hypercholesterolaemia were expected.

**Key inclusion criteria:** Men or women aged ≥10 years with homozygous familial hypercholesterolaemia (based on genetic, clinical or functional criteria); discontinuation of all cholesterol-lowering drugs and dietary supplements; and fasting triglyceride (TG) levels <6.77 mmol/L (< 600 mg/dL).

**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; known heterozygous familial hypercholesterolaemia; and usage of concomitant medications known to affect the lipid profile or present a potential safety concern (eg, through drug interaction).

**Dosage:** Subjects took oral doses of encapsulated trial treatment once daily, approximately 3 hours after the evening meal. During the forced-titration period of the trial, subjects took each titrated ZD4522 dose increment as a single encapsulated tablet (ie, 20 mg, 40 mg, and 80 mg) for 6 weeks. Batch numbers were as follows: ZD4522 20 mg (F12522, 00-0045), ZD4522 40 mg (F12566, 99-3159) and ZD4522 80 mg tablets (F12568, 99-3151).

**Key assessments:**

**Efficacy:** Fasting LDL-C, high density lipoprotein (HDL-C), TG, total cholesterol (TC), and lipid ratios were assessed at Weeks 0 (baseline), 6, 12 and 18; fasting apolipoprotein B (ApoB), apolipoprotein A-I (ApoA-I), apolipoprotein E (ApoE) and lipoprotein (a) (Lp(a)) and

inflammatory markers, C-reactive protein (CRP), interleukin-6 (IL-6) and E-selectin at Weeks 0 and 18.
Dietary compliance was assessed and evaluated throughout the trial (Weeks -4, 0, 6, 12 and 18).
The percentage change from baseline (Week 0) to Week 18 in LDL-C levels was the primary endpoint of this trial, and analyses were performed on the LOCF value from the ITT population. These analyses were repeated for the following secondary endpoints: LDL-C at Weeks 6 and 12, and TC, HDL-C, TG, LDL-C/HDL-C, TC/HDL-C, non-HDL-C/HDL-C at Weeks 6,12 and 18.
Summaries of the changes from baseline to Week 18 in ApoB, ApoA-I, ApoE and Lp(a) levels, and the ratio ApoB/ApoA-I; these analyses were performed on the LOCF values in the ITT population.
Descriptive statistics of percentage change from baseline were presented for the inflammatory markers (CRP, IL-6, E-selectin) at Week 18.
Data for very-low density lipoprotein subfraction 1 and 2 (VLDL-1, VLDL-2), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL), and serum and urinary mevalonic acid were collected at Weeks 0, 6, 12 and 18 and will be presented in the report of the crossover period of the trial.
**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 46 subjects were recruited from 4 centres, of whom 44 were eligible to enter the forced-titration treatment period following the dietary lead-in period. All 44 subjects received treatment. The mean body weight and mean body mass index of the subjects entering the forced-titration period were 71.13 kg and 24.72 kg/$m^2$, respectively. The majority of subjects were Caucasians aged between 10 and 63 years of age (8 subjects were aged <18 years old). Homozygous familial hypercholesterolaemia was genetically, clinically and/or functionally confirmed in 43 subjects. The first subject entered the trial (screened) on 19 April 2000 and the last subject completed the Week 18 visit on 4 December 2000. There were 44 subjects in the safety population, 2 of whom had no baseline or post-baseline assessments; the remaining 42 subjects comprised the ITT population. Six subjects withdrew during the forced-titration period (including the 2 subjects with no baseline or post-baseline assessments), 5 of these due to protocol non-compliance. In the ITT population, receptor status was negative in 4 subjects, defective in 22 subjects and unknown in 16 subjects; 9 subjects were receiving apheresis and 4 subjects had portacaval shunt. One subject (receptor negative status, receiving apheresis) from the ITT population had blood samples taken <7 days after apheresis at Weeks 0, 6 and 12, making the data invalid for ITT analysis at these time points. There were 4 subjects with major violations at baseline and 7 major deviations throughout the forced-titration period. Thus at Week 18, 31 subjects were included in the PP population. Thirty-eight subjects successfully completed the forced-titration period and entered the comparative, double-blind, crossover period.
**Efficacy:** A summary of the key efficacy findings for the first 18 weeks of treatment (forced-titration period) is presented in Table I.

**Table I Summary of key efficacy findings for the first 18 weeks of treatment; forced-titration period (LOCF on ITT population)**

| Efficacy variable | ZD4522 20/40/80 mg | | |
|---|---|---|---|
| | Overall (N = 42) | Receptor defective (N = 22) | Receptor unknown (N = 16) |
| **Mean of percentage change from baseline to Week 18 in lipids, lipid ratios, and lipoproteins (95% CI)** | | | |
| LDL-C | –21.40 (–28.12, –14.67) | –22.17 (–30.55, –13.79) | –33.60 (–33.60, –16.11) |
| TC | –19.95 (–25.51, –14.40) | –19.89 (–27.69, –12.10) | –22.72 (–30.16, –15.29) |
| HDL-C | 3.07 (–3.45, 9.60) | 2.08 (–5.49, 9.64) | 9.98 (–1.68, 21.64) |
| TG | 3.28 (–11.31, 17.87) | 3.60 (–14.61, 21.81) | 5.17 (–24.36, 34.70) |
| LDL-C/HDL-C | –20.52 (–29.11, –11.93) | –22.05 (–31.46, –12.64) | –29.35 (–38.77, –19.93) |
| TC/HDL-C | –19.42 (–26.69, –12.15) | –19.87 (–28.59, –11.15) | –27.41 (–36.33, –18.49) |
| non-HDL-C/HDL-C | –20.66 (–28.41, –12.92) | –21.18 (–30.56, –11.80) | –29.14 (–38.49, –19.79) |
| ApoB | –20.0 (–25.9, –14.0) | ND | ND |
| ApoA-I | 5.2 (–0.6, 11.1) | ND | ND |
| ApoE | –7.7 (–16.9, 1.4) | ND | ND |
| ApoB/ApoA-I | –20.71 (–28.57, –12.86) | ND | ND |
| Lp(a) | 28.5 (–2.9, 59.9) | ND | ND |
| **Median of percentage change from baseline to Week 18[a] in inflammatory markers (min, max)** | | | |
| CRP | –50.0 (–99, 9300) | ND | ND |
| IL-6 | –15.26 (–59.8, 40.4) | ND | ND |
| E-Selectin | –15.26 (–59.8, 40.4) | ND | ND |

[a] Analysis of observed data.
95% CI, = 95% Confidence Interval.
ND = not done.

At Week 18 (LOCF data from the ITT population) there was a clinically relevant reduction from baseline in LDL-C (the primary objective of this trial); ≥15% reduction in LDL-C is considered as a clinically relevant response. There were also clinically relevant reductions from baseline in LDL-C at Weeks 6 and 12 (observed data); the majority of the overall reduction was achieved by Week 6. Most subjects (29) were responders, having achieved a ≥15% reduction in LDL-C at Week 18 (including 1 negative receptor status subject and 2 apheresis subjects). There were decreases from baseline in TC and lipid ratios (LDL-C/HDL-C, TC/HDL-C and non-HDL-C/HDL-C) and ApoB and apolipoprotein ratio (ApoB/ApoA-I) at Weeks 6, 12 and 18. Changes in HDL-C and ApoA-I were slight, as were changes in ApoE; changes in TG were variable. Although the change from baseline at Week 18 in Lp(a), was larger than those observed in HDL-C, ApoA-I, TG and ApoE, results were inconclusive. Data for the inflammatory markers CRP, IL-6 and E-selectin were generally highly variable. The pattern of changes in lipids and lipid ratios was similar in the defective and unknown receptor status subgroups. The number of receptor negative subjects was too small (3 evaluable subjects from the ITT population) to draw inferences on mean percentage change from baseline data. There was a smaller decrease from baseline in LDL-C in the apheresis subgroup (8 evaluable subjects) compared with portacaval shunt (N=4) and neither apheresis nor portacaval shunt (N=29) subgroups; however, data were variable and there were small numbers of subjects in some of the subgroups. Results from the analyses of observed data from the PP population and Week 18

observed ITT data were consistent with results from the ITT efficacy analysis. Exploratory analyses did not show any clinically relevant impact of demographic factors (age, weight, race, sex) on change in LDL-C levels over time; no formal statistical analysis was performed.
**Safety:** ZD4522 20/40/80 mg was well tolerated. Overall, the types and incidences of treatment-emergent adverse events suggested no change in the adverse events profile of ZD4522 to that observed in previous trials. There were no adverse events leading to withdrawal and no deaths reported. There was no apparent increasing incidence of onset/worsening of adverse events as the forced-titration period progressed. Four subjects (9.1%) experienced 6 serious adverse events. During the forced-titration period, 2 subjects taking concomitant warfarin experienced 3 incidents of high INR with associated clinical adverse events: gum haemorrhage (serious and unrelated to treatment) and epistaxis (serious treatment related) in 1 subject and decreased prothrombin (treatment related) in another subject. The INR was stabilised in both subjects, who were reported as recovered; the individual with high INR and with associated bleeding continued in the trial on a modified (lower) warfarin scheme, while the other subject withdrew due to reasons unrelated to the high INR (protocol non-compliance). One subject experienced clinically raised ALT and AST (>3x ULN), reported as the adverse events “SGPT increased” and “SGOT increased”. Overall there were no reports of symptom pattern suggestive of liver injury in any subject during this trial. There were no clinically relevant rises in CK (>10x ULN) during the forced-titration period; there was 1 incident (2.3%) of myalgia. Other clinical biochemistry; haematology; and urinalysis data; and data from other safety assessments (vital signs, physical examination and ECGs) were all generally unremarkable with no apparent treatment-related patterns or trends.

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