2. SUMMARY

Sponsor: AstraZeneca K.K. (Japan)	Summary table of each study Relevant part of applying data Separate volume No.: Page:	(Use for Inspection Authorities)
Product name: Not yet determined		
Active ingredient C Calcium (JAN) Rosuvastatin (INN)		

Title: A Randomised, Double-Blind, Dose-Response Study with the HMG-CoA Reductase Inhibitor ZD4522 in Subjects with Hyperlipidaemis (A Phase II Clinical Study) (4522IL/0055)

Investigators and the institution:

Publication: Contents of this study have not been published. (As of December 10. 2001)

Study period:	Phase of development
(date of obtaining informed consent from the first subject): February 17, 2000 (date of starting the dosing to the first subject): April 27, 2000 (date of finishing the dosing to the last subject): February 7, 2001 (date of completing the observation of the last subject): April 3, 2001	Phase II

Objective:

•primary objectives

(1) to estimate the dose-response relationship between the dose of ZD4522 and the percentage reduction of low density lipoprotein cholesterol (LDL-C) [F equation] at Week +6 from the baseline value with respect to placebo.

(2) to have a bridge with a western phase II study (4522IL/0008) performed in patients with hyperlipidaemia (a separate bridging analysis report will be prepared).

•Secondary objectives

(1) to estimate the effect of ZD4522 on HDL-C (High density lipoprotain cholesterol), TG (Triglyseride), TC (Total cholesterol), ApoA-I (Apolipoprotain A-I), ApoA-II (Apolipoprotain A-II), Lp(a) (Lipoprotain a), ApoB (Apolipoprotain B), LDL- C [beta-quantification] and fibrinogen levels.

(2) to assess the pharmacokinetics of oral daily doses of 1, 2.5, 5, 10, 20, and 40 mg of ZD4522 over a 6-week period.

(3) to assess the tolerability and safety of ZD4522 in comparison with placebo.

*: Friedewald equation([LDL-C]=[TC]-[HDL-C] -0.2[TG])

Study method:

Multi-centre, randomised, Parallel-group, double-blind trial

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Number of subjects:
At planning: A total of 105 patients were to enter the treatment phase with 15 patients each in 7 groups (1, 2.5, 5, 10, 20, and 40 mg/day of ZD4522, or placebo). Considering drop-outs during the dietary run-in period, 400 patients were to be recruited in the run-in phase.

Subject observed for diet :	369 subjects
Subjects receiving investigational product :	113 subjects (placebo: 15, ZD 1 mg: 16, ZD 2.5 mg: 18, ZD 5 mg: 15, ZD 10 mg: 15, ZD 20 mg: 19, ZD 40 mg: 15)
Subject included in FAS :	112 subjects (placebo: 15, ZD 1 mg: 16, ZD 2.5 mg: 18, ZD 5 mg: 15, ZD 10 mg: 15, ZD 20 mg: 19, ZD 40 mg: 14)
Subject included in PPS :	101 subjects (placebo: 12, ZD 1 mg: 15, ZD 2.5 mg: 17, ZD 5 mg: 12, ZD 10 mg: 14, ZD 20 mg: 18, ZD 40 mg: 13)

Diagnosis and major inclusion criteria:
Diagnosis: Hyperlipidaemia
Inclusion criteria: To be eligible for the study, subjects had to meet all of the following criteria

- Outpatients
- Men aged 18 to 70 years and women aged 50 to 70 years.
- Lipid criteria:

(1)For entry into the dietary run-in phase (a value at Week -6);
Fasting LDL-C (F equation)
greater than 160 mg/dL but less than 240 mg/dL (greater than 4.14 mmol/L but less than 6.21 mmol/L)
Fasting TG less than 300 mg/dL (less than 3.39 mmol/L)
(2)For entry into the treatment phase (values at Weeks -2 and -1);
Fasting LDL-C (F equation)
greater than 160 mg/dL but less than 220 mg/dL (greater than 4.14 mmol/L but less than 5.69 mmol/L)
(with the proviso that a lower value was within 15% of a higher value.)
Fasting TG less than 300 mg/dL (less than 3.39 mmol/L)

Investigational product, dosage and administration, Lot No.:
<Investigational product>
ZD4522 was film-coated tablets containing 1, 2.5, 5, 10, 20 and 40 mg. To maintain blindness of tablets, ZD4522 film-coated tablets were encapsulated in dark-yellowish red, opaque capsule shells. Each capsule contained a ZD4522 1, 2.5, 5, 10, 20 or 40 mg tablet and lactose as an excipient. Placebo capsules contained only lactose.
<Dosage and administration>
The investigational product one capsule was administered orally once a day more than 3 hours after supper.
<Lot No.>
ZD4522 Capsule (included placebo): Lot No. S1522

Treatment period: Dietary run-in phase: 6 weeks, treatment phase: 6 weeks, follow-up phase: 4 weeks

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Evaluation Criteria

Efficacy

Primary endpoint: Reduction from baseline in LDL-C (F equation) at Week +6

Secondary endpoints: Percentage change from baseline in HDL-C, TG, TC, ApoA-I, ApoA-II, Lp(a), ApoB, LDL- C (beta-quantification) and fibrinogen.

Safety

Incidence of adverse events: The number of subjects, the number and incidence with adverse events and adverse drug reactions coded to COSTART terms were summarised.

Abnormal clinical laboratory values: The number and incidence of subjects with abnormal clinical laboratory values after dosing were summarised for each item by dose and grade. Haematology and clinical chemistry were summarised at each visit by dose, mean, SD etc.

Liver function tests and CK: Liver function tests (AST and ALT) and CK were summarised using the number of subjects with values ≥1 or 3×ULN after dosing. CK was further summarised using the number of subjects with values ≥5 or 10×ULN after dosing.

Pharmacokinetics

Plasma concentrations of ZD4522 were measured.

Statistical methods:

The relationship between the log-transformed dose of ZD4522 and the percentage change from baseline in LDL-C (F equation) at Week +6 (primary efficacy endpoint) was analysed using linear regression. Also placebo and ZD4522 dose groups were compared using Williams' test.

Summary-Conclusions:

Subject background

Of a total of 369 subjects who had entered the dietary run-in phase, 113 subjects were randomised to one of treatment groups. Of 256 subjects excluded from randomisation, 241 subjects did not meet the lipid criteria at randomisation. One (ZD 40 mg) of the 113 randomised subjects had not taken any investigational product and was excluded from FAS and PPS. Further 11 withdrawals, dropouts and having missing data on the primary efficacy endpoint were excluded from PPS. Consequently, FAS consisted of 112 subjects (placebo: 15, ZD 1 mg: 16, ZD 2.5 mg: 18, ZD 5 mg: 15, ZD 10 mg: 15, ZD 20 mg: 19, ZD 40 mg: 14) while PPS consisted of 101 subjects (placebo: 12, ZD 1 mg: 15, ZD 2.5 mg: 17, ZD 5 mg: 12, ZD 10 mg: 14, ZD 20 mg: 18, ZD 40 mg: 13). When the distribution of background factors was compared between treatment groups, no bias was observed for any factor in FAS or PPS. In FAS, mean ages of subjects in treatment groups were 51.1 – 58.5 years (mean of all subjects: 55.3 years), mean body weights were 55.88 – 65.57 kg (mean of all subjects: 61.83 kg), and mean values of BMI were 22.81 – 24.97 kg/m^2 (mean of all subjects: 23.97 kg/m^2).

Efficacy results:

A linear dose response was observed for percentage reduction in LDL-C (F equation) at Week +6, the primary endpoint (slope of regression line: $p<0.0001$). The relationship between the percentage change (y) from baseline in LDL-C (F equation) at Week +6 and log dose of ZD4522 (x) was expressed in the equation: "y=-36.84 – 7.39x". This equation suggests that a twofold increase in the dose of ZD4522 produces a further reduction in LDL-C by 5.12%. The mean percentage reduction in LDL-C (F equation) at Week +6 was -3.88% for placebo, -35.63% for ZD 1 mg, -44.99% for ZD 2.5 mg, -52.49% for ZD 5 mg, -49.60% for ZD 10 mg, -58.32% for ZD 20 mg and -65.77% for ZD 40 mg.

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LDL-C (F equation) levels at baseline and Week +6 and percentage changes from baseline to Week +6 are shown by treatment group in Table I.

Table I Regression analysis of relationship between log dose of ZD4522 and change from baseline in LDL-C (F equation) at Week +6 (FAS)

	Placebo	ZD 1mg	ZD 2.5mg	ZD 5mg	ZD 10mg	ZD 20mg	ZD 40mg
Baseline（mg/dL）							
N	15	16	18	15	15	19	14
Mean	190.04	184.04	184.93	181.27	182.19	185.84	181.00
SD	13.79	14.96	11.89	12.06	15.93	15.93	10.40
Week +6（mg/dL）							
N	11	15	17	12	14	18	13
Mean	182.00	117.40	101.29	86.58	92.50	76.22	62.08
SD	16.03	20.45	13.38	11.13	39.48	14.32	8.39
change at Week +6（%）							
N	11	15	17	12	14	18	13
Mean	-3.88	-35.63	-44.99	-52.49	-49.60	-58.32	-65.77
SD	7.74	10.29	6.35	5.83	20.94	9.22	5.04
ANOVA analysis of % change at (Week +6)							
N	11	15	17	12	14	18	13
Difference from placebo	NA	-32.6	-41.8	-49.5	-46.5	-55.0	-62.8
SE of difference from placebo	NA	4.2	4.1	4.5	4.3	4.1	4.4
Lower limit of 95% CI of difference from placebo	NA	-41.0	-50.0	-58.3	-55.1	-63.1	-71.5
Upper limit of 95% CI of difference from placebo	NA	-24.2	-33.6	-40.6	-38.0	-47.0	-54.1
Williams' test	NA	p<0.0001	p<0.0001	p<0.0001	p<0.0001	p<0.0001	p<0.0001

NA: Not applicable

Thepercents of changes for secondary efficacy endpoints from the baseline are shown in Table II.

Of the secondary endpoints, a linear dose response was observed for percentage reductions in TC, LDL-C (beta-quantification) and ApoB at Week +6 (slope of regression line for all these parameters: p<0.0001). Mean percentage reductions in these parameters at Week +6 were as follows: TC -2.25% for placebo vs -25.26 to -45.30% for ZD4522; LDL-C (beta-quantification) -0.28% for placebo vs -32.19 to -64.99% for ZD4522; and ApoB -1.99% for placebo vs -31.91 to -57.70% for ZD4522.

No dose-response relationship was observed for percentage changes in TG, HDL-C, ApoAI, ApoAII or fibrinogen. Compared with placebo, percentage changes in some lipids were observed at some doses (see Table II). The percentage changes in these parameters at Week +6 were as follows: TG +1.70% for placebo vs -17.01 to -25.91% for ZD4522; HDL-C +2.00% for placebo vs +7.64 to +14.04% for ZD4522; ApoA-I -1.01% for placebo vs +5.42 to +10.61% for ZD4522; and ApoA-II -2.88% for placebo vs +0.38 to +7.78% for ZD4522.

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Percentage changes in Lp(a) at Week +6 suggested a linear dose response (slope of regression line: p=0.0049). When differences between placebo and ZD4522 groups were assessed with Williams' test, ZD4522 had a Lp(a) elevating effect at doses of 20 mg or higher in comparison to placebo.

ZD4522 tended to reduce lipid ratios (LDL-C/HDL-C, TC/HDL-C, non-HDL-C/HDL-C, ApoB/ApoA-I) in comparison to placebo.

The above results confirmed that ZD4522 significantly reduced LDL-C in hyperlipidaemic patients and its LDL-C lowering effect was dose dependent in the range of 1 – 40 mg/day.

Table II Summary of results of efficacy endpoint assessments(FAS Endpoint parameters)

Endpoint parameters	% change from baseline to Week +6		Regression analysis (slope of regression line)	Between-group comparison (placebo vs ZD4522)
	ZD4522 [a]	Placebo		
TC	-25.26 - -45.30	-2.25	p<0.0001	All dose: p<0.0001
LDL-C (beta-quantification)	-32.19 - -64.99	-0.28	p<0.0001	All dose: p<0.0001
TG	-17.01 - -25.91	+1.70	p=0.7335	ZD 1mg：p=0.0358
HDL-C	+7.64 - +14.04	+2.00	p=0.8207	ZD 1mg：p=0.0434 ZD 10mg：p=0.0260 ZD 20mg：p=0.0463
ApoB	-31.91 - -57.70	-1.99	p<0.0001	All dose: <0.0001
ApoA-I	+5.42 - +10.61	-1.01	p=0.5038	ZD 10mg：p=0.0118 ZD 20mg：p=0.0065
ApoA-II	+0.38 - +7.78	-2.88	p=0.0940	ZD 10mg：p=0.0149 ZD 20mg：p=0.0043
Lp(a)	-8.67 - +17.06	-2.10	p=0.0049	ZD 20mg：p=0.0344 ZD 40mg：p=0.0232
Fibrinogen	+0.43 - +24.48	+14.22	p=0.5688	All dose: p>0.05

[a]: Range of % change in ZD4522 groups (1 – 40 mg)

Results of pharmacokinetics:

The dose-normalised plasma concentrations were similar for all dose groups, suggesting the linearity in the plasma concentrations in the range of ZD4522 1 to 40 mg/day.

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Results of safety:

There was no death in this study. Serious adverse events were reported in 1, 2 and 1 subject on ZD 10, 20 and 40 mg, respectively. Except for 1 subject on ZD 20 mg (gastrointestinal hemorrhage), all these events were judged unrelated to the investigational product. Of the 97 subjects in the ZD4522 groups, 5 subjects withdrew from the study due to adverse events. Almost all adverse events were of mild or moderate severity except two subjects in ZD4522 treatment groups (ZD 10 mg: anemia, ZD 20 mg: gastrointestinal hemorrhage/anemia) of severe cases.

There was no substantial difference in incidence of adverse events between ZD4522 and placebo groups, showing no trend toward dose-dependent increase in incidence of adverse events. When the incidence rates in all treatment groups were compared with χ^2 test, the p value was 0.2642. The incidence of adverse events considered related to the investigational product was slightly higher for ZD 20 and 40 mg than for placebo. When the incidence rates of adverse events related to the investigational product in all treatment groups were compared with χ^2 test, the p value was 0.0185. It must be noted, however, that an analysis of this kind takes no account of the type of adverse event experienced, only the incidence of any adverse event, and therefore should be interpreted with caution. Common adverse events reported in the ZD4522 groups (total of 97 subjects) were pharyngitis (12.4%), CK increased (8.2%), abdominal pain (5.2%), dizziness (5.2%). Common adverse events related to the investigational product with incidence of > 3% were abdominal pain (4.1%), CK increased (4.1%), diarrhea (3.1%), dizziness (3.1%), albuminuria (3.1%), γ-GTP increased (3.1%) and serum ALT increased (3.1%).

The incidence of abnormal clinical laboratory values and abnormal values of ≥ Grade 2 in the ZD4522 groups was equivalent to that in the placebo group. AST, ALT and CK were considered test parameters requiring special attention in the use of HMG-CoA reductase inhibitors. The mean changes from pretreatment values suggested elevations of AST and ALT, but none of the subjects showed clinically significant abnormal elevations of AST or ALT ≥ 3 × ULN (≥ Grade 2). The results of this study suggest that ZD4522 has no clinically significant effects on AST or ALT. One subject had a clinically significant abnormal CK elevation ≥ 3 × ULN (≥Grade 2), but this subject had an abnormal elevation before treatment and this event was judged unrelated to the investigational product. None of the subjects showed abnormal elevations of CK ≥ 5 × ULN. The results of this study show no problem that ZD4522 may cause CK elevation ≥ × ULN which was related to the investigational product or its associated symptoms of myopathy and myositis.

There were no changes in blood pressure, pulse rate or body weight from the values before treatment in any treatment group. Abnormal ECG changes possibly related to the investigational product were observed only in 1 subject on ZD 20 mg (AV block of Grade 1 and elevation of R wave).

The results of this study as mentioned above showed that it is indicated that AEs where the causality can not be ruled out tend to present slightly more in 20 mg and 40 mg of ZD4522. However, the incidence of serious adverse events and withdrawals due to adverse events was not high, and other tests and examinations revealed no clinically significant findings. With no clinically significant problems, the subjects of this study are considered to be well tolerated 6 weeks of administration of ZD4522 1 - 40 mg/day.