SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT:

ACTIVE INGREDIENT: ZD4522

Trial title (number): The Pharmacokinetics of ZD4522 (10 mg and 20 mg) in Stable Cardiac Transplant Subjects Taking an Anti-rejection Regimen Containing Cyclosporine (4522IL/0021).

Developmental phase:	I	**First subject recruited:**	18 July 1999
		Last subject completed:	27 August 2000
		AstraZeneca approval date:	23 March 2001

Publications: none at the time of writing this report

OBJECTIVES

The primary objective in both parts of this trial was to assess the effect of cyclosporine on the pharmacokinetics of single and multiple doses of ZD4522 (10 mg in the first part of the trial [Cohort 1] and 20 mg in the second part [Cohort 2]). The secondary objectives were to evaluate the effect of ZD4522 on the pharmacokinetics of cyclosporine and to evaluate the safety of this drug combination.

METHODS

Design: This was an open-label, single center trial in which 2 cohorts of heart transplant recipients on stable regimens of cyclosporine (plus prednisone and azathioprine) were given single- and multiple-doses of ZD4522 (10 mg in Cohort 1 and 20 mg in Cohort 2). Screening and determination of eligibility was to be carried out within 3 weeks before Day 1 and Day A1 for subjects entering Cohort 1 and Cohort 2, respectively. There was a minimum 1-week washout of pretrial statin therapy before the start of each period of the trial. Subjects from Cohort 1 could also participate in Cohort 2. An overview of the trial is given in Table I. Enrolled subjects entered the clinic for assessments (Day 1 in Cohort 1 and Day A1 in Cohort 2), were given the single ZD4522 dose (10 mg on Day 3 in Cohort 1 and 20 mg on Day A3 in Cohort 2), and had pharmacokinetic samples taken periodically (Days 3 through 6 in Cohort 1 and Days A3 through A6 in Cohort 2). In Cohort 1, daily doses of ZD4522 10 mg were then

given on Days 6 through 15, and multiple-dose pharmacokinetic assessments were made. In Cohort 2, single-dose pharmacokinetic assessments were followed by a hiatus of approximately 10 days while pharmacokinetic results were determined. During this period, subjects were discharged from the clinic and did not receive trial medication or undergo any trial assessments. Only subjects with C_{max} ≤750 ng/ml and AUC ≤250 ng.h/ml for the single dose of ZD4522 20 mg re-entered the clinic on Day B1, were given daily doses of ZD4522 20 mg on Days B2 through B11, and had multiple-dose pharmacokinetic assessments.

Table I Overview of the trial

	ZD4522 dose	Single-dose days	Single-dose PK assessments[a]	Non-dosing days	Dosing days	Multiple-dose PK assessments[a]
Cohort 1	10 mg	Day 3	Days 3 to 6	—	Days 6 to 15	Days 15 to 18
Cohort 2	20 mg	Day A3	Days A3 to A6	10-day hiatus + Day B1	Days B2 to B11	Days B11 to 14

[a] Blood drawn within 30 minutes predose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 48, and 72 hours after ZD4522 administration beginning on Days 3 and 15 in Cohort 1 and on Days A3 and B11 in Cohort 2.
PK Pharmacokinetic.

Population: In Cohort 1, up to 18 subjects were to be treated to obtain 10 evaluable subjects; In Cohort 2, up to 8 subjects were to be treated to obtain 5 evaluable subjects. Those subjects in Cohort 1 who also participated in Cohort 2 were subgrouped as Cohort 1B for paired comparisons with results in Cohort 2. Because diltiazem affects cyclosporine pharmacokinetics and could conceivably have a marginal effect on ZD4522 pharmacokinetics, the investigator attempted to recruit half of the study subjects from the pool of those transplant subjects not taking diltiazem. The subjects on diltiazem had stable cyclosporine dosing regimens. Pharmacokinetic data were displayed according to diltiazem, and no formal analysis was planned.

Key inclusion criteria: cardiac transplant subjects at least 6 months posttransplant, male or female, greater than 18 years of age and on stable doses of cyclosporine, prednisone and azathioprine. Laboratory values were required to be within specified limits. Women were to have undergone hysterectomy, be postmenopausal, or have a negative pregnancy test at screening.

Key exclusion criteria: various concomitant illnesses, including clinically significant ophthalmic abnormalities, any acute illness within 2 weeks before screening, history of malignancy (except basal or squamous cell carcinoma); history of specified disorders (including neurologic, renal, endocrine, hepatic, metabolic disease, gastrointestinal surgery, allergic rash or other allergic conditions); use of medications known to present a potential safety concern (eg, through drug interaction) within the previous 6 weeks; excessive alcohol intake; values of hemoglobin below the specified limit; administration of warfarin or any drug known to interfere with cyclosporine metabolism.

Dosage: All subjects continued on their pretrial regimens of cyclosporine, prednisone, and azathioprine throughout the trial. Subjects took oral doses of ZD4522 once daily at 0800 on scheduled days (single dose and then 10 daily doses). Doses of treatments were 10 mg in Cohort 1 and 20 mg in Cohort 2. The ZD4522 formulation was F12420 encapsulated for oral use (lots 983167C and 983167D for clinic and take-home use, respectively).
Restrictions: Subjects were required to follow a set of nondietary (no change in normal physical activities, no vigorous activity, minimal exposure to sun) and dietary (no change in diet or vitamin intake) restrictions.
Key assessments:
Pharmacokinetic: Blood samples were collected before and up to 72 hours after single and multiple dosing. The primary endpoints were ZD4522 pharmacokinetic parameters (AUC[0-24], C_{max}) following single and multiple doses of ZD4522 in Cohorts 1 and 2. The pharmacokinetic parameter estimates following multiple dosing facilitated a visual comparison with pharmacokinetic values after multiple dosing obtained in healthy subjects after morning dosing (ZD4522 10 mg) in Trial 4522IL/0004, used as a reference. Secondary endpoints included AUC(0-t), AUC, t_{max}, $t_{1/2}$, and the ratio for these variables of Cohort 2/Cohort 1 (for subjects who participated in both cohorts, which was used as an aid to assess the dose proportionality of pharmacokinetics). Formal statistical methods were not used in the comparison between trials. In addition, 90% confidence intervals were constructed for the ZD4522 accumulation and temporal change ratios in the presence of cyclosporine, based on log-transformed AUC(0-24) and AUC values, respectively. Secondary endpoints also included the pharmacokinetic variables of cyclosporine. The effects of single and multiple doses of ZD4522 on the pharmacokinetics of cyclosporine were evaluated using the 90% confidence intervals constructed for the ratios of log-transformed AUC(0-12) and C_{max} before and after dosing with concomitant ZD4522. ZD4522 pharmacokinetics were also summarized by diltiazem use.
Pharmacodynamic: Plasma lipid levels (low-density lipoprotein cholesterol [LDL-C] total cholesterol [TC], high-density lipoprotein cholesterol [HDL-C], and triglycerides [TG]), their changes from baseline and screening to the end of the dosing period (Day 15 for Cohort 1 and Day B11 for Cohort 2), and the differences between cohorts (for subjects who participated in both cohorts) were summarized in an exploratory analysis.
Safety: Standard safety assessments included adverse event reports, clinical laboratory data (hepatic biochemistry, CK, renal biochemistry hematology, and other biochemistry), vital signs, ECGs and physical examination. All safety data were summarized.

RESULTS
Demography: Cohort 1 consisted of 9 men and 1 woman who had a mean age, height, and weight of 53.2 years (range 30.0 to 69.0 years), 169.5 cm (range 156.0 to 182.8 cm), and 89.0 kg (range 68.1 to 109.5 kg), respectively. Five subjects (4 men, 1 woman, all Caucasian, 36 to 59 years of age) in Cohort 1 (Cohort 1B) also participated in Cohort 2. Cohort 2 consisted of the 5 subjects in Cohort 1B and 1 additional man. The 6 subjects in Cohort 2 had a mean age, height, and weight of 54.3 years (range 37.0 to 62.0 years), 171.1 cm (range 156.0 to 185.4 cm), and 87.7 kg (range 78.0 to 108.1 kg), respectively. All but 1 subject in the trial was Caucasian (1 Hispanic in Cohort 1). The 1 subject in Cohort 2 who had not previously participated in

Cohort 1 did not undergo pharmacokinetic assessments, as he was withdrawn for protocol noncompliance. All subjects had safety assessments.

Pharmacokinetics: A summary of the multiple-dose pharmacokinetic findings is presented in Table II.

Table II Multiple-dose pharmacokinetics of ZD4522 in the presence and absence of cyclosporine

PK parameter	ZD4522 + cyclosporine			ZD4522 only
	Cohort 1 (10 mg) (n = 10)	Cohort 1B[a] (10 mg) (n = 5)	Cohort 2 (20 mg) (n = 5)	4522IL/0004[b] (10 mg) (n = 21)
C_{max} (ng/ml)[c]	48.67 (47.2)	57.60 (37.44)	83.40 (37.3)	4.58 (46.9)
AUC(0-24) (ng.h/ml)[c]	284.37 (31.33)	313.25 (28.33)	423.69 (21.70)	40.10 (39.39)
AUC(0-t) (ng.h/ml)[c]	341.46 (27.68)	369.73 (23.48)	506.82 (20.94)	50.35 (46.98)
AUC (ng.h/ml)[c]	360.54 (16.89)[f]	337.33 (19.30)[g]	463.08 (4.08)[g]	71.81 (30.93)[h]
t_{max} (h)[d]	2.0 (1.0 to 4.0)	2.0 (1.0 to 4.0)	2.0 (1.0 to 2.0)	3.0 (1.0 to 6.0)
$t_{1/2}$ (h)[e]	14.76 (4.05)[f]	15.20 (5.27)[g]	20.20 (5.37)[g]	31.28 (12.02)[h]
Cohort 2 (20 mg) / Cohort 1B (10 mg) ratio[i]				
C_{max} (ng/ml)[c]	—	1.485 (0.367)		—
AUC(0-24) (ng.h/ml)[c]	—	1.379 (0.295)		—

Data derived from Table T5.2.1 and Trial 4522IL/0004

[a] Cohort 1B consists of subjects in Cohort 1 who also participated in Cohort 2.

[b] Data for ZD4522 only are from the morning dosing treatment group of Trial 4522IL/0004.

[c] Geometric mean (coefficient of variation).

[d] Median (range).

[e] Arithmetic mean (standard deviation).

[f] n = 5; some subjects' values were not calculated because no reliable estimate of the terminal elimination could be obtained due to concentrations below the sensitivity of the assay.

[g] n = 3; as above. Mean values less than those for AUC(0-t) are a result of the different number of included subjects.

[h] n = 16; as above.

[i] Produced for the ratio of log transformed paired data for Day B11/Day 15 values (standard deviation) and includes only those subjects who participated in both cohorts (n = 5).

PK Pharmacokinetic.

In comparison to the exposure in healthy subjects receiving multiple doses of ZD4522 10 mg/day in Trial 4522IL/0004, the C_{max} and AUC(0-24) values for ZD4522 10 mg/day in heart transplant recipients treated with cyclosporine were higher (10-fold and 7-fold, respectively). The C_{max} and AUC(0-24) for ZD4522 increased with the higher dose (ZD4522 20 mg/day), though the increase was less than proportional. Accumulation of ZD4522 after multiple dosing at 10 mg and at 20 mg was small (accumulation and temporal change ratios were 1.44 and 1.11, respectively, in Cohort 1 with 10 mg and 1.28 and 0.85, respectively, in Cohort 2 with 20 mg) and consistent with the respective single-dose kinetics. Co-administration of diltiazem resulted in numerically lower C_{max} and AUC(0-24) values for ZD4522 than when

diltiazem was not co-administered. Concomitant administration of ZD4522 with cyclosporine had no clinically relevant effect on cyclosporine pharmacokinetic parameters.
Pharmacodynamics: A summary of the pharmacodynamic findings is presented in Table III. LDL-C was substantially lowered and HDL-C was increased by both 10 and 20 mg doses of ZD4522 after 10 days of once daily therapy.

Table III Change in plasma lipids

Lipid	Mean (SD) of % change from baseline to end of dosing period[a]		
	Cohort 1 (10 mg) (n = 10)	Cohort 1B[b] (10 mg) (n = 5)	Cohort 2 (20 mg) (n = 5)
LDL-C	–28.95 (26.23)	–31.86 (37.25)	–34.47 (21.12)
TC	–24.08 (11.52)	–24.09 (15.61)	–21.60 (10.50)
HDL-C	11.34 (9.63)	9.94 (9.52)	6.37 (10.78)
TG	–32.08 (22.98)	–32.06 (16.75)	0.55 (40.53)

Data derived from Table 4.5
[a] Baseline was defined as lipid values on Day 2 in Cohort 1 and the mean of values on Days A2 and B1 in Cohort 2; the end of the dosing period for Cohort 1 was Day 16 and for Cohort 2 was Day B12.
[b] Cohort 1B consists of subjects in Cohort 1 who also participated in Cohort 2.
HDL-C = High-density lipoprotein cholesterol; LDL-C = Low-density lipoprotein cholesterol; TC = Total cholesterol; TG = Triglycerides.

Safety: ZD4522 was well tolerated as concomitant medication with cyclosporine in heart transplant recipients. Adverse events and changes in clinical laboratory variables were few and not dose related. There was no case of myopathy, and the serum CK concentrations were not elevated in either dose group. No deaths, serious adverse events, or withdrawals due to adverse events occurred. In the 1 subject with elevated ALT and AST, values above the normal limit were also found at baseline. No new safety concerns were identified. Although exposure at both the 10- and 20-mg doses was increased when given concomitantly with cyclosporine, ZD4522 was well tolerated in heart transplant recipients in this trial.