# SUMMARY

**ZENECA PHARMACEUTICALS**

**FINISHED PRODUCT:**

**ACTIVE INGREDIENT:** ZD4522

**Trial title (number):** Pharmacokinetics and Pharmacodynamics of ZD4522 10 mg in Subjects with Hepatic Impairment (4522IL/0018)

**Developmental phase:** I

**First subject recruited:** 6 July 1999
**Last subject completed:** 27 August 1999
**Zeneca approval date:** 7 April 2000

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

## OBJECTIVES

The primary objective of this trial was to compare the pharmacokinetics of ZD4522 in subjects with hepatic impairment with those in healthy subjects with normal liver function.
The secondary objectives were to assess the pharmacodynamics and safety and tolerability of ZD4522 in subjects with hepatic impairment and in healthy subjects with normal liver function.

## METHODS

**Design:** open-label, parallel, multiple-dose, pharmacokinetic, and pharmacodynamic trial at a single center
**Population:** adult subjects with normal liver function or hepatic impairment with Child-Pugh classifications A (CP-A) or B (CP-B), to obtain 6 evaluable subjects in each of 3 strata (21 subjects enrolled, maximum); subjects in the strata of normal liver function and CP-B (the subjects with the greatest degree of hepatic impairment in this study) were matched with respect to age, race, sex, weight, and smoking history.

**Key inclusion criteria:** men or women aged over 18 years with no clinically significant abnormalities in medical histories or deviations from normal ranges in clinical laboratory parameters with the exception of hepatic abnormalities in subjects assigned to the hepatically impaired study groups; for subjects with hepatic impairment, serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) within 2 times the upper limit of normal and normal levels of creatine kinase (CK)
**Key exclusion criteria:** history of metabolic endocrine disease known to be associated with alterations in plasma lipid levels; use of drugs suspected of affecting the liver drug-metabolizing enzymes within 6 weeks
**Dosage:** 10 mg ZD4522 (formulation F12420; lot 983167E; batch not applicable) once daily at 0700, with fasting 2 hours before and 3 hours after administration, for 14 consecutive days from Day 2 to Day 15
**Restrictions:** meals and study medication taken at regimented times, some dietary restrictions including limited intake of caffeine and alcohol, limited use of tobacco, limited exercise
**Key assessments:**
**Pharmacokinetics:** primary end endpoints: for ZD4522, the area under the plasma concentration versus time curve from 0 to 24 hours (AUC(0-24)) and maximum plasma concentration ($C_{max}$) based on the pharmacokinetic profiles on Day 15. Secondary endpoints: for ZD4522, time to maximum plasma concentration ($t_{max}$), half-life ($t_{1/2}$), renal clearance ($CL_R$), fraction of the dose excreted on Day 15 in urine as ZD4522 ($F_e$), time to steady-state concentration plasma concentration (from $C_{min}$ on Days 2, 3, 8, 9, 12, 13, 14, 15, 16), and minimum concentration at steady-state based upon 24-hour assessment following Day 15 dose ($C_{min}$); for the ZD4522-lactone, $C_{max}$ and $t_{max}$. The primary comparisons of the primary endpoints were between subjects with CP-B relative to subjects with normal liver function. If the confidence interval included the value one and was not artificially inflated by dropouts, no difference between subjects with CP-B and subjects of normal liver function would be concluded. Secondary assessments also included a repeated-measures analysis and a linear regression analysis to assess the time to steady-state by stratum and day for all subjects, and a multiple linear regression analysis to describe the relationship between albumin, PT, and total bilirubin measures at Day 1 (Screening for PT) and log-transformed PK parameters at Day 15 for only hepatically impaired subjects. In addition, an exploratory ad hoc classification was performed for all hepatically impaired subjects using the Maddrey discriminant function.
**Pharmacodynamics**: percent changes from baseline (defined as the mean of the Screening and Day 1 values) in low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) at Days 8 and 16. Changes from baseline in lipid levels were analyzed ad hoc using the t-test.
**Safety:** adverse event monitoring, clinical laboratory data (hepatic biochemistry, CK, renal biochemistry, hematology, urinalysis, and prothrombin and activated partial thromboplastin times), physical examinations, vital signs, and electrocardiograms

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**RESULTS**
**Demography:** Eighteen subjects, 6 in each of the 3 strata, were recruited and completed the trial. Subjects in the strata of normal liver function and CP-B were matched. Twelve men and 6 women were enrolled with a mean age, height, and weight of 51 years, 173 cm, and 84 kg,

respectively. Twelve subjects were White, 5 Hispanic, and 1 Black. The etiology of hepatic impairment of all subjects with CP-A and CP-B was alcohol-induced cirrhosis of the liver. Three subjects with CP-A and 2 subjects with CP-B had positive tests for hepatitis C antibody. The first subject enrolled 6 July 1999; the last subject completed 27 August 1999.

**Pharmacokinetics:** There were no statistically significant differences in geometric mean AUC(0-24) and $C_{max}$ of ZD4522 attributed to degree of hepatic impairment although geometric means and variability were numerically greater in subjects with CP-B (Tables I and II). Visual inspection of the AUC(0-24) and $C_{max}$ data indicated that the Child-Pugh B stratum was not homogenous with respect to ZD4522 PK parameters. The 4 subjects with Child-Pugh scores of 7 (the lowest value in the B category) appeared to have AUC(0-24) and $C_{max}$ values similar to subjects in the CP-A stratum. The subject with a CP score of 9 (the highest value in the CP-B category) had substantially elevated $C_{max}$ and AUC(0-24) values. The subject with a CP score of 8 had the second highest values for $C_{max}$ and AUC(0-24), but these values were much closer to those of subjects with CP-A and subjects with CP-B of lower scores. Thus, there was an indication that as hepatic impairment increased (as reflected by higher CP scores) there was increased exposure to ZD4522. Interestingly, ad hoc application of a second categorical system for scoring liver disease, the Maddrey discriminant function, identified this possible threshold for increased exposure with increasing severity of liver disease more precisely. When the Maddrey discriminant function was applied to all subjects with hepatic impairment, the only 2 subjects identified with severe hepatic impairment, the highest level seen in this trial, were those with the highest AUC(0-24) and $C_{max}$ values for ZD4522.

The median time to $C_{max}$ for ZD4522 was shorter in hepatically impaired subjects (1.5 and 2.5 hours for CP-A and CP-B, respectively) relative to subjects with normal liver function (3.5 hours). Approximately 5% of the administered dose of ZD4522 was excreted unchanged in urine in each stratum. Geometric mean peak plasma concentrations of ZD4522-lactone were much lower than ZD4522 and were similar across the different strata at approximately 1 ng/ml.

**Table I Statistical comparison of AUC(0-24) and $C_{max}$ in subjects with impaired hepatic function relative to subjects with normal liver function**

| Pharmacokinetic parameter | Ratios (90% CI) relative to subjects with normal liver function | |
|---|---|---|
| | Subjects with Child-Pugh Classification A | Subjects with Child-Pugh Classification B |
| AUC(0-24) | 1.05 (0.58, 1.91) | 1.21 (0.51, 2.84) |
| $C_{max}$ | 1.54 (0.94, 2.52) | 2.13 (0.65, 6.95) |

CI Confidence interval.
AUC(0-24) Area under the plasma concentration versus time curve from 0 to 24 hours.
$C_{max}$ Maximum plasma concentration.

**Table II Pharmacokinetic parameters of ZD4522**

| Pharmacokinetic parameter | Subjects with normal hepatic function | Subjects with Child-Pugh Classification A | Subjects with Child-Pugh Classification B |
|---|---|---|---|
| AUC(0-24) (ng.h/ml) | | | |
| Geometric mean | 60.7 | 63.7 | 73.3 |
| CV (%) | 76 | 47 | 105 |
| Range | 24, 116 | 31, 106 | 22, 242 |
| N | 6 | 6 | 6 |
| $C_{max}$ (ng/ml) | | | |
| Geometric mean | 6.0 | 9.3 | 12.8 |
| CV (%) | 63 | 33 | 187 |
| Range | 2.9, 12.2 | 6.2, 14.8 | 2.7, 96.7 |
| N | 6 | 6 | 6 |

AUC = Area under the plasma concentration-time curve; CV (%) = Coefficient of variation expressed as a percentage of the geometric mean.

**Pharmacodynamics:** The pharmacodynamic results are summarized in Table III.

**Table III Baseline and percent changes from baseline at Day 16 in lipid profiles by stratum**

| Parameter | Baseline and percent changes from baseline ± standard deviation | | |
|---|---|---|---|
| | Subjects with normal liver function N = 6 | Subjects with Child-Pugh Classification A N = 6 | Subjects with Child-Pugh Classification B N = 6 |
| **LDL-C** | | | |
| Baseline, mg/dL<br>mmol/L | 124 ± 15<br>3.20 ± 0.69 | 113 ± 27<br>2.93 ± 0.70 | 90 ± 41<br>2.32 ± 1.05 |
| % change, mean ± SD | -45 ± 13 | -34 ± 10 | -11 ± 31 |
| p-value[a]<br>95% CI[a] | 0.001<br>(-78, -35) | 0.003<br>(-58, -21) | 0.310<br>(-59, 23) |
| **Total cholesterol** | | | |
| Baseline, mg/dL<br>mmol/L | 198 ± 18<br>5.13 ± 0.45 | 191 ± 40<br>4.94 ± 1.03 | 175 ± 52<br>4.53 ± 1.35 |
| % change, mean ± SD | -32 ± 9 | -23 ± 9 | -15 ± 19 |
| p-value[a]<br>95% CI[a] | 0.001<br>(-87, -42) | 0.005<br>(-68, -21) | 0.078<br>(-71, 5) |
| **HDL-C** | | | |
| Baseline, mg/dL<br>mmol/L | 40 ± 9<br>1.05 ± 0.24 | 53 ± 17<br>1.37 ± 0.44 | 51 ± 15<br>1.32 ± 0.39 |
| % change, mean ± SD | 11 ± 18 | -3 ± 13 | -4 ± 21 |
| p-value[a]<br>95% CI[a] | 0.260<br>(-4, 11) | 0.827<br>(-7, 6) | 0.786<br>(-13, 11) |
| **Triglycerides** | | | |
| Baseline, mg/dL<br>mmol/L | 171 ± 61<br>1.92 ± 0.69 | 123 ± 50<br>1.39 ± 0.56 | 177 ± 135<br>1.99 ± 1.53 |
| % change, mean ± SD | -30 ± 16 | -11 ± 23 | -33 ± 15 |
| p-value[a]<br>95% CI[a] | 0.016<br>(-100, -16)[b] | 0.227<br>(-63, 19) | 0.068<br>(-153, 8)[b] |

[a] p-values and 95% CI are determined from absolute changes from baseline using a paired t-test where the null hypothesis is that the change from baseline is 0.
[b] Lower confidence bounds are a function of the mean, standard deviation, and the percentile point from a t distribution and are not necessarily indicative of biologically realistic values.
SD Standard deviation.
CI Confidence interval.

**Safety:** The safety profile of ZD4522 was similar in subjects in the strata of hepatic impairment and in the stratum of normal liver function. Eleven subjects reported 24 mild AEs, 19 were attributed to trial treatment by the investigator. Four subjects with normal liver function reported

7 AEs, 4 subjects with CP-A reported 8 AEs, and 3 subjects with CP-B reported 9 AEs. The most frequently occurring AEs experienced by all subjects were flatulence, constipation, and headache. No symptom complex suggestive of liver disturbances was observed during this trial. No AEs were reported for abnormal liver function. No subject had elevations in ALT or AST of 3 or more times the upper limit of normal; no subject had elevations in CK of 5 or more times the upper limit of normal. No signs or symptoms suggestive of muscle damage were observed for any subjects. No subject withdrew because of an adverse event, and no subject died or experienced a serious adverse event during or within 30 days following the Treatment Period.