SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT:

ACTIVE INGREDIENT: ZD4522

Trial title (number): A Phase I Trial to Assess the Effect of Coadministration of Oral Contraceptives and ZD4522 (40 mg) on the Pharmacokinetics of Exogenous Plasma Estrogen and Progesterone in Healthy Women (4522IL/0009).

Developmental phase: I

First subject recruited: 4 July 1999
Last subject completed: 23 October 1999
AstraZeneca approval date: 31 July 2000

Publications: none at the time of writing this report

OBJECTIVES

The objectives of this trial were: (1) to assess the effect of multiple doses of ZD4522 on the pharmacokinetics of ethinyl estradiol (EE), norgestimate (NGM), 17-desacetyl norgestimate (DesAc-NGM), norgestrel (NG), and endogenous hormones during dosing with oral contraceptives, (2) to characterize the steady-state pharmacokinetics of ZD4522 in women taking oral contraceptive steroids (OCS), and (3) to determine the safety and tolerance of the coadministration of ZD4522 and OCS. Plasma lipids and lipoproteins during OCS administration and during coadministration of ZD4522 and OCS were also measured.

METHODS

Design: This was an open-label, multiple-dose, nonrandomized trial conducted at a single center. The trial consisted of two sequential treatment-assessment cycles (Cycle A followed by Cycle B) as shown in Table I. All subjects received OCS once daily for 21 days during both cycles and ZD4522 40 mg once daily in Cycle B.

Table I Overview of treatment regimen

	Days 1 to 21	Days 22 to 28
Cycle A	OCS	Placebo OCS
Cycle B	OCS plus ZD4522	Placebo OCS

Population: healthy women receiving estrogen-progestin OCS for a minimum of the last 3 menstrual cycles before the start of the trial. A total sample size of 16 had 90% power to detect a 30% difference in the AUC(0-24) of EE between Cycle A (OCS alone) and Cycle B (OCS + ZD4522). Up to a total of 24 subjects were to be enrolled.
Key inclusion criteria: nonpregnant, nonbreastfeeding, and nonsmoking women aged 18 to 40 years with intact ovarian function and receiving one of the specified OCS (monophasic or triphasic) throughout the previous three menstrual cycles; willing to use a reliable method of barrier contraception throughout the trial; weight within the target range**.**
Key exclusion criteria: values outside the normal range for total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), or creatine kinase (CK); Class III or IV Pap test; history of clinically significant adverse drug reactions or hypersensitivity to drugs chemically or mechanistically similar to ZD4522; clinically significant ophthalmic abnormalities; use of drugs that affect the liver drug-metabolizing enzymes within 6 weeks before the start of the trial**.**
Dosage: The choice of trial OCS was dependent on pretrial OCS, and in this trial all subjects were given Ortho Tri-Cyclen (3 weeks of EE 0.035 mg and NGM 0.180 mg during week 1, 0.215 mg week 2, and 0.250 mg week 3; and 1 week of OCS placebo) for two 28-day cycles (Cycles A and B). Each subject was also given concomitant ZD4522 40 mg (formulation F12420, lot 983167E) once daily for the first 21 days in Cycle B. All trial treatments were to be taken at approximately 0800.
Restrictions: Subjects were required to follow a set of special dietary and nondietary (tobacco use, concomitant medications, sunbathing and vigorous physical activities) restrictions because of the potential for these activities to affect pharmacokinetic assessments, lipid levels, or safety.
Key assessments:
Pharmacokinetic: (1) The effect of concomitant ZD4522 on the pharmacokinetics (AUC[0-24], C_{max}, $t_{1/2}$, and T_{max}) of exogenous hormones was determined. Blood samples were collected at specified times beginning on Day 21 of each cycle, and were analyzed for EE, NGM, DesAc-NGM and NG. Summary statistics were used to describe concentrations and pharmacokinetic parameters, and the 90% confidence intervals (CI) were constructed for geometric mean ratios with and without ZD4522. The criterion for no interaction was a CI that included 1 and was not artificially wide because of dropouts. Clinical significance was prespecified as a >30% change in AUC(0-24) or C_{max} (CI of the exponentiated ratio within 0.70 to 1.43) based on OCS efficacy with lower EE doses. (2) The steady-state pharmacokinetics of ZD4522 when coadministered with OCS were determined and described using summary statistics. (3) Urinary excretion of cortisol and 6β-hydroxycortisol with and without ZD4522 administration were determined to assess effect on CYP3A4, and the mean difference between treatments with 95% CIs was determined.

Pharmacodynamic: (1) Plasma concentrations of luteinizing hormone (LH), follicle stimulating hormone (FSH), sex hormone binding globulin (SHBG) and progesterone with and without ZD4522 administration; and (2) the change from baseline in plasma lipids and lipoproteins (total cholesterol [TC], low- and high-density lipoprotein cholesterol [LDL-C, HDL-C], triglycerides [TG], apolipoprotein B-100 [ApoB], apolipoproteins A-I and A-II [ApoA-I, ApoA-II], lipoprotein (a) [Lp(a)]) were determined with and without ZD4522. Summary statistics were used to present data, mean differences with 95% CIs were constructed, and p-values were presented based on a paired t test.
Safety: Standard safety assessments included adverse event reports, clinical laboratory data (hepatic biochemistry, creatine kinase, renal biochemistry, hematology, urinalysis), vital signs, ECGs, physical examination, and subject OCS bleeding data. Adverse events, clinical laboratory values, vital signs, and quantitative ECG measurements were summarized.

RESULTS
Demography: A total of 18 healthy women with a mean age, height, and weight of 25 years (20 to 33 years), 163 cm (150 to 173 cm), and 60 kg (51 to 70 kg), respectively, were enrolled at a single center in this trial. The first subject entered the trial on 4 July 1999, and the last subject completed the trial on 23 October 1999. All 18 subjects were on Ortho Tri-Cyclen, completed the trial, and were included in the pharmacokinetic, pharmacodynamic, and safety assessments.
Pharmacokinetics: Coadministration of OCS and ZD4522 resulted in increases in AUC(0-24) for EE (26%), DesAc-NGM (15%) and NG (34%) and in C_{max} for EE (25%) and NG (23%) (Table II). The 90% CIs for all but one of these parameters were within the protocol-specified limits (0.7 to 1.43) indicating no clinically relevant effect. The upper confidence limit for the increase in the NG AUC(0-24) was at the upper limit of the prespecified range for no clinical significance (upper 90% confidence limit of 1.43). NGM is a prodrug that is rapidly converted to the active metabolites DesAc-NGM and NG; concentrations of NGM were low and not quantifiable. The statistically significant increase in the EE $t_{1/2}$ with ZD4522 treatment (mean difference of 2.4 hours with 90% CI of 0.9 to 3.8) was not considered clinically relevant. Elimination rates for DesAc-NGM and NG did not appear to differ between treatment with OCS + ZD4522 and OCS alone. In the absence of meaningful changes in elimination rates, the increase in exposure to the three exogenous hormones was attributed to a change in bioavailability.

Table II Effect of ZD4522 on AUC(0-24) and C_{max} of selected exogenous hormones

Hormone	PK parameter	n	Geometric mean ratio[a]	Lower 90% CL[b]	Upper 90% CL[b]
EE	AUC(0-24)	18	1.262	1.187	1.343
	C_{max}	18	1.245	1.165	1.331
DesAc-NGM	AUC(0-24)	18	1.150	1.103	1.198
	C_{max}	18	1.025	0.906	1.159
NG	AUC(0-24)	18	1.337	1.246	1.434
	C_{max}	18	1.234	1.143	1.333

Data derived from Table T5.7

[a] Geometric mean ratio is the geometric mean of the ratio of the PK parameter for (OCS+ZD4522)/OCS.

[b] Confidence intervals that contain one indicate that the ratio is not different from one.

CL = Confidence limit; EE = Ethinyl estradiol; DesAc-NGM = 17-Desacetyl norgestimate; NG = Norgestrel; PK = Pharmacokinetic.

The geometric mean AUC(0-24) and C_{max} for ZD4522 were 290 ng.h/ml and 35 ng/ml respectively. The arithmetic mean $t_{1/2}$ and median T_{max} for ZD4522 were 15 hours and 3 hours, respectively. No significant change in urinary excretion of cortisol or 6β-hydroxycortisol occurred with the coadministration of OCS and ZD4522 as compared to OCS alone, indicating that ZD4522 did not induce CYP3A4, which is known to be responsible for metabolism of EE.

Pharmacodynamics:

Small decreases in mean concentrations of the endogenous hormones (LH, FSH, and progesterone) between corresponding days (Days 7, 14, 20, and 21) in Cycle A and Cycle B were not statistically significant. Mean SHBG concentrations tended to be higher with coadministration of ZD4522, but these increases were not statistically significant. The persistent low progesterone concentrations with coadministration of ZD4522 strongly suggest ovulation did not occur, and contraceptive efficacy was maintained. Coadministration of ZD4522 with OCS did result in statistically significant decreases in plasma LDL-C, TC, and TG and a statistically significant increase in HDL-C (Table III).

Table III Effect of ZD4522 on plasma lipids

Lipid	n	Baseline mean[a] (mg/dL)	Mean % change from baseline	Mean change from baseline (mg/dL)	Lower 95% CL	Upper 95% CL	p-value[b]
LDL-C	18	96.36	–54.89	–53.14	–60.79	–45.49	0.001
TC	18	178.65	–27.22	–49.20	–57.94	–40.47	0.001
HDL-C	18	62.84	11.11	6.82	3.01	10.64	0.002
TG	18	97.29	–12.33	–15.18	–27.71	–2.64	0.021

Data derived from Tables T4.2 and T4.3

[a] Baseline was defined as the mean of up to three values (on Days A-1, A-21, and B-1) before treatment with ZD4522.

[b] p-values determined by t-test are based on the null hypothesis of a mean change from baseline of zero.

CL = Confidence limit; HDL-C = High-density lipoprotein cholesterol; LDL-C = Low-density lipoprotein cholesterol; TC = Total cholesterol; TG = Triglycerides.

Safety: Repeated oral doses of ZD4522 coadministered with OCS were well tolerated over the 21 day treatment period (Cycle B). There were no deaths, no serious adverse events, and no withdrawals. No changes in clinical laboratory values, vital signs, ECG parameters or physical examinations that were of clinical concern were reported. No evidence of myopathy or liver function abnormalities was observed. Two women had small increases in CK (maximum values of 429 U/L associated with transient myalgia and 552 U/L) near the end of Cycle B (OCS + ZD4522) that were associated with exercise and returned to within the normal range when treatment and exercise had ceased. Adverse events were mild, transient, and occurred with higher frequency during Cycle B (OCS + ZD4522) than Cycle A (OCS alone). The most frequently occurring adverse events in Cycle B (OCS + ZD4522) were headache (3 subjects), followed by generalized edema, diarrhea, anemia, increased CK, pharyngitis, and breast pain (2 subjects each). Breakthrough bleeding occurred in one subject during both cycles and in one subject during Cycle B (OCS + ZD4522).