Clinical Study Report Synopsis

Drug Substance	AZD1981
Study Code	D9830C00015
Edition Number	1
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A Phase I, Double-blind, Randomised, Placebo-controlled, Two-cycle Crossover, Drug-drug Interaction Study to Investigate the Effects of AZD1981 Tablets 400 mg Twice Daily on the Pharmacokinetics and Pharmacodynamics of Oral Contraceptives in Healthy Female Volunteers

Study dates:	First subject enrolled: 4 May 2010 Last subject last visit: 28 October 2010
Phase of development:	Clinical pharmacology (I)
Co-ordinating Investigator:	
Sponsor's Responsible Medical Officer:	

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To investigate the effect of AZD1981 on the PK of the exogenous hormones EE and LNG in healthy female volunteers using OCs during the menstrual cycle	AUC_{τ} and $C_{ss,max}$ of EE and LNG **Secondary** C_{trough} and $t_{max\ ss}$ of EE and LNG	PK
Secondary	**Secondary**	
To investigate the effect of AZD1981 on the endogenous substances LH, FSH, SHBG, progesterone and E2 in healthy female volunteers using OCs during the menstrual cycle	Serum concentrations of LH, FSH, SHBG, progesterone and E2	PD
To evaluate the safety and tolerability of AZD1981 administered in combination with OCs	AEs, safety laboratory variables, pulse, blood pressure, ECG and physical examinations	Safety
To characterise the steady state PK of AZD1981 administered in combination with OCs	AUC_{τ}, $C_{ss,max}$, $t_{max\ ss}$ and CL_{ss}/F of AZD1981	PK
Exploratory[a]	**Exploratory**	
To collect and store DNA for future exploratory research into genes that may influence response, ie, distribution, safety, tolerability and efficacy of AZD1981 treatment	DNA/genotype (optional)	PGx

AE: Adverse event, AUC_{τ}: Area under the plasma concentration-time curve during a dosing interval at steady state, CL_{ss}/F: Apparent plasma clearance at steady state, $C_{ss,max}$: Maximum peak plasma concentration at steady state during a dosing interval, C_{trough}: The last plasma concentration measured before the next dose in a repeated dosing study, ECG: Electrocardiogram, EE: Ethinyl estradiol, E2: Estradiol, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, LNG: Levonorgestrel, OC: Oral contraceptive, PD: Pharmacodynamic(s), PGx: Pharmacogenetic(s), PK: Pharmacokinetic(s), SHBG: Sex hormone-binding globulin, $t_{max\ ss}$: Time to $C_{ss,max}$.

[a] To be reported separately from the Clinical study report (CSR).

Study design

This was a double-blind, placebo-controlled, randomised, 2-period crossover, repeat dose study to assess the effect of AZD1981 (at steady state conditions) on the PK of the exogenous hormones EE and LNG and on the levels of the endogenous substances LH, FSH, SHBG, progesterone and E2.

Target subject population and sample size

The target population was healthy females of childbearing potential, aged 18 to 45 years inclusive, with a body mass index between 19 and 30 kg/m^2. Eligible healthy volunteers had to have been treated with the OCs Neovletta® or Neovletta® 28 during the last 3 months prior to enrolment and had to have 2 negative pregnancy tests (at least 7 days apart) prior to first dose of AZD1981 or placebo.

Twenty-eight healthy female volunteers were planned to be randomised to treatment.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Healthy volunteers receiving treatment A received:

- 4 x 100 mg AZD1981 as oral tablets (manufactured by AstraZeneca; batch number 10-002999AZ) twice daily and
- Neovletta or Neovletta 28 (manufactured by Bayer; batch numbers 10-001329AZ/10-001533AZ and 10-001327AZ, respectively) once daily.

Healthy volunteers receiving treatment B received:

- placebo administered as 4 oral tablets (manufactured by AstraZeneca; batch number 10-000225AZ) twice daily and
- Neovletta or Neovletta 28 once daily.

If the healthy volunteer received Neovletta, a 7-day cessation of the OCs occurred during each treatment period (in accordance with the dosing recommendations) to allow for bleeding.

Duration of treatment

The duration of each healthy volunteer's participation was about 3 months, including a screening period of up to 21 days, 2 treatment periods of 4 weeks each and a follow-up visit 7 to 10 days after the last dose of AZD1981 or placebo in the second treatment period. There was no washout between the 2 treatment periods. In order to avoid measuring potential carry-over effects, no measurements were performed during the first 2 weeks of each treatment period.

Statistical methods

Pharmacokinetic concentrations and parameters were presented by descriptive statistical methods. The natural log-transformed variables AUC_τ and $C_{ss,max}$ of EE and LNG were analysed as dependent variables in a linear mixed effect model with treatment (interpreted as AZD1981 or placebo) and period as fixed effects and subject as a random effect. Estimates of the mean differences (AZD1981 – placebo) and corresponding 90% confidence intervals (CIs) were calculated. The mean and the confidence limits were transformed back to the original

scale in order to give an estimate of the true ratios (AZD1981/placebo]) and 90% CIs for these ratios. No clinically relevant effect on the PK of EE or LNG after co-administration of AZD1981 was to be concluded if the 2-sided 90% CIs for the ratios of both AUC_{τ} and $C_{ss,max}$ were within 80.00% and 125.00%.

There was no formal hypothesis testing of the PD or safety variables. These were presented by descriptive statistical methods.

Subject population

In total, 34 healthy volunteers were enrolled (consented) and 28 healthy volunteers (14 in each treatment sequence) were randomised to treatment in the study, which was conducted at 2 centres in Sweden.

The number of healthy volunteers who completed the study was 25 (13 in treatment sequence AB [OCs and AZD1981 in treatment period 1, and OCs and placebo in treatment period 2] and 12 in treatment sequence BA [OCs and placebo in treatment period 1, and OCs and AZD1981 in treatment period 2]). Three healthy volunteers were discontinued from the study. One healthy volunteer was discontinued due to severe non-compliance to the clinical study protocol (CSP). The healthy volunteer received Neovletta at the clinic on Study day 1 and continued to take OCs at home for 3 days (Study days 2 to 4) instead of having a 7-day cessation to allow for bleeding on Study days 1 to 7 before commencing the OC treatment. Two healthy volunteers were discontinued from the study due to AEs (impetigo).

All 28 randomised healthy volunteers were included in the safety and PD populations. Twenty-seven healthy volunteers were included in the PK population (all except the healthy volunteer who was discontinued from the study due to severe non-compliance to the CSP).

The number of healthy volunteers and their demographic characteristics were in line with the population that was intended to be included in the study. The treatment sequences were comparable in terms of demographics. This was according to the CSP and was considered appropriate for this Phase I study.

Summary of pharmacokinetic results

Oral administration of AZD1981 tablets 400 mg twice daily increased the steady-state plasma exposures of EE and LNG in female volunteers on this oral contraceptive combination. The increases in AUC_{τ} and $C_{ss,max}$ were 52% and 31%, respectively, for EE, and 22% and 30%, respectively, for LNG.

Oral administration of AZD1981 tablets 400 mg twice daily in combination with EE and LNG resulted in a geometric mean AUC_{τ}, $C_{ss,max}$, and CL_{ss}/F of 48100 h*nmol/L, 13500 nmol/L, and 21.4 L/h, respectively, for AZD1981 in the investigated panel of women.

Summary of pharmacodynamic results

The effects on typical contraceptive biomarkers were negligible or in keeping with the altered PK of EE and LNG; oral administration of AZD1981 tablets 400 mg twice daily tended to

increase the suppressive effects on LH and FSH (decreased serum concentrations), and stimulant effect on SHBG (increased serum concentration) in female volunteers using the combination of EE and LNG, whereas the effects on E2 and progesterone were essentially unaltered (maintained serum concentrations).

Summary of pharmacogenetic results

The results from the future exploratory genetic research are not reported in the CSR.

Summary of safety results

AZD1981 in combination with the OC pill was well tolerated in this study.

Two healthy volunteers discontinued due to AEs (impetigo). There were no serious AEs or other significant AEs. All AEs were of mild or moderate intensity, except 1 event of headache that was of severe intensity. The most common AEs (in order of frequency) were nasopharyngitis, headache and dysmenorrhoea after concomitant treatment with AZD1981 and OCs, and nasopharyngitis, dysmenorrhoea and headache after concomitant treatment with placebo and OCs.

There were no clinically relevant changes in clinical laboratory, vital signs, ECG or physical examination variables.