Clinical Study Report Synopsis

Drug Substance	AZD5069
Study Code	D3550C00011
Edition Number	1
Date	

An open-label, fixed-sequence, single-centre phase I study to assess the effect of ketoconazole on the pharmacokinetics of AZD5069 after oral administration of a single dose AZD5069 to healthy male volunteers

Study dates: First subject enrolled: 14 December 2012
Last subject last visit: 11 February 2013

Phase of development: Clinical pharmacology (I)

Principal 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 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	PK	To evaluate the effect of ketoconazole on the PK of AZD5069, a carboxylic acid metabolite (AZ13587715), and other potential metabolite(s)	For both treatments, AZD5069, and AZ13587715: AUC, $AUC_{(0-t)}$, C_{max}, λ_z, $t_{1/2\lambda z}$, t_{max}, t_{last}, CL/F (AZD5069 only), V_z/F (AZD5069 only), MRAUC, $MRAUC_{(0-t)}$, and MRC_{max} For ketoconazole+AZD5069 treatment, ketoconazole: $AUC_{(0-t)}$ and C_{max}
Secondary	Safety	To evaluate the safety and tolerability of AZD5069 alone and in combination with ketoconazole	Adverse events, laboratory assessments, vital signs (blood pressure, pulse rate, body temperature), physical examination, and 12-lead electrocardiogram
Exploratory	PD	To evaluate the effect of AZD5069 alone and in combination with ketoconazole on circulating neutrophil numbers in blood	Observed, change, and percent change from baseline blood neutrophil count, blood neutrophil count ratio, ANC_{min} and $ANCt_{min}$
	PK/PD	To investigate the relationship between PD and PK parameters	Plots of ANC_{min} versus AZD5069 C_{max} and AUC
	Pharmacogenetic[a]	To collect and store deoxyribonucleic acid (DNA) samples for possible retrospective exploratory genetic analysis, investigating the influence of genotype on the PD and PK responses, safety and tolerability of AZD5069 and AZD5069 with ketoconazole, and associated biomarkers, where appropriate	Not applicable

a If performed, these results will be reported in a separate stand-alone report and not in this Clinical Study Report.

λ_z: terminal rate constant; ANC_{min}: minimum absolute circulating neutrophil number; $ANCt_{min}$: time to minimum absolute circulating neutrophil number; AUC: area under the plasma concentration-time curve from zero to infinity; $AUC_{(0-t)}$: area under the plasma concentration-time curve from zero to time of last quantifiable

concentration; CL/F: apparent oral clearance; C_{max}: maximum plasma concentration; MR: metabolite to parent ratio; PD: pharmacodynamic; PK: pharmacokinetic; $t_{1/2\lambda z}$: terminal half-life; t_{last}: time at which the last quantifiable plasma concentration was observed; t_{max}: time to reach maximum plasma concentration; V_z/F: apparent volume of distribution.

Study design

This was an open-label, fixed-sequence study to evaluate the effect of a cytochrome P450 (CYP) 3A4 inhibitor, ketoconazole, on the pharmacokinetics (PK) of AZD5069, AZ13587715, and other potential metabolite(s) at 1 study centre.

The following treatments were administered in a fixed order, separated by a washout period of at least 4 days (between Day 1 Period 1 and Day -2 Period 2):

- Period 1: single administration of 15 mg AZD5069 on Day 1
- Period 2: once daily administrations of 400 mg ketoconazole from Day -2 to Day 3 and a single administration of 15 mg AZD5069 on Day 1

Target subject population and sample size

Up to 15 healthy male volunteers (to ensure 12 evaluable healthy volunteers) aged 18 to 50 years (inclusive) who signed informed consent were to be enrolled in this study.

Screened: 40 healthy volunteers

Planned: 15 healthy volunteers

Treated: 15 healthy volunteers

Completed: 14 healthy volunteers

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

Table S2 Details of the investigational product(s)

Investigational product	Dosage form and strength	Manufacturer	Batch number
AZD5069	5 mg capsule	AstraZeneca	12-003088AZ

Ketoconazole (Nizoral®, 200 mg white tablets), manufactured by Janssen-Cilag, was supplied in volunteer-specific labelled dosing containers by AstraZeneca (Sweden). Licence number: PL0242/0083UK.

Duration of treatment

Single administration of AZD5069 on Day 1 (Period 1) and once daily administrations of ketoconazole from Day -2 to Day 3 + a single administration of AZD5069 on Day 1 (Period 2). Period 1 and Period 2 were separated by a washout period of at least 4 days.

Statistical methods

Plasma concentrations and pharmacokinetic parameters for AZD5069 and AZ13587715 including AUC, $AUC_{(0-t)}$, C_{max}, λ_z, $t_{1/2\lambda z}$, t_{last}, t_{max}, CL/F (AZD5069 only), V_z/F (AZD5069 only), MRAUC, $MRAUC_{(0-t)}$, and MRC_{max} were summarised using descriptive statistics. AZD5069 PK parameters were compared for AZD5069 + ketoconazole treatment with AZD5069 treatment as the reference. Mean AZD5069 and AZ13587715, concentrations are presented graphically. Plasma concentrations and pharmacokinetic parameters for ketoconazole, including $AUC_{(0-t)}$ and C_{max}, were summarised using descriptive statistics. Mean ketoconazole concentrations are presented graphically.

Analyses of pharmacokinetic parameters were performed by fitting a linear mixed effects model, using natural log (ln) transformed AUC, $AUC_{(0-t)}$, and C_{max}. Estimates of the geometric means from the fitted model, with corresponding 95% confidence intervals (2-sided) were presented. The ratio of the geometric means for AZD5069+ketonazole treatment versus AZD5069 treatment is also presented together with corresponding 90% confidence intervals (2-sided). Additionally, MRAUC, $MRAUC_{(0-t)}$, and MRC_{max} were analyzed using the same analyses approach.

All recorded circulating neutrophil numbers in blood are listed by treatment group. The absolute value, along with change and percentage change from baseline, was summarised by treatment.

Adverse events (AEs) were summarised by Preferred Term and System Organ Class using the Medical Dictionary for Regulatory Activities by treatment. Furthermore, listings of serious adverse events (SAEs) and discontinuations of the AZD5069 and/or ketoconazole administration due to an AE (DAEs) were made. Tabulations and listings of data for vital signs (blood pressure, pulse rate, and body temperature), clinical laboratory tests, 12-lead electrocardiograms (ECG), and physical examination findings are presented. Where applicable, data were summarised for the absolute value at each scheduled assessment, and for the corresponding change from baseline. For clinical laboratory tests, listings of values for each healthy volunteer are presented with abnormal or out-of-range values flagged.

Subject population

A total of 40 healthy volunteers signed informed consent and 15 healthy volunteers (100.0%) received treatment. One healthy volunteer (6.7%) was withdrawn from the study due to non-compliance and 14 healthy volunteers (93.3%) received all planned AZD5069 and ketoconazole administrations and completed the study. Volunteer E0001012 received 1 administration of AZD5069 before withdrawal on Day -2 Period 2.

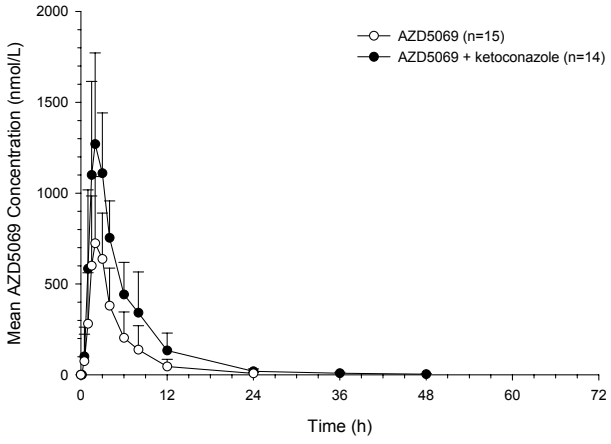
All healthy volunteers were male with an age range of 21 to 44 years (mean 32 years; median 33 years). The body mass index (BMI) ranged from 21.83 to 29.31 kg/m^2 (mean 25.44 kg/m^2; median 25.06 kg/m^2) and the weight from 55.6 to 98.2 kg (mean 78.5 kg; median 77.9 kg), in accordance with the inclusion criteria.

Summary of pharmacokinetic results

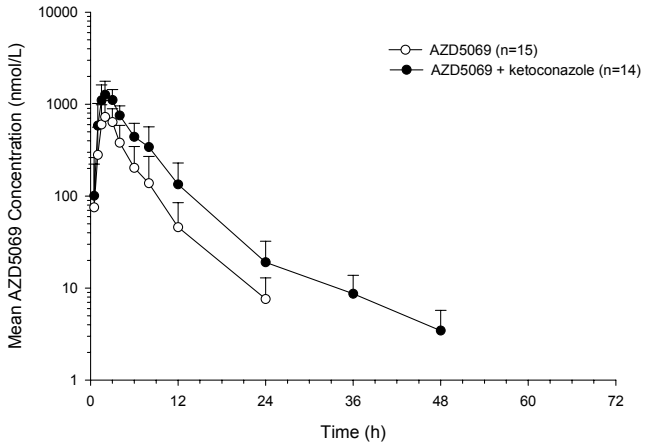
The arithmetic mean (+SD) AZD5069 plasma concentration-time profiles are presented in Figure S1 below. The plasma sampling period was 48 hours postdose in AZD5069 treatment and 72 hours postdose in AZD5069 + ketoconazole treatment.

Figure S1 Arithmetic mean (+SD) plasma concentration (nmol/L) of AZD5069 versus time on linear and semi-logarithmic scales

Linear



Semi-logarithmic



Most subjects' AZD5069 plasma concentrations dropped below quantifiable limits by 48 hours postdose in AZD5069 treatment, and 72 hours postdose in the AZD5069 + ketoconazole treatment.

Point estimates of the geometric least-squares mean ratios and associated 90% confidence intervals for the AZD5069 primary PK parameters are presented in Table S3.

Table S3 Statistical comparison of primary AZD5069 pharmacokinetic parameters

					Pairwise comparison of AZD5069 + ketoconazole to AZD5069	
Parameter	**Treatment[a]**	**n**	**Geometric LS mean**	**95% CI**	**Ratio (%)**	**90% CI**
AUC	AZD5069	15	3068	(2421, 3887)		
(h·nmol/L)	AZD5069 + ketoconazole	14	6480	(5108, 8221)	211.23	(192.37, 231.93)
C_{max}	AZD5069	15	831.5	(704.2, 982.0)		
(nmol/L)	AZD5069 + ketoconazole	14	1370	(1156, 1623)	164.72	(145.27, 186.78)

CI confidence interval; LS least square

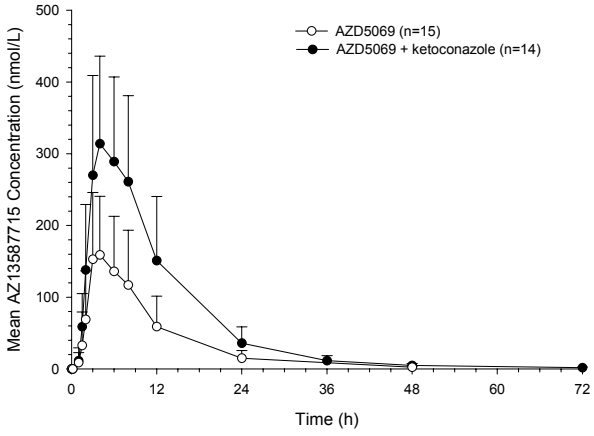
[a] AZD5069: Single 15 mg AZD5069 administration
AZD5069 + ketoconazole: 400 mg ketoconazole administration once daily from Day -2 to Day 3 + a single 15 mg AZD5069 dose on Day 1

The fold increase in AZD5069 systemic exposure when coadministered with ketoconazole (AUC and C_{max}) is less than 5 indicating that AZD5069 is not a sensitive substrate of CYP3A.

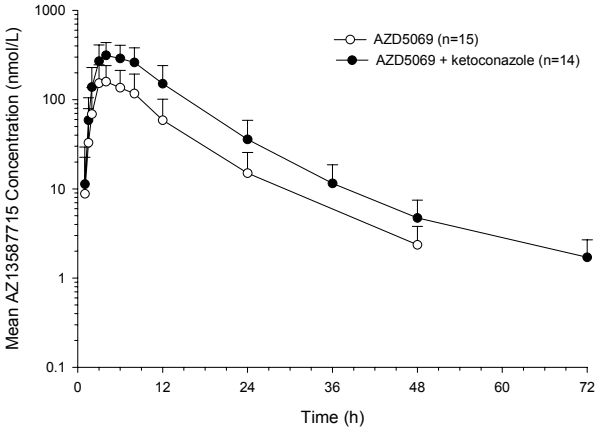
The arithmetic mean (+SD) AZ13587715 plasma concentration-time profiles are presented in Figure S2 below. The plasma sampling period was 48 hours postdose in AZD5069 treatment and 72 hours postdose in AZD5069 + ketoconazole treatment.

Figure S2 Arithmetic mean (+SD) plasma concentration (nmol/L) of AZ13587715 versus time on linear and semi-logarithmic scale

Linear



Semi-logarithmic



Point estimates of the geometric least-squares mean ratios and associated 90% confidence intervals for the AZ13587715 primary pharmacokinetic parameters are presented in Table S4.

Table S4 Statistical comparison of primary AZ13587715 pharmacokinetic parameters and metabolite to parent ratios

					Pairwise comparison of AZD5069 + ketoconazole to AZD5069	
Parameter	**Treatment[a]**	**n**	**Geometric LS mean**	**95% CI**	**Ratio (%)**	**90% CI**
AUC	AZD5069	15	1393	(971.0, 1998)		
(h·nmol/L)	AZD5069 + ketoconazole	14	3389	(2356, 4874)	243.33	(205.88, 287.59)
C_{max}	AZD5069	15	157.1	(120.4, 205.1)		
(nmol/L)	AZD5069 + ketoconazole	14	313.8	(239.6, 411.0)	199.70	(170.83, 233.46)
MRAUC	AZD5069	15	0.4541	(0.3565, 0.5785)		
	AZD5069 + ketoconazole	14	0.5221	(0.4094, 0.6657)	114.96	(105.64, 125.12)
MRC_{max}	AZD5069	15	0.1890	(0.1464, 0.2439)		
	AZD5069 + ketoconazole	14	0.2298	(0.1777, 0.2971)	121.61	(108.71, 136.04)

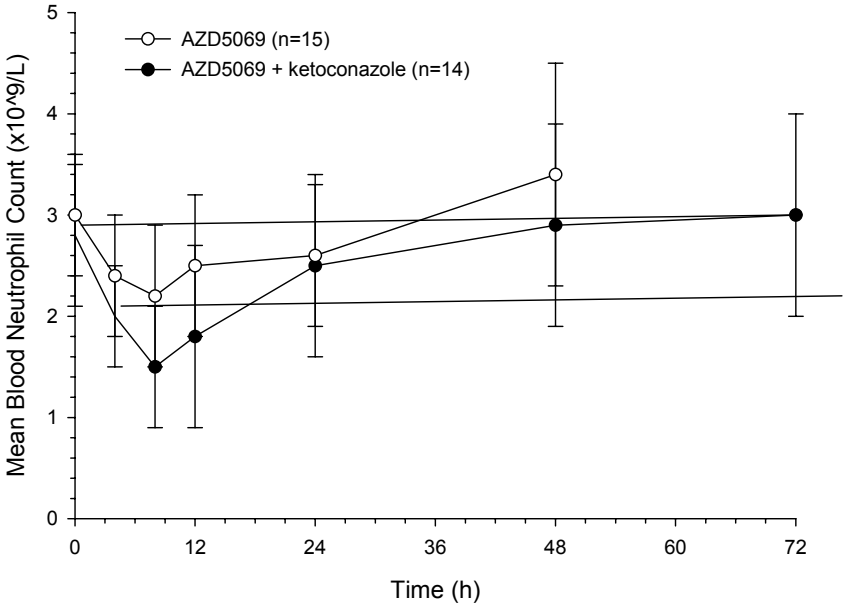
CI confidence interval; MR metabolite ratio

[a] AZD5069: Single 15 mg AZD5069 administration
AZD5069 + ketoconazole: 400 mg ketoconazole administration once daily from Day -2 to Day 3 + a single 15 mg AZD5069 dose on Day 1

Summary of pharmacodynamic results

The arithmetic mean (±SD) blood neutrophil count versus time profiles is presented in Figure S3. Blood neutrophil counts were measured for 48 and 72 hours postdose for AZD5069 and AZD5069 + ketoconazole treatments, respectively.

Figure S3 Arithmetic mean (±SD) blood neutrophil count (x 10^9/L) versus time after AZD5069 dosing for each treatment



The summary statistics of blood neutrophil count pharmacodynamic parameters after a single 15 mg AZD5069 administration with and without ketoconazole are presented in Table S5.

Table S5 Summary of blood neutrophil count pharmacodynamic parameters

Treatment[a]		**ANC_{min} (x 10^9/L)**	**$ANCt_{min}$**[b] **(h)**
AZD5069	Geo mean	1.99	8.00
(n=15)	CV%	33.2	ND
	Minimum	1.00	4.00
	Maximum	3.00	24.00
AZD5069 + ketoconazole	Geo mean	1.25	8.00
(n=14)	CV%	47.4	ND
	Minimum	0.600	4.00
	Maximum	2.30	12.00

CV% geometric coefficient of variation; Geo mean geometric mean; ND not done

[a] AZD5069: Single 15 mg AZD5069 administration
AZD5069 + ketoconazole: 400 mg ketoconazole administration once daily from Day -2 to Day 3 + a single 15 mg AZD5069 dose on Day 1

[b] presented as median

Following coadminstration of AZD5069 and ketoconazole, mean ANC_{min} values were lower compared to AZD5069 administered alone. The median time to minimum blood neutrophil counts was the same for both treatments.

Summary of safety results

No deaths, SAEs, or DAEs were reported. The number of AEs reported was similar between the 2 treatments (AZD5069 and AZD5069+ketoconazole).

All of the AEs were considered to be mild in severity and not related to AZD5069 and/or ketoconazole.

There was an expected decrease in the blood neutrophil count when AZD5069 was administered alone. Coadministration of ketoconazole resulted in a larger decrease.

No clinically important safety laboratory, vital signs, or ECG changes were reported for any healthy volunteer.