Drug Substance(s)	AZD5672	**SYNOPSIS**	(For national authority use only)
Study Code	D1710C00004		
Date	23 August 2007		

A Phase I, 3-part Study to Assess the Safety and Tolerability, Pharmacokinetics (including Food Effect) and Pharmacodynamics of Oral Doses of AZD5672 Following Single and Multiple Doses Administered for up to 28 Days in Healthy Volunteers

Part C: Food Effect

NOTE: This Clinical Study Report documents Part C of the study only. Parts A and B are reported separately.

Study centre

AstraZeneca Clinical Pharmacology Unit, Alderley Park, Macclesfield, Cheshire, SK10 4TG. UK.

Study dates		**Phase of development**
First subject enrolled	5 September 2006	Clinical pharmacology (I)
Last subject completed	7 November 2006	

Objectives (Part C)

Primary

- To investigate the effect of food on the rate and extent of absorption of single oral doses of AZD5672 in healthy volunteers.

Secondary

- To investigate safety and tolerability of single doses of AZD5672 in healthy volunteers in the fed state.

Study design

This Phase I study consisted of 3 separate parts designed to investigate the safety and tolerability, pharmacokinetics (including food effect) and pharmacodynamics of oral doses of AZD5672 administered for up to 28 days in healthy volunteer subjects. This Clinical Study Report documents Part C of the study only. Part C was an open, randomised, 2-period crossover study, conducted at a single centre. Subjects were to receive single oral doses of AZD5672 in the fed and fasted states, in randomised order (fed/fasted or fasted/fed).

Target subject population and sample size

12 Healthy volunteers

Investigational product and comparators: dosage, mode of administration and batch numbers

AZD5672 was supplied as 50 mg capsules, to be dispersed in purified water, and administered as a suspension. Each subject was to receive a single oral dose of 100 mg AZD5672 in the fasted state, and a single oral dose of 100 mg AZD5672 in the fed state.

Batch number: 06-0098734AZ

Duration of treatment

Each subject received a single dose of AZD5672 on 2 occasions separated by a minimum 7-day washout period (the actual washout period was 21 days).

Variables

- **Pharmacokinetic**

  AUC, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, $t_{½}$, t_{max}, CL/F, Vz/F, in the fed and fasted states.

- **Safety**

  Adverse events, clinical chemistry, haematology, urinalysis, 12-Lead ECG, blood pressure, pulse, telemetry, pupillometry.

Statistical methods

Each variable was summarised using standard summary statistics, according to their fed/fasted state or their regimen sequence (fed/fasted or fasted/fed). In addition to these standard summary statistics, the plasma PK parameters of AUC, $AUC_{(0-24)}$, C_{max} and $t_{½}$ under fed and fasted states were examined using an analysis of variance model (ANOVA), fitting for the effects of subject, period and state (fed or fasted). Previous experience suggested that these variables are log-normally distributed and they were therefore logarithmically transformed prior to analysis. The results of the analysis are presented in terms of the geometric least squares means for each state (fed or fasted), the ratio of the geometric least squares means for fed/fasted and the corresponding 90% confidence interval. The t_{max} data were examined using a non-parametric analysis on untransformed data; the food effect, as measured by the difference (fed - fasted), was analysed using a Wilcoxon signed rank test. The Hodges-

Lehman estimator of median food effect was calculated and corresponding 90% confidence intervals constructed. Standard bioequivalence limits (80%, 125%) were used to indicate if there was a trend in the differences between fed and fasted regimens.

Subject population

A total of 12 subjects were randomised, 6 to the fed/fasted sequence and 6 to the fasted/fed sequence; all 12 subjects completed the fed period and 11 subjects completed both the fed and fasted periods of the study. One subject, from the fed/fasted sequence group, prematurely discontinued after Visit 2 due to an AE (mild neutropenia that was not considered to be treatment-related). There were no major protocol deviations and all subjects were included in the safety and per protocol analysis sets. All subjects were Caucasian. The treatment sequence groups (fed/fasted and fasted/fed) were balanced for gender (3 males and 3 females in each), and the mean age was 43 years (see Table S1). Subject height, weight and BMI were comparable between the sequence groups.

Table S1 Subject population and disposition

		Treatment Sequence		
Characteristic	**Statistic**	**Fed/Fasted (n=6)**	**Fasted/Fed (n=6)**	**Total (n=12)**
Sex	N	6	6	12
(n (%) subjects)	Male	3 (50%)	3 (50%)	6 (50%)
	Female	3 (50%)	3 (50%)	6 (50%)
Race	N	6	6	12
(n (%) subjects)	Caucasian	6 (100%)	6 (100%)	12 (100%)
Age	N	6	6	12
(years)	Mean	45	41	43
	SD	5.8	5.5	5.7
	Median	46	44	44
	Minimum	35	32	32
	Maximum	52	46	52
Randomised				12 (100%)
Received Treatment		6 (100%)	6 (100%)	12 (100%)
Completed Study		5 (83%)	6 (100%)	11 (92%)
Prematurely Discontinued (Adverse Event)		1 (17%)	0 (0%)	1 (8%)

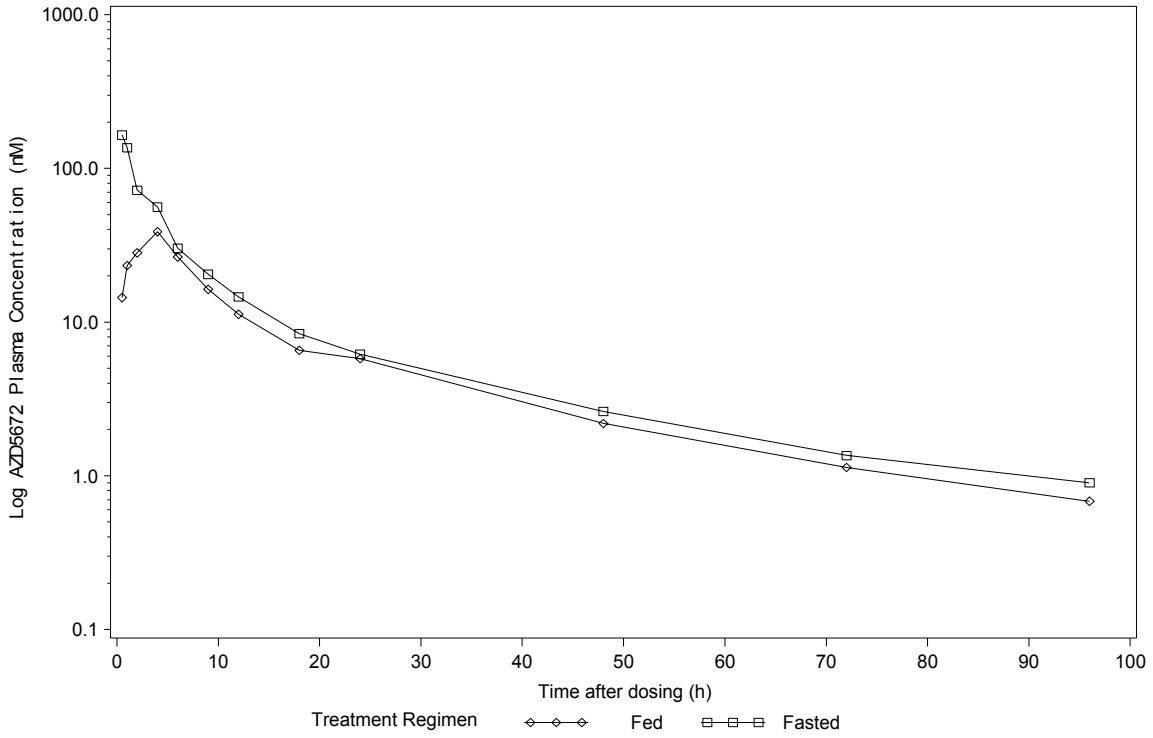
Summary of pharmacokinetic results

The mean plasma concentrations of AZD5672 over time for the fed and fasted regimens are shown in Figure S1, and key pharmacokinetic parameters are summarised in Table S2.

Following a high fat meal the rate of absorption of an oral dose of AZD5672 (100 mg) in healthy volunteers was reduced (median t_{max} increased from 0.5 h to 4.0 h). The extent of absorption was also lower when AZD5672 was administered after food compared with administration in the fasting state, and the variability in exposure (C_{max} and AUC) was greater in the fasted state (see Table S2). There was a trend towards a decrease in the half life following food, but no evidence that C_{24h} was affected. For one subject (Subject 502) who vomited post-dose there was a marked reduction in $t_{1/2}$ in the fed state.

Figure S1 Mean AZD5672 concentration against time by regimen (fed or fasted)

Study Code D1710-C00004 userid(tetlow_s) 12APR2007 17:1
Data as of : 05MAR2007
Figure 11.2.4 : Plot of log of mean AZD5672 concentration against time by regimen (Fed or Fasted)
Safety Analysis Set



Reference : pk09 Page 1 of 1

Table S2 Summary of plasma pharmacokinetic parameters of AZD5672

Regimen	Parameter	N	Geometric mean	CV (%)	Arithmetic mean	SD	Median	Min	Max
Fed	C_{max} (nM)	12	34.63	69.45	40.63	22.22	41.95	10.3	87.0
	C_{24h} (nM)	12	5.502	34.08	5.788	1.945	5.285	3.20	9.64
	t_{max} (h)	12	NA	NA	NA	NA	4.00	1.0	6.0
	AUC (nM.h)	12	513.7	37.59	546.3	208.2	520.4	283	1042
	$AUC_{(0-t)}$ (nM.h)	12	488.1	38.92	521.1	203.3	495.6	259	1001
	$AUC_{(0-24)}$ (nM.h)	12	342.9	40.67	367.3	143.7	348.9	159	704
	$t_{1/2}$ (h)	12	22.53	21.98	22.97	4.184	23.50	12.3	28.6
	CL/F (L/h)	12	304.3	37.59	322.7	114.6	301.3	150	551
	V_z/F (L)	12	9891	35.76	10431	3446	9278	5236	15468
Fasted	C_{max} (nM)	11	142.1	76.76	177.5	138.4	149.0	52.5	538
	C_{24h} (nM)	11	5.283	56.12	6.171	4.621	4.410	3.12	19.4
	t_{max} (h)	11	NA	NA	NA	NA	0.50	0.5	4.0
	AUC (nM.h)	11	768.9	54.53	893.1	661.9	664.7	465	2792
	$AUC_{(0-t)}$ (nM.h)	11	733.6	54.94	853.0	631.8	645.2	439	2661
	$AUC_{(0-24)}$ (nM.h)	11	584.3	54.13	676.8	493.8	511.2	342	2088
	$t_{1/2}$ (h)	11	25.28	25.94	26.08	7.361	24.89	18.2	44.1
	CL/F (L/h)	11	203.3	54.53	223.3	83.93	235.1	56.0	336
	V_z/F (L)	11	7412	49.72	8108	3376	7366	2569	14698

Min minimum; Max maximum.

C_{max} decreased by 77% [90% CI 67% to 84%] after food; the ratio of GLS means (fed/fasted) was 0.23 (90%CI 0.163 to 0.331) (Table S3). After food the AUC decreased by 35% [90% CI 21% to 47%]); the ratios of GLS means (fed/fasted) for AUC and $AUC_{(0-24)}$ were 0.65 (90% CI 0.533 to 0.786) and 0.57 (90% CI 0.458 to 0.699), respectively. These results suggest that the extent of absorption was lower when AZD5672 was administered after food compared with administration in the fasting state. The Hodges-Lehman Estimator for the difference in t_{max} (fed – fasted) was 2.76 h (90%CI 2.00 to 3.50), indicating a delay in absorption in the fed state (Table S4). There was a trend towards decrease in half-life following food (decrease of 13%, 90% CI (-2.3%, 25.2%); the ratio of GLS means for $t_{1/2}$ was 0.87 and the 90%CI (0.748 to 1.023) (Table S3). This potential effect was of a smaller magnitude than that observed for AUC and C_{max}.

Table S3 Statistical analysis of AZD5672 PK parameters following a single oral 100mg dose in the fed and fasted states (Per protocol analysis set)

	Treatment Regimen										
	100mg Fasted (n=11)				100mg Fed (n=12)						
	N	GLS mean	Lower 90% CI	Upper 90% CI	N	GLS mean	Lower 90% CI	Upper 90% CI	Ratio Fed / Fasted	Lower 90% CI	Upper 90% CI
AUC (nM.h)	11	777.8	678.4	891.7	11	503.6	439.2	577.3	0.65	0.533	0.786
$AUC_{(0-24)}$ (nM.h)	11	590.8	509.1	685.5	11	334.3	288.1	387.9	0.57	0.458	0.699
C_{max} (nM)	11	143.9	112.2	184.5	11	33.4	26.1	42.9	0.23	0.163	0.331
$t_{1/2}$ (h)	11	25.4	22.8	28.4	11	22.2	19.9	24.8	0.87	0.748	1.023

GLS mean=Geometric least squares mean CI=Confidence interval
GLS means and CIs were obtained from an ANOVA model fitting for the effects of subject, period and regimen (fed or fasted)
Subject 505 has been excluded from the analysis because she only completed the fed period.

Table S4 Statistical analysis of AZD5672 t_{max} following a single oral 100mg dose in the fed and fasted states (Per protocol analysis set)

	Treatment Regimen										
	100mg Fasted n=11				100mg Fed n=12						
	N	Median	Min	Max	N	Median	Min	Max	Difference Fed-Fasted[a]	Lower 90% CI	Upper 90% CI
t_{max} (h)	11	0.50	0.50	4.00	11	4.00	1.00	6.00	2.75	2.00	3.50

CI Confidence interval; Min minimum; Max maximum.
a The Hodges-Lehman estimator
Subject 505 has been excluded from the analysis because she only completed the fed period.

Summary of pharmacodynamic results (not applicable)

No pharmacodynamic variables were measured.

Summary of pharmacokinetic/pharmacodynamic correlations (not applicable)

No pharmacodynamic variables were measured.

Summary of population pharmacokinetics (not applicable)

No population pharmacokinetic analysis was performed.

Summary of pharmacogenetics

A single blood sample was taken from each subject to provide pharmacogenetic data for the AZD5672 project that can be pooled with genetic data from other AZD5672 studies for exploration of the influence of genotype on variability in PK disposition, PD response, tolerability and safety. No pharmacogenetic data are reported here.

Summary of safety results

There were no deaths, SAE or other significant AE during the study (Table S5). Adverse events were most commonly reported in the System Organ Classes (SOCs) 'Nervous System Disorders' (50% subjects, mainly headache) and 'Infections and Infestations' (33% subjects, mainly viral upper respiratory tract infection). More subjects reported AE in the fasted state but there was no marked difference between the fed and fasted treatment regimens in the types of AE reported. One subject in the fed/fasted sequence group discontinued treatment due to an AE of mild neutropenia after the first single dose of ADZ5672 (100 mg, in the fed state). The neutropenia was considered to be unrelated to study drug but, as it was a clinically significant haematological abnormality, it precluded the subject's continued participation in the study.

Except for one subject with neutropenia, there were no clinically important changes from baseline in the mean or individual values of any other laboratory parameter. Thus there was no evidence of an effect of AZD5672 on haematology, clinical chemistry or urinalysis variables, in either the fed or fasted state.

There did not appear to be any evidence of an effect of AZD5672 on vital signs or ECG, in either the fed or fasted state. There was no clear effect of treatment on pupil diameter that might indicate an anti-muscarinic effect in either the fed or fasted state.

Table S5 Number (%) of subjects who had an adverse event in any category (safety analysis set)

Category of adverse event	Fed n=12	Fasted n=11
	Number (%) subjects	Number (%)subjects
SAE	0 (0%)	0 (0%)
Deaths	0 (0%)	0 (0%)
Discontinued Study Drug due to AE	1 (8%)	0 (0%)
Other Significant AE	0 (0%)	0 (0%)
Any AE[a]	6 (50%)	9 (82%)
Total Number of AE's	14	22

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.