Clinical Study Report Synopsis

Drug Substance	AZD4721
Study Code	D5200C00001
Edition Number	1
Date	07 July 2014

A Phase I Single-blind, Randomised, Placebo-controlled, Single-centre Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Oral AZD4721 Solution After Single Ascending Doses, and to Compare the Oral Bioavailability of Single Doses of Solution and Suspension in Healthy Subjects

Study dates:	First subject enrolled: 19 July 2013
	Last subject last visit: 16 December 2013
Phase of development:	Clinical pharmacology (I)

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

Publications

Not Applicable.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Safety	To assess the safety and tolerability of AZD4721, including blood neutrophils, following administration of oral single doses and estimate the maximum tolerated dose (MTD) of AZD4721 if within the predefined exposure and dose limits (Part A).	AEs; vital signs, including blood pressure, heart rate and body temperature; ECGs; clinical chemistry; haematology assessments, including serial blood neutrophil counts and urinalysis.
Secondary	PK	To characterise the pharmacokinetics (PK) of AZD4721, including assessment of dose proportionality, following oral administration of single ascending doses of AZD4721 (Part A). To estimate the bioavailability of AZD4721 in suspension formulation relative to that in oral solution formulation (Part B).	AZD4721 and its carboxylic acid metabolite: Part A and Part B: C_{max}, t_{max}, $t_{½\lambda z}$, λ_z, AUC, $AUC_{(0-24)}$, $AUC_{(0-last)}$; CL/F (AZD4721 only), V_z/F (AZD4721 only), MRT (AZD4721 only), t_{lag} (AZD4721 only), AUC/D, C_{max}/D, $t_{½(eff)}$, t_{last}, $R_{ac,pred}$, λ_z,Interval and λz,N, Rsq, $\%AUC_{ex}$, MRAUC, and MRC_{max}. Part B: RC_{max}, $F_{rel.}$

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
	PD	To characterize the pharmacodynamics (PD) of AZD4721, as assessed by growth-regulated oncogene-alpha (GRO-α) induced expression of cluster of differentiation molecule 11B (CD11b) on blood neutrophils, including characterisation of the dose and concentration response relationship (Part A).	Dose ratio (GRO-α induced CD11b) values (Part A).
Exploratory	PD	To explore the pharmacodynamics of AZD4721, as assessed by the CXCR2 ligands interleukin 8 and growth-regulated oncogene-alpha including characterisation of the dose and concentration response relationship.	Serum Ill-8 and GRO-α: absolute values at each time point; percentage of change from baseline (baseline defined as morning predose value on Day 1) at each time point.
		To collect blood samples for possible genetic research. These data will not form part of the clinical study report for this study and are aimed at identifying/exploring genetic variations that may affect the pharmacokinetic, pharmacodynamic, safety, and tolerability profile related to AZD4721 treatment.	Pharmacogenetics
		To investigate the presence and/or identity of drug metabolites of AZD4721 and, if appropriate, characterise their pharmacokinetics	

AUC: Area under plasma concentration-time curve from time zero extrapolated to infinity; $AUC_{(0-24)}$: Area under the plasma concentration-time curve from time zero to 24 hours after dosing; $AUC_{(0-last)}$: Area under plasma concentration-time curve from zero to time of last quantifiable analyte concentration; $\%AUC_{ex}$: Percentage of AUC obtained by extrapolation; AUC/D: Dose-adjusted area under the plasma concentration-time curve from time zero extrapolated to infinity; C_{max}: Maximum plasma (peak) drug concentration after single dose

administration; CL/F: Oral clearance of drug from plasma; C_{max}/D: Dose-adjusted observed maximum plasma concentration; F_{rel}: Relative bioavailability; MRT: Mean residence time; MRAUC: Ratio of metabolite AUC to parent AUC; MRC_{max}: Ratio of metabolite C_{max} to parent C_{max}; $R_{ac,pred}$: Predicted accumulation ratio; Rsq: Regression coefficient for calculation of the terminal rate constant; RC_{max}: Comparison of maximum plasma concentration; t_{max}: Time to reach peak or maximum concentration; $t_{½}\lambda_z$: Terminal half-life; $t_{½(eff)}$: Effective half-life; t_{last}: Time of last quantifiable plasma concentration; Vz/F: Oral volume of distribution (apparent) during terminal (λ_z) phase; λ_z,Interval: Time interval included in the log-linear regression to determine terminal half-life; λ_z N: Number of data points included in the log-linear regression to determine terminal half-life

Study design

Part A

Part A was a Phase I, first-in-human, randomised, single-blind, placebo-controlled single ascending dose (SAD) study in which single ascending orally administered doses of AZD4721 solution formulation was to be investigated in 8 sequential cohorts with an optional additional 3 cohorts, conducted at a single study centre, in healthy Caucasian male and female volunteers of non-childbearing potential. There were 29 volunteers in AZD4721 group and 9 volunteers in the placebo group participated in dose escalation part of the study in maximum of 5 cohorts. Within each cohort, 6 volunteers were randomised to receive AZD4721 and 2 volunteers to placebo with exception of the cohort 3 (150 mg), where 5 volunteers were randomised to AZD4721 and 1 volunteer to placebo. A total of 5 dose levels were included for dose escalations in this study. The starting dose was 19 mg. Following completion of each dose level, an SRC evaluated the safety (a minimum of 96 hours postdose data), PK and PD data before commencing the next dose level. The provisional dose levels included in the study were 19 mg, 50 mg, 150 mg, 350 mg, and 730 mg. An interval of at least 10 days between the last administration of the dose in the previous dose level and the first administration of the dose in the next dose level separated the investigation of dose levels to permit a timely review and evaluation of data prior to proceeding to the next dose level. Dose escalations were to continue up to the MTD.

Following a 28 days screening period, the volunteers were admitted to the clinical study centre 1 day prior to dosing (Day -1). Volunteers remained resident in the study centre under medical supervision until discharge on Day 5 (provided a blood neutrophil level $\geq 1.5 \times 10^9$/L was reached). Discharge from the study centre was followed by the volunteers returning to the study centre for PK, PD, and safety sampling on Day 7 (Visits 3) and a follow-up visit (Visit 4) on/or between Days 10 to 14 postdose.

Part B:

Part B was an open-label, randomised, 2-way crossover relative bioavailability study in healthy Caucasian male and female volunteers of non-childbearing potential, randomised to 2 treatment sequences where single dose of orally administered AZD4721in suspension formulation was compared to single dose of orally administered AZD4721 in solution formulation. There were 6 volunteers randomised to 2 treatment sequences and each volunteer received a total of 2 dose administrations of AZD4721 (1 oral dose of AZD4721 suspension formulation and 1 oral dose of AZD4721 solution formulation). Each volunteer participated in 2 treatment periods. A washout period of at least 10 days separated the

2 treatments periods. The dose used for Part B was 500 mg AZD4721 (in solution and suspension formulation).

Following a 28 days screening period, the volunteers were admitted to the study centre 1 day prior to dosing (Day -1). Volunteers remained resident in the study centre under medical supervision until discharge on Day 5 and returned on Day 7 (Visits 3) for PK sampling and safety assessments.

Following the washout period of at least 10 days between doses, volunteers returned to the study centre and were admitted on Day -1 of Period 2 (Visit 4). The second dose was administered on Day 1 of Period 2 (Visit 4). Volunteers remained resident in the study centre under medical supervision until discharge on Day 5 and returned for assessments on Day 7 (Visit 5) following the second administration. Visit 5 assessments corresponded to the Visit 3 assessments. Volunteers returned to the study centre for final follow-up visit assessments on Days 10 to 14 (Visit 6) of Period 2.

Target subject population and sample size

Up to 112 healthy Caucasian male and/or female volunteers of non-childbearing potential aged 18 to 50 years (inclusive) with body mass indices (BMI) between 18 and 30 kg/m^2 (inclusive) and weights between 50 and 100 kg (inclusive) were to be enrolled in this 2-part study with up to 100 volunteers in Part A (dose escalation) and up to 12 volunteers in Part B (relative bioavailability); however only 44 healthy male volunteers were randomised across Part A and Part B, as the overall voting members in SRC agreed that AZD4721 had been well tolerated and was confirmed that Part A was complete and no further dose levels were required.

Part A:

A total of 38 healthy male volunteers were randomised in Part A to AZD4721 or placebo, such that for the first 2 volunteers in each cohort, 1 received AZD4721 and 1 received placebo and all 38 received the treatment and completed the study.

Part B:

A total of 6 volunteers were randomised in Part B, to 1of the 2 treatment sequences and all 6 volunteers received the treatment and completed the study.

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

Table S2 Details of investigational product

Investigational product	Dosage form and strength	Manufacturer	Packaging Lot No./Lot ID
AZD4721[a]	9 mg/mL liquid solution	AstraZeneca	13-001408AZ/ 13-001232AZ

Table S2 Details of investigational product

Investigational product	Dosage form and strength	Manufacturer	Packaging Lot No./Lot ID
AZD4721[b]	9 mg/g liquid suspension	AstraZeneca	13-002062AZ/ 13-001725AZ
Placebo[c]	Liquid solution	AstraZeneca	13-001410AZ/ 13-001234AZ

[a] For the dose escalation part of the study (Part A), and for the dose level to be included in Part B
[b] For the relative bioavailability part of the study (Part B). No placebo included
[c] For the comparator in the dose escalation part of the study (Part A)

The investigational product (IP) was supplied centrally by AstraZeneca as study specific labelled bulk. Details of the batch numbers were included in the trial master file.

Duration of treatment

Part A:

The duration of the study for each volunteer was up to 42 days, including a screening period of at least 2 and up to 28 days; a residential treatment period of 5 days (from check-in on Day -1 until discharge on Day 5); 1 outpatient visit for PK, PD, and safety assessments; and a final follow-up visit 10 to 14 days postdose administration.

Part B:

The duration of the study for each volunteer was up to 60 days, including a screening period of at least 2 and up to 28 days; 2 residential treatment periods of 5 days each (from check-in on Day -1 until discharge on Day 5) including 1 outpatient visit for PK, PD, and safety assessments (separated by at least 10 days between doses); and a final follow-up visit 10 to 14 days postdose administration in Period 2.

Statistical methods

The analyses were performed using Quintiles' Standard Operating Procedures and Work Instructions. SAS® Version 9.2 (SAS Institute, Inc., Cary, North Carolina, United States) was used for all analyses and preparation of tables and listings.

Due to the exploratory nature of the study, the sample size was not based on formal statistical considerations. All statistical testing in this study were exploratory.

For Part A, dose proportionality of AZD4721 was assessed graphically and was analyzed using the power model approach with the logarithm of PK parameters AUC and C_{max}. The intercept α and the slope β together with 90% confidence intervals were estimated and presented for AUC and C_{max}.

For Part B, to assess the relative bioavailability of the suspension versus the solution, the PK parameters C_{max} and AUC of AZD4721 were analysed using an analysis of variance model on

the log-transformed PK parameters. Transformed back from the logarithmic scale, geometric means together with 2-sided 95% confidence intervals for AUC and C_{max} were estimated. Also, ratios of geometric means, together with 2-sided 90% confidence intervals of AZD4721 suspension formulation and AZD4721 in solution formulation, were estimated.

All recorded blood neutrophil counts are listed. The absolute value, along with change and percentage change from baseline were summarised.

The relationship between AZD4721 plasma concentration and effect on blood neutrophil counts are presented graphically. In addition, PK-PD correlations for CD11b (DR_{20}), IL8, and GRO-α were explored graphically.

Adverse events were summarised by Preferred Term and System Organ Class using the Medical Dictionary for Regulatory Activities (Version 16.1) by dose/treatment group. Furthermore, listings of serious adverse events and adverse events that led to discontinuation were made and the number of volunteers who had any adverse events, serious adverse events, adverse events that led to discontinuation, and adverse events with severe intensity were summarised.

Tabulations, listings, and figures (electrocardiograms only) of data for vital signs, clinical laboratory tests, electrocardiograms, 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 volunteer are presented with abnormal or out-of-range values flagged.

Subject population

Part A:

All 38 volunteers were healthy males aged 21 to 50 years and their BMI ranged from 24.94 to 29.92 kg/m^2. All volunteers completed the study.

Part B:

All 6 volunteers were healthy males aged 31 to 44 years and their BMI ranged from 21.56 to 28.92 kg/m^2. All volunteers completed the study.

Summary of efficacy results

Not applicable.

Summary of pharmacokinetic results

The predefined maximum exposure limit applied to mean values for $AUC_{(0-24)}$ (2340 h*µmol/L) and C_{max} (350 µmol/L), was not reached at 730 mg. Peak AZD4721 plasma concentrations occurred at 1 hour, and the mean apparent elimination half-life ranged from 22.8 hours to 25.6 hours.

Table S3 Summary of pharmacokinetic parameters of AZD4721 for Part A

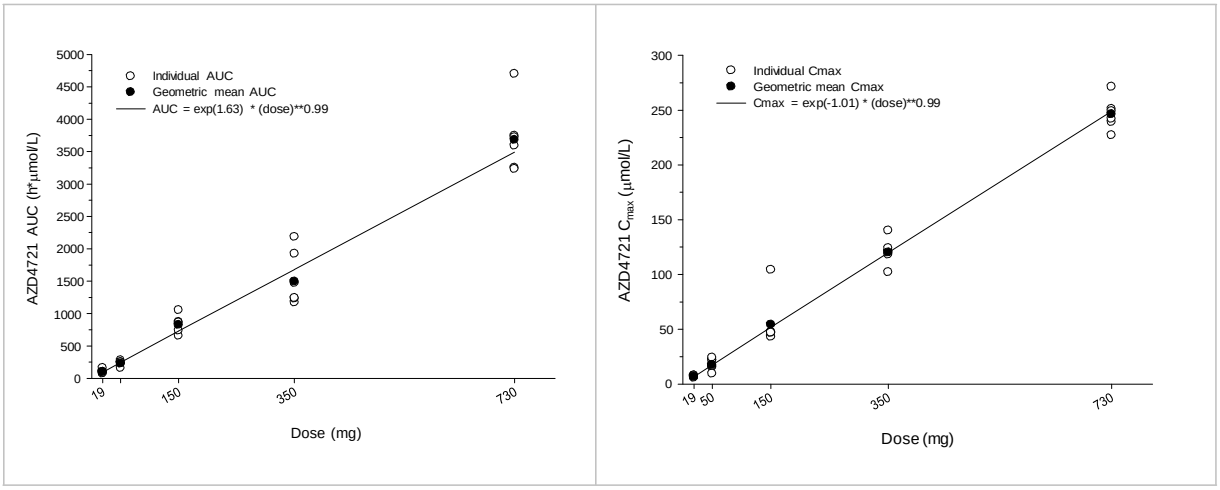
Variable	Dose[a]	n	Geometric mean	Geometric CV (%)	Arithmetic mean	SD	Min	Median	Max
AUC	19 mg	6	97.5	27.9	101	29.9	72.4	94.3	155
(h*µmol/L)	50 mg	6	226	19.8	230	39.9	155	242	273
	150 mg	5	823	18.0	833	150	656	856	1050
	350 mg	6	1490	26.5	1540	420	1170	1360	2180
	730 mg	6	3680	13.7	3710	536	3230	3660	4700
$AUC_{(0-24)}$	19 mg	6	60.2	17.5	60.9	10.6	47.3	62.8	77.3
(h*µmol/L)	50 mg	6	137	21.9	139	27.8	92.6	138	176
	150 mg	5	483	12.1	486	61.9	436	477	591
	350 mg	6	1020	18.4	1040	193	819	961	1280
	730 mg	6	2270	8.1	2280	188	2090	2260	2610
C_{max}	19 mg	6	6.72	11.6	6.76	0.771	5.64	6.61	7.65
(µmol/L)	50 mg	6	17.3	36.0	18.1	5.49	9.40	18.9	24.1
	150 mg	5	54.1	38.0	57.6	26.0	43.1	46.8	104
	350 mg	6	120	10.2	121	12.2	102	121	140
	730 mg	6	246	5.9	247	14.7	227	246	271
t_{max}	19 mg	6	NA	NA	NA	NA	1.00	1.00	1.03
(hour)	50 mg	6	NA	NA	NA	NA	0.67	1.03	2.00
	150 mg	5	NA	NA	NA	NA	0.33	1.03	2.02
	350 mg	6	NA	NA	NA	NA	1.02	1.03	1.03
	730 mg	6	NA	NA	NA	NA	0.67	1.03	2.03
$t_{1/2}$	19 mg	6	22.8	28.3	23.6	6.51	15.4	21.6	31.5
(hour)	50 mg	6	23.9	8.7	24.0	2.11	21.3	23.6	27.3
	150 mg	5	25.6	20.8	26.0	5.12	18.9	25.7	31.7
	350 mg	6	23.0	18.9	23.4	4.40	18.5	23.1	29.8
	730 mg	6	23.9	17.8	24.2	4.67	20.0	23.1	33.1
$t_{1/2(eff)}$	19 mg	6	17.1	22.0	17.5	3.96	13.3	16.6	24.1
(hour)	50 mg	6	17.9	10.1	18.0	1.81	16.0	17.9	20.1
	150 mg	5	18.7	14.2	18.9	2.47	14.7	20.1	20.6
	350 mg	6	14.2	20.9	14.4	2.95	10.5	15.0	19.0
	730 mg	6	17.2	16.2	17.4	2.68	13.2	17.4	20.5

CV: Coefficient of variation; Max: Maximum; Min: Minimum; NA: Not applicable; SD: Standard deviation

[a] Single ascending oral administration of AZD4721 in solution

The systemic exposure of AZD4721 (AUC and C_{max}) appeared to increase proportionally to the dose from 19 mg to 730 mg (Figure 1). The relationships were well described by a power model, predicting a 37–fold increase in exposure with a 38.4-fold increase in dose (19 mg to 730 mg).

Figure 1 **AUC (h*µmol/L) and C_{max} (µmol/L) versus dose of AZD4721 (pharmacokinetic analysis set)**



The statistical details of dose proportionality assessment are presented in Table S4.

Table S4 **Assessment of dose proportionality for AZD4721 in Part A (pharmacokinetic analysis set)**

		Intercept			Slope			
Variable	**n**	**Estimate**	**SE**	**90% CI**	**Estimate**	**SE**	**90% CI**	**Coefficient of determination**
AUC (h*µmol/L)	29	1.63	0.16	(1.36, 1.90)	0.99	0.03	(0.94, 1.04)	0.9738
C_{max} (µmol/L)	29	-1.01	0.15	(-1.27, -0.75)	0.99	0.03	(0.94, 1.04)	0.9750

CI: Confidence interval; SE: Standard error

Summary PK parameters for AZ13622093, a carboxylic acid metabolite of AZD4721, are presented in Table S5.

Table S5 Summary of pharmacokinetic parameters of AZ13622093 for Part A (pharmacokinetic analysis set)

Variable	Dose[a]	n	Geometric Mean	Geometric CV (%)	Arithmetic mean	SD	Min	Median	Max
AUC	19 mg	6	28.1	31.1	29.3	10.5	21.5	26.4	49.9
(h*µmol/L)	50 mg	6	51.0	39.7	54.0	18.0	30.1	60.4	70.4
	150 mg	5	126	94.8	153	83.0	34.3	206	219
	350 mg	6	480	40.6	514	223	337	458	922
	730 mg	6	801	49.4	879	431	436	717	1600
$AUC_{(0-24)}$	19 mg	6	5.41	27.1	5.55	1.26	3.26	5.97	6.85
(h*µmol/L)	50 mg	6	9.36	35.2	9.84	3.51	6.09	9.76	16.0
	150 mg	5	26.1	87.6	31.4	18.1	7.96	34.8	55.3
	350 mg	6	137	35.9	145	55.5	93.1	132	247
	730 mg	6	180	34.5	188	55.5	99.2	196	264
C_{max}	19 mg	6	0.290	24.1	0.297	0.0628	0.188	0.311	0.370
(µmol/L)	50 mg	6	0.595	34.9	0.622	0.187	0.338	0.659	0.810
	150 mg	5	1.38	86.0	1.65	0.899	0.417	1.84	2.72
	350 mg	6	7.36	35.8	7.75	2.87	4.88	7.10	12.8
	730 mg	6	9.44	40.3	9.98	3.26	4.75	10.8	13.8
t_{max}	19 mg	6	NA	NA	NA	NA	9.03	18.52	36.00
(hour)	50 mg	6	NA	NA	NA	NA	5.02	11.05	24.05
	150 mg	5	NA	NA	NA	NA	9.00	18.00	24.02
	350 mg	6	NA	NA	NA	NA	7.02	9.00	18.03
	730 mg	6	NA	NA	NA	NA	9.00	13.01	24.13
$t_{1/2}$	19 mg	6	53.0	30.1	54.9	15.6	34.9	53.6	73.0
(hour)	50 mg	6	65.1	50.5	73.1	46.1	43.6	57.9	166
	150 mg	5	52.2	8.1	52.3	4.20	47.7	53.0	56.6
	350 mg	6	43.9	26.3	45.2	12.6	32.8	42.8	68.2
	730 mg	6	53.1	25.2	54.6	14.2	40.9	52.7	79.0

CV: Coefficient of variation; Max: Maximum; Min: Minimum; NA: Not applicable; SD: Standard deviation
[a] Single ascending oral administration of AZD4721 in solution

Summary of PK parameters for Part B is presented in Table S6.

Table S6 Summary of pharmacokinetic parameters of AZD4721 for Part B (pharmacokinetic analysis set)

Variable	Treatment[a]	n	Geometric mean	Geometric CV (%)	Arithmetic mean	SD	Min	Median	Max
AUC	suspension	6	1610	41.1	1730	760	990	1570	3150
(h*µmol/L)	solution	6	2970	36.4	3140	1240	2160	2670	5370
$AUC_{(0-24)}$	suspension	6	777	20.7	791	164	587	759	1050
(h*µmol/L)	solution	6	1660	17.0	1680	288	1350	1620	2080
F_{rel}	suspension	6	0.544	23.8	0.556	0.125	0.383	0.585	0.736
	solution		-	-	-	-	-	-	-
C_{max}	suspension	6	55.1	18.1	55.9	9.77	44.1	57.8	66.3
(µmol/L)	solution	6	167	12.1	168	20.0	140	169	193
RC_{max}	suspension	6	0.329	25.5	0.338	0.0815	0.228	0.352	0.456
	solution		-	-	-	-	-	-	-
t_{max}	suspension	6	NA	NA	NA	NA	2.00	2.00	3.12
(hour)	solution	6	NA	NA	NA	NA	0.67	1.00	1.20
$t_{1/2}$	suspension	6	29.1	25.8	30.0	8.60	23.3	27.1	46.4
(hour)	solution	6	28.2	18.9	28.6	5.77	24.0	26.1	38.8

CV: Coefficient of variation; Max: Maximum; Min: Minimum; NA; Not applicable; SD: Standard deviation
[a] Treatment A: single dose of AZD4721 500 mg suspension formulation administered orally
Treatment B: single dose of AZD4721 500 mg solution formulation administered orally

The AZD4721 systemic exposure (AUC and C_{max}) after administration of the suspension formulation was appreciably less than the systemic exposure after administration of the solution formulation. The statistical details of the relative bioavailability of the suspension versus the solution at the 500 mg dose level are presented in Table S7.

Table S7 Statistical comparison of key pharmacokinetic parameters of AZD4721 in Part B (pharmacokinetic analysis set)

					Pairwise Comparisons		
Variable	Treatment[a]	n	Geometric LS mean	95% CI	Pair	Ratio (%)	90% CI
AUC	suspension	6	1494	(959.6, 2327)	susp/soln	50.78	(45.87, 56.21)
(h*µmol/L)	solution	6	2943	(1890, 4583)			
C_{max}	suspension	6	52.33	(47.17, 58.05)	susp/soln	30.66	(27.48, 34.21)
(µmol/L)	solution	6	170.7	(153.9, 189.3)			

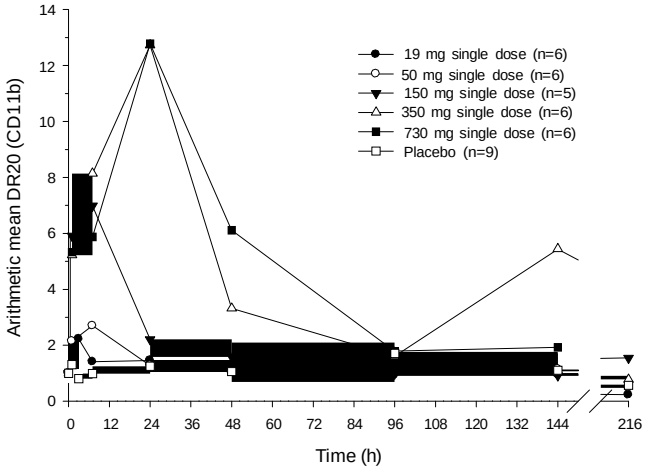
CI: Confidence interval; LS: Least squares; soln: Solution; susp: Suspension

[a] Treatment A: single dose of AZD4721 500 mg suspension formulation administered orally
Treatment B: single dose of AZD4721 500 mg solution formulation administered orally

Summary of pharmacodynamic results

Mean dose ratio (GRO-α induced CD11b) values versus time are illustrated for Part A below in Figure 2.

Figure 2 Arithmetic mean dose ratio (GRO-α induced CD11b) versus time, by AZD4721 dose in Part A (pharmacodynamic analysis set)



Summary of pharmacokinetic/pharmacodynamic relationships

The relationship between mean dose ratio (GRO-α induced CD11b) values and mean AZD4721 plasma concentrations indicates a delayed response (peak dose ratio values occurred after peak AZD4721 concentration values)

Summary of blood neutrophil parameters

No volunteer in this study had a blood neutrophil count $<0.5 \times 10^9$/L. Also, no volunteer receiving placebo or a dose of AZD4721 19 mg, 50 mg, or 350 mg had a blood neutrophil count $<1.5 \times 10^9$/L. After receiving a 150 mg AZD4721 dose, a volunteer had a minimum blood neutrophil count (ANC_{min}) of 0.9×10^9/L, and after receiving a 730 mg dose, 3 volunteers had ANC_{min} values of 1.3×10^9/L, 1.2×10^9/L, and 0.9×10^9/L. In Part B (500 mg AZD4721 dose) a volunteer had ANC_{min} value of 1.2×10^9/L after administration of the solution.

Mean blood neutrophil count and percentage change from baseline are plotted against time for Part A (see Figure 3 and Figure 4).

Figure 3 **Arithmetic mean blood neutrophil count versus time, by AZD4721 dose in Part A (safety analysis set)**

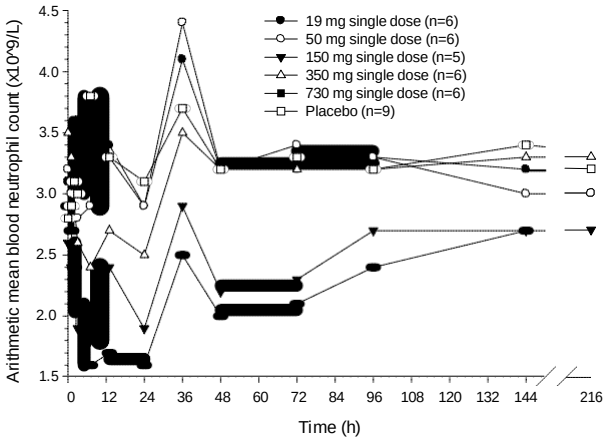
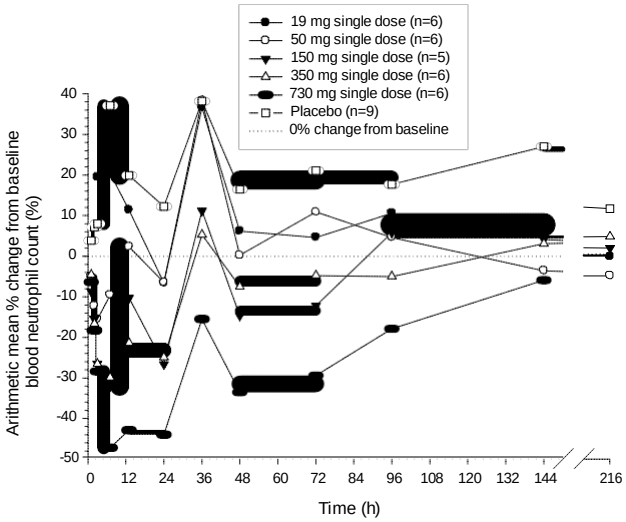


Figure 4 **Arithmetic mean percent change from baseline blood neutrophil count versus time, by AZD4721 dose in Part A (safety analysis set)**



Summary parameters for blood neutrophil count values (Part A and Part B) are presented in **Error! Reference source not found.**

Table S8 **Descriptive statistics for blood neutrophil parameters in Part A and Part B (safety analysis set)**

Variable	Study part[a]	Dose	n	Arithmetic mean	SD	Min	Median	Max
ANC_{min} (10^9/L)	Part A	placebo	9	2.7	0.6	1.9	2.5	4.0
		19 mg	6	2.7	0.6	1.7	2.7	3.4
		50 mg	6	2.5	0.5	2.0	2.4	3.3

Table S8 **Descriptive statistics for blood neutrophil parameters in Part A and Part B (safety analysis set)**

Variable	Study part[a]	Dose	n	Arithmetic mean	SD	Min	Median	Max
		150 mg	5	1.7	0.5	0.9	1.7	2.3
		350 mg	6	2.0	0.3	1.6	2.1	2.3
		730 mg	6	1.4	0.4	0.9	1.4	1.9
	Part B	suspension	6	2.1	0.2	1.7	2.2	2.3
		solution	6	1.7	0.3	1.2	1.8	2.0
$ANCt_{min}$ (hour)	Part A	placebo	9	ND	ND	1.02	3.02	216.03
		19 mg	6	ND	ND	24.02	24.09	216.00
		50 mg	6	ND	ND	2.00	15.56	216.02
		150 mg	5	ND	ND	3.03	7.03	24.25
		350 mg	6	ND	ND	3.00	5.08	216.17
		730 mg	6	ND	ND	7.02	7.03	24.13
	Part B	suspension	6	ND	ND	3.00	18.50	48.00
		solution	6	ND	ND	6.98	7.00	7.03

Max: Maximum; Min: Minimum; ND: Not determined; SD: standard deviation

[a] Part A: Single ascending oral administration of AZD4721 as solution (or placebo)
Part B: Treatment A: single dose of AZD4721 500 mg suspension formulation administered orally
Treatment B: single dose of AZD4721 500 mg solution formulation administered orally.

Figure 5 **Individual ANC_{min} values versus individual AZD4721 AUC values in Part A (safety analysis set)**

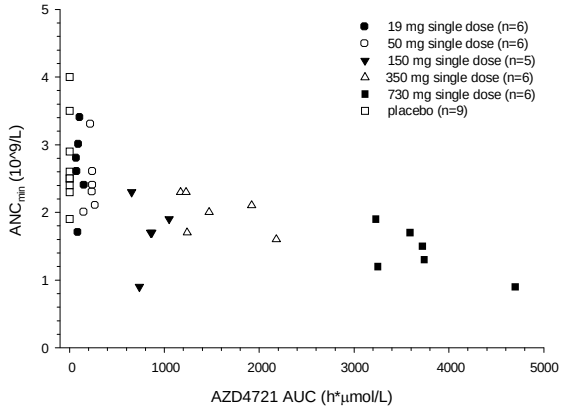
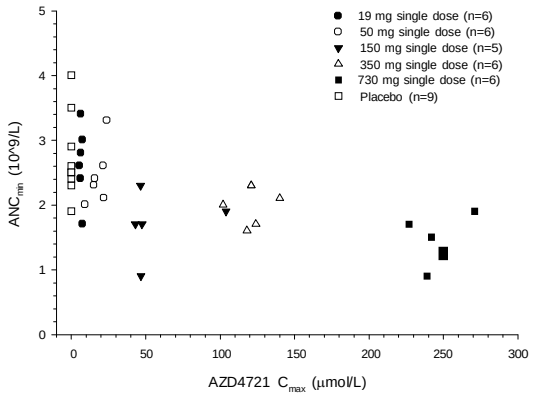


Figure 6 Individual ANC_{min} values versus individual AZD4721 C_{max} values in Part A (safety analysis set)



Summary of safety results

Part A:

- No deaths, serious adverse events, or DAEs, were reported in this study
- Overall, a similar number of volunteers reported AEs for all AZD4721 dose groups and placebo
- The majority of AEs were considered to be mild. Moderate AEs were reported by 2 volunteers in cohort 2 (50 mg) and cohort 3 (350 mg). No severe AEs were reported. All AEs resolved
- No trends were observed in haematology, biochemistry, and urinalysis parameters, apart from the expected reduction in blood neutrophil counts, for any volunteer during the study.
- No relevant trends were observed over time and between treatments in mean or median vital signs values
- No volunteers showed any abnormal variations in QT interval corrected using Fridericia's formula (QTcF) values and no trends were evident in mean HR, QRS, QTcF, or PR intervals in the AZD4721 or placebo groups. Abnormal 12-lead ECG readings were reported, but none were considered to be clinically significant
- No abnormal physical examination findings or concomitant medication use were reported

Part B:

- No deaths, serious adverse events, or DAEs, were reported in this study

- Overall, at least 1 AE was reported for 3 volunteers (50.0%) in Part B. Volunteer E0002008 reported 2 AEs (1 each in Treatment A and Treatment B), and Volunteers E0002004 and E0002010 reported 1 AE each in Treatment B. All AEs were considered to be mild in intensity and majority of AEs resolved

- Majority of AEs were not related to the IP. Only 1 AE, abdominal pain, was considered to be related to the IP administration

- No trends were observed in haematology, biochemistry, and urinalysis parameters, apart from the expected reduction in blood neutrophil counts, for any volunteer during the study

- No relevant trends were observed over time and between treatments in mean or median vital signs values

- No abnormal physical examination findings or concomitant medication use were reported