AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD4721
Study Code	D5200C00002
Edition Number	1
Date	

A Phase I Study in Healthy Volunteers to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AZD4721 after Once Daily Administration of Multiple Ascending Doses for 10 days, and an Open-label Comparison with the Pharmacodynamics of AZD5069 Given Twice Daily for 3 days

Study dates: First subject enrolled: 21 December 2013
Last subject last visit: 03 June 2014

Phase of development: Clinical Pharmacology (I)

International 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

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	Safety	To investigate the safety and tolerability of AZD4721, particularly change in blood neutrophil counts, following administration of multiple ascending doses at steady state.	AEs, vital signs, ECGs, laboratory variables including ANC ratio, $ANC_{min,Day\ 1}$, $ANC_{tmin,Day\ 1}$, $ANC_{min,ss}$, $ANC_{tmin,ss}$, $ANC_{mean,ss}$, $ANC_{min\ ratio,Day\ 1}$, $ANC_{min\ ratio,ss}$, and $ANC_{mean\ ratio,ss}$.
Secondary	Pharmacokinetic	To characterise the PK of AZD4721 following oral administration of multiple ascending doses, including assessment of the time required to reach steady state, the degree of accumulation, and potential dose and time dependencies of the PK.	**Part-A**: C_{max}, C_{max}/D, t_{max}, AUC_{tau}, t_{lag}, MRAUC, MRC_{max}, $C_{ss,max}/D$, $t_{ss,max}$, $C_{ss,min}$, $t_{ss,min}$, $C_{ss,av}$, $C_{ss,max}/C_{ss,min}$, $AUC_{ss,tau}/D$, CL/F, V_z/F, $C_{ss,max}$, λ_z, $t_{1/2\lambda z}$, $AUC_{ss,tau}$, $MRAUC_{ss,tau}$, $MRC_{ss,max}$, $RAUC_{tau}$, RC_{max}, $Ae_{(0\text{-}tau)}$, $fe_{(0\text{-}tau)}$, CL_R **Part-B**: Part-B:$C_{ss,max}$, $t_{ss,max}$, $C_{ss,min}$, $t_{ss,min}$, $C_{ss,av}$, $C_{ss,max}/C_{ss,min}$, $AUC_{tau,morning}$, $AUC_{tau,evening}$, $AUC_{(0\text{-}24)}$, $AUC_{ss,tau}$, CL/F
	Pharmacodynamic	To assess the induction potential of AZD4721 on cytochrome P450 3A by measuring 4-β-hydroxy-cholesterol at baseline and at steady state.	CD11b blood assays (inhibition of GROα-induced CD 11b)
		To characterise the pharmacodynamics of AZD4721 as assessed by GRO-α induced expression of cluster of differentiation molecule 11B on blood neutrophils ex vivo, including characterisation of the dose and concentration response relationship.	

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
		To compare the effects of AZD4721 administered once daily (od) and AZD5069 administered twice daily (bd) on blood neutrophil counts and growth-regulated oncogene α induced expression of cluster of differentiation molecule 11B on blood neutrophils.	

AE: adverse event; $Ae_{(0\text{-}tau)}$: cumulative amount of AZD4721 and AZ13622093 excreted over the dosing interval; ANC ratio: ratio of post treatment value to baseline; $ANC_{min\ Day\ 1}$: minimum of ANC during the 0 to 24 hours after the first dose; $ANCt_{min,Day\ 1}$: time to reach ANC_{min}; $ANC_{min,ss}$: minimum of ANC from predose to 24 hours after the last morning dose; $ANCt_{min,ss}$: time to reach ANC_{min} from predose to 24 hours after the last morning dose; $ANC_{mean,ss}$: mean of ANC from predose to 24 hours after the last morning dose; $ANC_{min\ ratio,Day\ 1}$: minimum of ANC ratio during the 0 to 24 hour after first dose; $ANC_{min\ ratio,ss}$: minimum of ANC ratios calculated predose to 24 hours after the last morning dose; $ANC_{mean\ ratio,ss}$: mean of ANC ratios calculated pre-dose to 24 hours after the last morning dose; $AUC_{(0\text{-}24)}$: area under the plasma concentration-time curve 0 to 24 hours post morning dose, calculated as $AUC_{tau,morning} + AUC_{tau,evening}$; AUC_{tau}: area under the plasma concentration-time; $AUC_{tau,morning}$: area under the plasma concentration-time curve during the 12 hour dosing interval after the morning dose (µmol*h/L); $AUC_{tau,evening}$: area under the plasma concentration-time curve during the 12 hour dosing interval after the evening dose (µmol*h/L); $AUC_{ss,tau}$: area under the plasma concentration-time curve during a dosing interval at steady state; $AUC_{ss,tau}/D$: area under the steady state plasma concentration-time curve during the dosing interval divided by the dose administered; C_{max}: maximum observed concentration in plasma; C_{max}/D: observed maximum plasma concentration on Day 1 divided by the dose administered on Day 1; $C_{ss,av}$: average concentration over the dosing interval tau (µmol/L); $C_{ss,max}$: observed maximum concentration at steady state (µmol/L); $C_{ss,min}$: observed minimum concentration at steady state (µmol/L); CL/F: apparent clearance (L/h); CL_R: renal clearance; $C_{ss,max}/C_{ss,min}$: peak to trough concentration ratio; CSP: clinical study protocol; ECG: electrocardiogram; $fe_{(0\text{-}tau)}$: fraction of dose excreted into the urine over the dosing interval; MR: metabolite to parent ratio; MRAUC: ratio of metabolite AUC to parent AUC; MRC_{max}: ratio of metabolite C_{max} to parent C_{max}; $MRC_{ss,max}$: ratio of metabolite $C_{ss,max}$ to parent $C_{ss,max}$; $MRAUC_{ss,tau}$: ratio of metabolite $AUC_{ss,tau}$ to parent $AUC_{ss,tau}$; PK: pharmacokinetics; $t_{ss,max}$: time to reach observed maximum concentration at steady state(h); t_{max}: time to C_{max}; $t_{ss,min}$: time of observed minimum concentration at steady state (h); λz: terminal rate constant (1/h); $RAUC_{tau}$: accumulation ratio for AUC_{tau}; RC_{max}: accumulation ratio for C_{max}; t½: apparent terminal half-life; $t_{1/2\lambda z}$: terminal half-life (h); t_{lag}: amount of time from dosing to the time corresponding to the first measurable concentration, lag-time (h); V_z/F: oral volume of distribution (apparent) during terminal phase

Study design

This phase I study comprised 2 parts, 1 conventional multiple ascending dose (MAD) study (Part A), and 1 pharmacodynamic (PD) comparison between AZD4721 and AZD5069 (Part B).

Part A (Dose escalation)

This was a phase I, randomised, single-blind placebo-controlled, parallel-group, MAD study in healthy male and female, of non-childbearing potential, volunteers conducted at a single study centre. AZD4721 or placebo was administered, orally, od for 10 days.

The study design allowed a gradual escalation of dose with intensive safety monitoring to ensure the safety of the healthy volunteers. Approximately 27 healthy volunteers aged 18 to 50 years participated in 3 cohorts, randomised to AZD4721:placebo in a 6:3 ratio within each cohort. If the maximum tolerated dose (MTD) was not defined and the maximum allowed exposure had not reached after 3 cohorts, up to an additional 2 cohorts would be added, ie, up to 45 healthy volunteers. Because of the potential risk that cyclodextrin (a major excipient in both AZD4721 and placebo solutions) might cause gastrointestinal side effects, up to 3 additional healthy volunteers receiving placebo may be added to a cohort in order to compare adverse events (AEs) more directly. Hence, up to 48 healthy volunteers in total were administered the investigational product in Part A. The maximum allowed exposure was 350 µmol/L for observed maximum plasma concentration (C_{max}) and 2340 µmol*h/L for the area under the plasma concentration-time curve during a dosing interval at steady state ($AUC_{ss,tau}$) (mean group values within the cohort).

Following completion of each dose level, the safety data up to a minimum of 96 hours following the last investigational product administration, and available/relevant AZD4721 plasma PK and PD data were reviewed by a Safety Review Committee (SRC) (Section 3.1.2 of the clinical study protocol [CSP]) who would determine the next dose level. If possible all randomised healthy volunteers per cohort were included in the review, with a minimum of 4 volunteers on active treatment and 1 volunteer on placebo. The SRC recommended additional healthy volunteers to receive placebo in a cohort if adverse gastrointestinal effects were reported.

There was a minimum period of 10 days between the final investigational product administration of the previous cohort and the first investigational product administration of the next cohort.

The total duration for a healthy volunteer participating in Part A was approximately 7 to 8 weeks. Each healthy volunteer were enrolled in a single cohort.

Healthy volunteers were assessed for eligibility during screening (Visit 1) from 28 to 2 days before start of the investigational product administration on Day 1 (Visit 2). Volunteers remained in the study centre from Day -1 up to Day 12 (Visit 2) and were discharged on Day 12 if they had a blood neutrophil count of at least 1.5 x 10^9/L.

The planned duration of the investigational product administration, the residential period (at least 96 hours following the last investigational product administration in Part A), PK sampling period (216 hours), and follow-up period (at least 7 days) were based on a predicted half-life of 42 hours, but would be altered if the observed half-life from the initial cohort(s) in the single ascending dose (SAD) D5200C00001 study differs significantly from the expected half-life of AZD4721.

Part B

Part B was an open-label, non-randomised, sequential study in healthy male and female of non-childbearing potential volunteers, to compare the effect on blood neutrophil counts of AZD4721 administered od with that of AZD5069 administered bd.

Part B commenced following a satisfactory review by the SRC of the safety, PK, and PD data from Part A. The dose of AZD5069 (30 mg bd) and AZD4721 (382 mg od), for Part B was provided by AstraZeneca following SRC approval. The dose level of AZD4721 was anticipated to be approximately equipotent to the AZD5069 dose, as estimated by the receptor occupancy at the trough concentration[1]. The main purpose of this was to compare the effect on blood neutrophils using AZD4721 and AZD5069 at equipotent doses (Section 3.2.1 of CSP).

The number of healthy volunteers to be enrolled in Part B was guided by the Part A results. The estimation was that at least 12 healthy volunteers need to complete Part B.

Healthy volunteers were assessed for eligibility during screening (Visit 1) from 28 to 2 days before start of AZD5069 administration (Visit 2). Eligible volunteers were admitted to the study centre on Day -1 and remained in the study centre up to Day 4 (Visit 2). Healthy volunteers received AZD5069 orally, once in the morning and once in the evening (12 hours apart) from Day 1 up to Day 3, at least 1 hour after a light meal. A second meal was provided 2 hours after AZD5069 administration. Volunteers were discharged on Day 4.

The Follow-up Visit (Visit 4) was planned for 7 to 10 days after the last administration of investigational product, ie, Day 18 to 21.

The total duration for a healthy volunteer participating in Part B was approximately 9 to 10 weeks.

Blood samples (predose, 0 to 24 hours) were collected for AZD4721, AZ13622093, and AZD5069 PK evaluation. Pharmacodynamic assessments included GRO-α induced CD11b on blood neutrophils expression and exploratory GRO-α and IL-8.

Target subject population and sample size

Healthy Caucasian male and female of non-childbearing potential volunteers aged 18 to 50 years were planned to be enrolled in this study.

[1] Receptor occupancy was estimated by *in vitro* assessment of the dose-response curves of GRO-α induced expression of CD11b on blood neutrophils, in the presence and absence of antagonist. DR20 values were calculated and pA2 values were estimated from Schild plots (7.9 for AZD5069 and 5.5 for AZD4721). The doses selected were approximately 7 x A2 for both compounds in order to obtain a significant change in blood neutrophils.

Part A (Dose escalation): Approximately 27 healthy volunteers (3 cohorts consisting of 9 volunteers were randomised with an option of an additional 2 cohorts, eg, up to 45 healthy volunteers). Additionally up to 3 volunteers receiving placebo were added to a cohort to compare AEs more directly.

Part B (PD comparison): At least 12 healthy volunteers (to be guided by results of Part A).

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

Table S2 Details of investigational product

Investigational product	Dosage form and strength	Manufacturer	Batch number
AZD4721[a,b]	9 mg/mL oral solution	AstraZenenca	11-2014
Placebo[a]	Placebo oral solution	AstraZenenca	09-2016
AZD5069[b]	Capsules 5 mg and/or 20 mg	AstraZenenca	02-2015 and 10-2015

a Part A
b Part B

Duration of treatment

Part A

The total duration for a healthy volunteer participating in a cohort was approximately 7 to 8 weeks. The volunteers received investigational product from Day 1 to Day 10 after randomisation.

Part B

The total duration for a healthy volunteer participating in Part B was approximately 9 to 10 weeks. The volunteers received AZD5069 orally bd for 3 days, followed by AZD4721 orally od for 10 days. The 2 treatment periods were separated by a washout period of at least 6 days between the investigational product administrations.

Statistical methods

For Part A and Part B blood neutrophil counts, line plots, and descriptive summaries were presented for the whole treatment periods as well as for the 24 hours after the last morning investigational product administration. Analyses were performed by fitting a mixed-effect linear model for natural log transformed minimum of ANC from predose to 24 hours after the last morning dose ($ANC_{min,ss}$), mean of ANC from predose to 24 hours after the last morning dose ($ANC_{mean,ss}$), minimum of ANC ratios calculated predose to 24 hours after the last morning dose ($ANC_{min\ ratio,ss}$), and mean of ANC ratios calculated predose to 24 hours after the last morning dose ($ANC_{mean\ ratio,ss}$). Transformed back from the logarithmic scale, the estimates of the geometric means from the fitted model, together with corresponding 95%

confidence intervals (CI) (2-sided) are presented. Also the ratio of the geometric means for AZD5069 versus AZD4721 was presented together with corresponding 95% CI (2-sided).

For Part A only, dose proportionality of AZD4721 was assessed graphically and was analysed using the power model approach for the logarithm of pharmacokinetic parameters, $AUC_{ss,tau}$, and maximum concentration at steady state ($C_{ss,max}$). The intercept α and the slope β together with 90% CIs will be estimated and presented for $AUC_{ss,tau}$, C_{max}, and $C_{ss,max}$.

Additionally, for each dose level separately, a linear mixed-effect analysis of variance (ANOVA) model for the logarithm of $AUC_{ss,tau}$ and AUC_{tau} (or $C_{ss,max}$ and C_{max}) was performed to assess AZD4721 accumulation following multiple dosing. Transformed back from the logarithm scale, geometric means together with CIs (2-sided 95%) was estimated and the ratios of geometric means together with CIs (2-sided 90%) for $AUC_{ss,tau}$ (Day 10)/AUC_{tau} (Day 1) and $C_{ss,max}$ (Day 10)/C_{max} (Day 1) was estimated and presented.

Subject population

A total of 27 male volunteers were randomised in Part A of this study and 12 male volunteers in Part B. All volunteers in Part A completed the study. Four volunteers discontinued from the study during Part B: withdrawal by subject (Volunteers E001013, E001018, E0010120) and protocol deviation (Volunteer E001014).

Volunteer E001014, discontinued from Part B of the study due to a protocol deviation of testing positive for drug abuse at admission to the study centre.

All volunteers in Part A were healthy white males aged 22 to 50 years and their BMI ranging from 20.26 to 29.66 kg/m^2.

In Part B of the study, all volunteers were heathy white males aged 29 to 48 years and their BMI ranging from 21.12 to 27.15 kg/m^2.

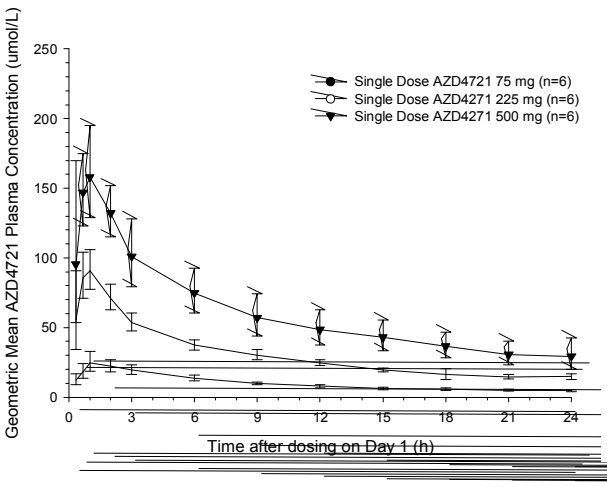
Summary of pharmacokinetic results

The predefined AZD4721 maximum exposure limit for $AUC_{ss,tau}$ (2340 h*µmol/L) and C_{max} (350 µmol/L) were not reached. Peak plasma concentrations occurred at approximately 1 to 1.5 hour, and the mean apparent elimination half-life was 21 to 24 h after 10 days of od administration across all 3 dose levels. The ratio between peak and trough concentration during a 24 hour administration interval on Day 10 was on average 4-to 5-fold.

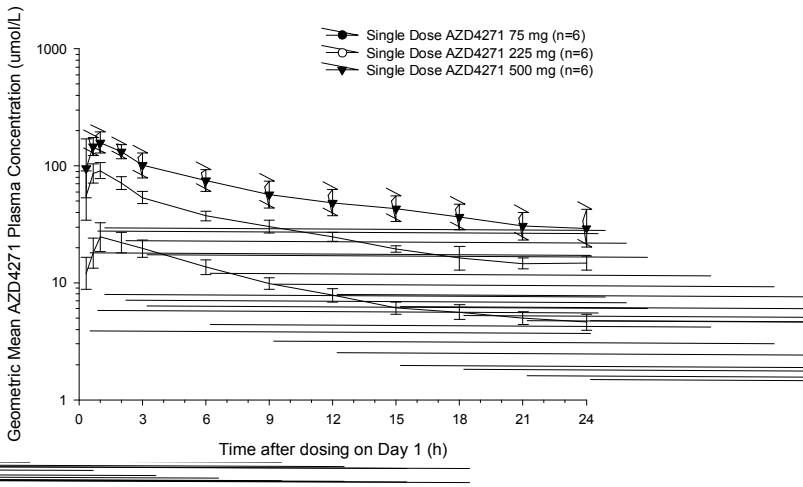
The plasma concentration versus time profiles, following administration of AZD4721 as an oral solution, were characterised by a rapid absorption phase and the curves declined in parallel, see Figure S1.

Figure S1 Geometric mean (±SD) plasma concentration (µmol/L) of AZD4721, Day 1 and Day 10 versus time by treatment, Part A

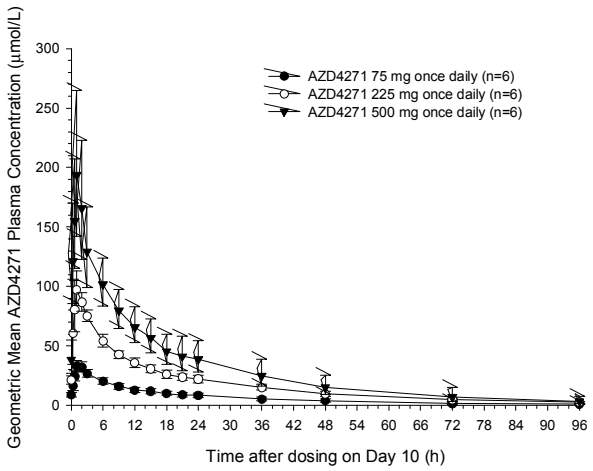
Day 1 – Linear



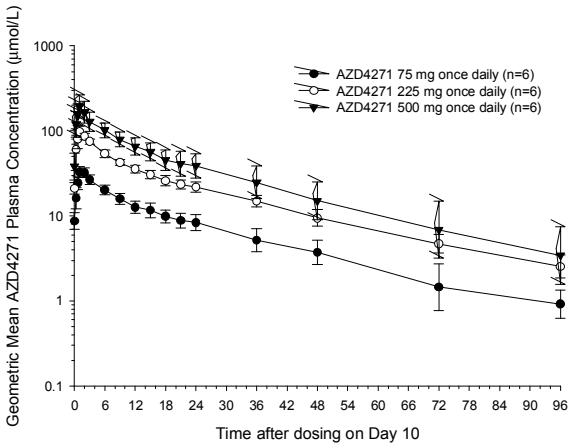
Day 1 – Semi-logarithmic



Day 10 - Linear



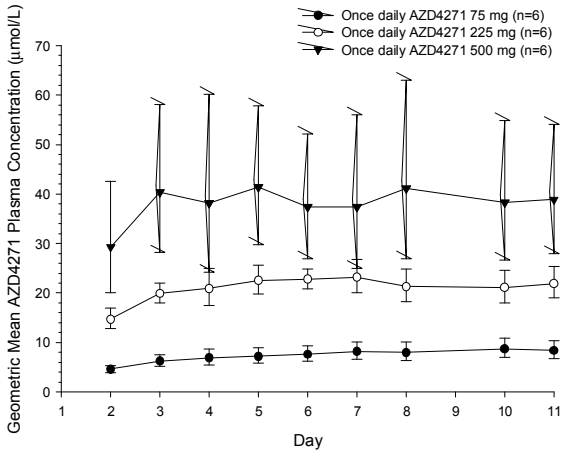
Day 10 – Semi-logarithmic



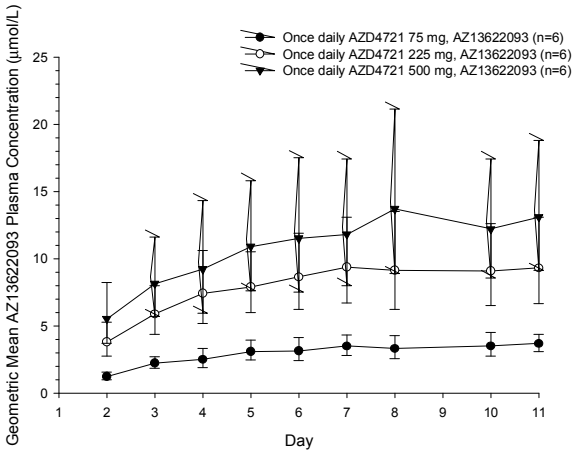
The geometric mean trough concentrations for AZD4721 and AZ13622093 are presented in Figure S2.

Figure S2 Geometric mean (±SD) plasma trough concentrations (µmol/L) of AZD4721 and AZ13622093 versus day by treatment, Part A

AZD4721



AZ13622093



The AZD4721 accumulation was lower than expected from single-dose data. The mean accumulation ratio (Day 10/ Day 1) was 1.05 to 1.29 based on C_{max} and 1.32 to 1.56 based on AUC_{tau} (see Table S3)

Table S3 Statistical comparison of key pharmacokinetic parameters to assess accumulation, (Day 10/Day 1) of AZD4721 (Pharmacokinetic analysis set), Part A

AZD4721 Dose (Unit)[a]	PK parameter	n	Geometric LS mean	Geometric LS mean 95% CI	Point estimate of geometric mean ratio of Day 10/Day 1 (%)	90% CI of geometric mean ratio of Day 10/Day 1
75 mg	AUC_{tau}	6	239.9	(213.4, 269.6)		
	$AUC_{ss,\tau au}$	6	373.4	(332.2, 419.7)	155.66	(141.78, 170.90)
	C_{max}	6	25.79	(21.04, 31.63)		
	$C_{ss,max}$	6	33.33	(27.19, 40.87)	129.23	(114.00, 146.50)
225 mg	AUC_{tau}	6	738.9	(671.9, 812.6)		
	$AUC_{ss,\tau au}$	6	1022	(929.1, 1124)	138.27	(129.13, 148.07)
	C_{max}	6	93.89	(81.26, 108.5)		
	$C_{ss,max}$	6	98.21	(85.01, 113.5)	104.61	(88.70, 123.36)
500 mg	AUC_{tau}	6	1433	(1133, 1812)		
	$AUC_{ss,\tau au}$	6	1886	(1492, 2386)	131.67	(121.23, 143.02)
	C_{max}	6	165.0	(126.0, 216.1)		
	$C_{ss,max}$	6	196.1	(149.8, 256.8)	118.85	(100.26, 140.88)

CI: confidence interval; LS: least squares
[a] AZD4721 or placebo was administered, orally, od for 10 days

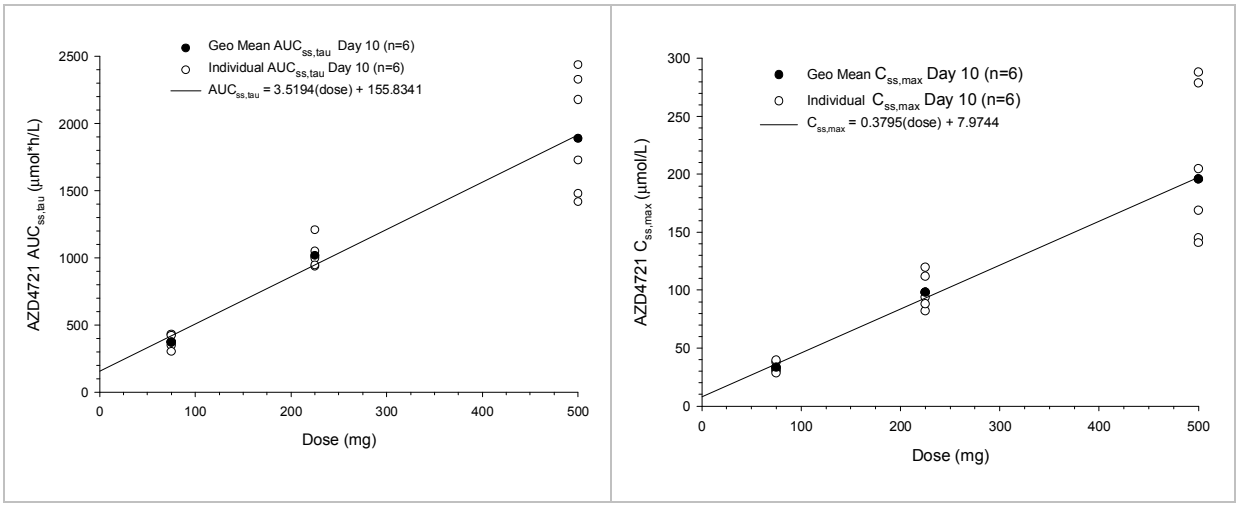
The systemic exposure (AUC and C_{max}) appeared to increase in a dose proportional manner across the 75 mg to 500 mg dose levels for $C_{ss,max}$ and only slightly less than proportional for $AUC_{ss,tau}$ on Day 10 (Table S4 and Figure S3).

Table S4 Statistical assessment of dose proportionality of AZD4721

			Slope			Intercept			
Study Day	PK parameter	n	Estimate	SE	90% CI	Estimate	SE	90% CI	Coefficient of Determination
Day 1	AUC_{tau}	18	0.95	0.05	(0.86, 1.03)	1.42	0.26	(0.97, 1.87)	0.9605
	C_{max}	18	0.99	0.07	(0.86, 1.12)	-0.96	0.40	(-1.66, -0.27)	0.9186
Day 10	$AUC_{ss,\tau au}$	18	0.86	0.05	(0.77, 0.94)	2.24	0.27	(1.78, 2.70)	0.9495
	$C_{ss,max}$	18	0.94	0.06	(0.83, 1.05)	-0.52	0.34	(-1.12, 0.07)	0.9323

CI: confidence interval; SE: standard error

Figure S3 **$AUC_{ss,tau}$ (h*µmol/L) and $C_{ss,max}$ (µmol/L) versus dose of AZD4721 (Pharmacokinetic analysis set)**



4-β-hydroxy-cholesterol concentrations were measured predose on Day 1 and Day 10 to assess the induction potential of AZD4721 on cytochrome P450 3A. For placebo and all 3 AZD4721 dose levels, the mean concentrations of 4-β-hydroxy-cholesterol were very similar from Day 1 to Day 10 and across all treatments and days, the geometric mean concentrations ranged from 21.6 to 26.7 ng/mL.

Summary of pharmacodynamic results

Dose ratio (GRO-α induced CD11b on blood neutrophils) was generally greater after AZD4721 administration compared to placebo. Mean IL-8 percent change from baseline values increased with increasing AZD4721 dose and were greater than placebo on Day 1 of Part A. On Day 10 of Part A, the percent change in IL-8 response appeared to level off at the 225 mg AZD4721 dose level with similar percent change in IL-8 values observed at the 225 mg and 500 mg dose levels. Mean GRO-α percent change from baseline values increased with increasing AZD4721 dose and were greater than placebo on Day 1 and Day 10 of Part A.

For Part B, the dose ratio (GRO-α induced CD11b on blood neutrophils), IL-8 percent change from baseline, and GRO-α percent change from baseline values versus time are provided in Figure S4, Figure S5, and Figure S6.

Figure S4 **Arithmetic mean (±SD) dose ratio (GRO-α induced CD11b on blood neutrophils), AZD5069, Day 3 after morning and evening doses, and AZD4721, Day 10, versus time (Pharmacodynamic analysis set), Part B**

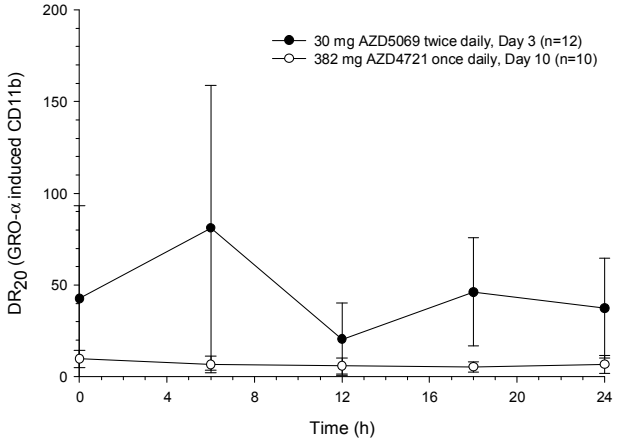


Figure S5 **Arithmetic mean (±SD) IL-8 percent change from baseline, AZD5069, Day 3 after morning and evening doses, and AZD4721, Day 10, versus time (Pharmacodynamic analysis set), Part B**

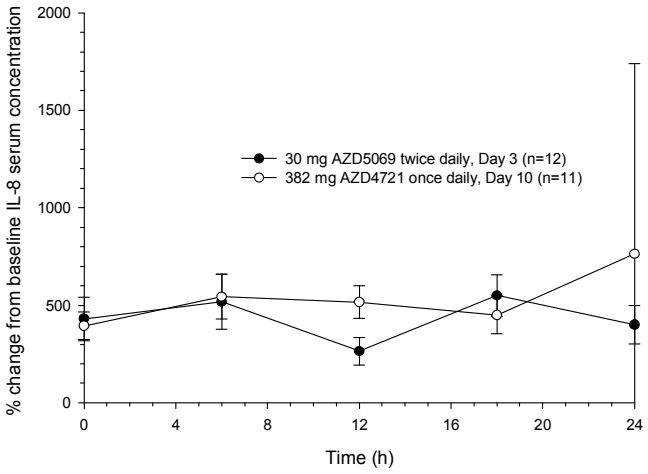
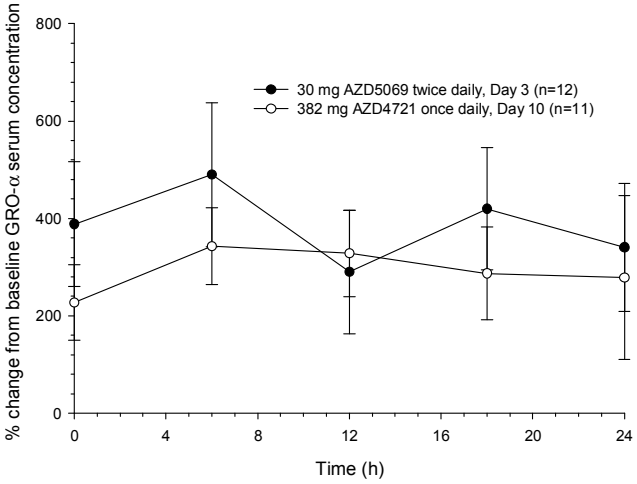


Figure S6 **Arithmetic mean (±SD) GRO-α percent change from baseline, AZD5069, Day 3 after morning and evening doses, and AZD4721, Day 10, versus time (Pharmacodynamic analysis set), Part B**



Summary of pharmacokinetic/pharmacodynamic relationships

The relationship between individual $ANC_{mean\ ratio,ss}$ parameters and AZD4721 PK parameters is explored below in Figure S7, and Figure S8 for Part A.

Figure S7 **Individual $ANC_{mean\ ratio,ss}$ versus individual AZD4721 $AUC_{ss,tau}$ Day 10 by treatment, Part A**

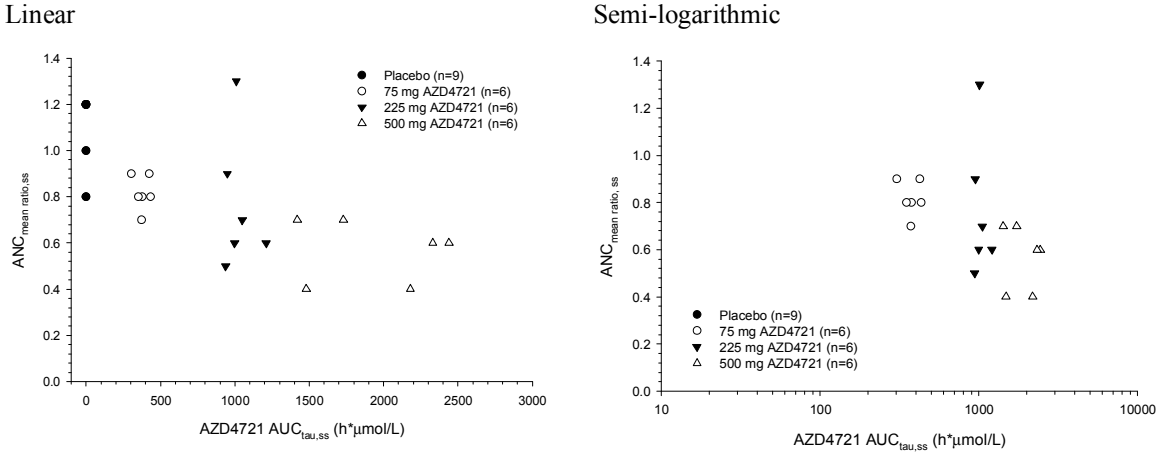
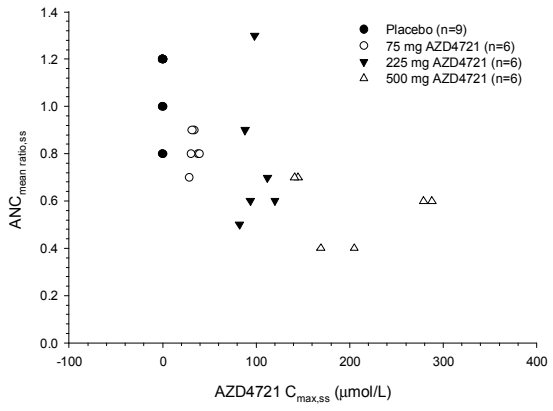
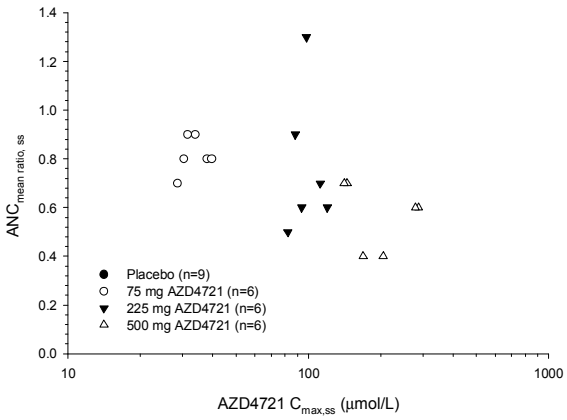


Figure S8 **Individual $ANC_{mean\ ratio,ss}$ versus individual AZD4721 $C_{ss,max}$ Day 10 by treatment, Part A**

Linear



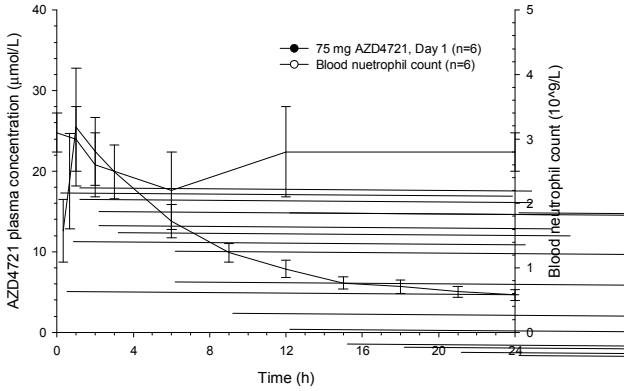
Semi-logarithmic



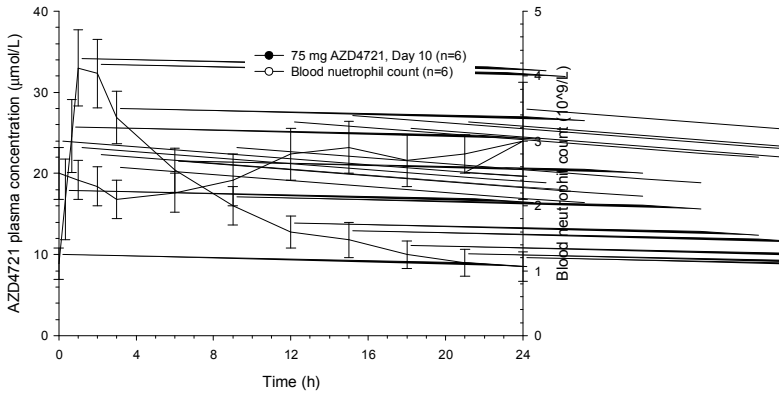
The mean blood neutrophil counts and AZD4721 plasma concentrations versus time are provided in Figure S9 for Part A.

Figure S9 **Arithmetic mean (±SD) blood neutrophil counts and arithmetic mean AZD4721 plasma concentration (µmol/L) versus time, Day 1 and Day 10 (Safety analysis set), Part A**

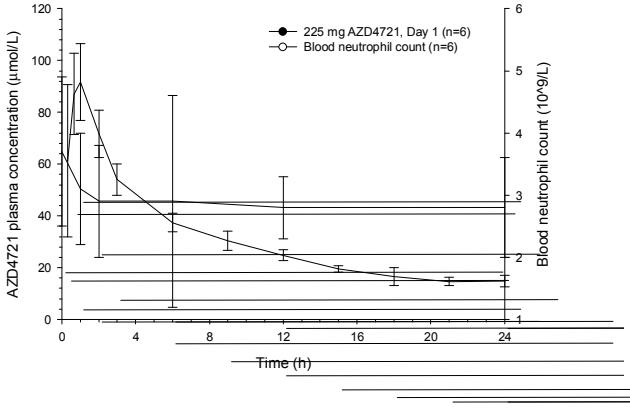
Day 1 – 75 mg AZD4721



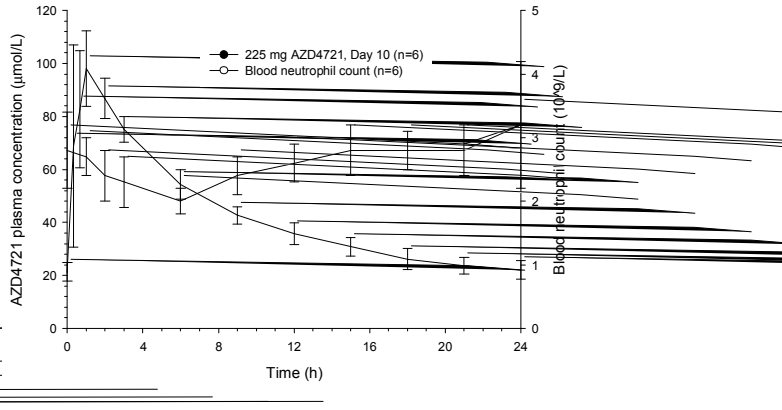
Day 10 – 75 mg AZD4721



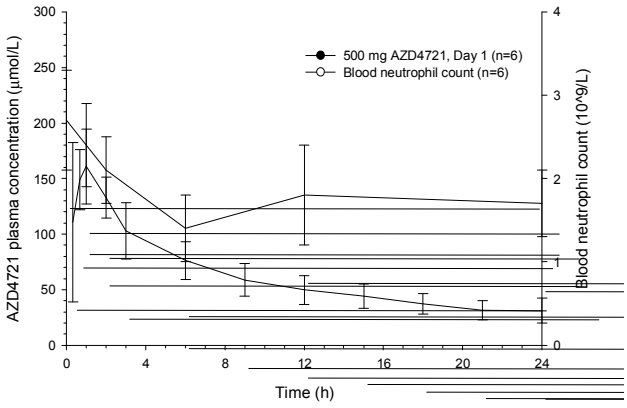
Day 1 – 225 mg AZD4721



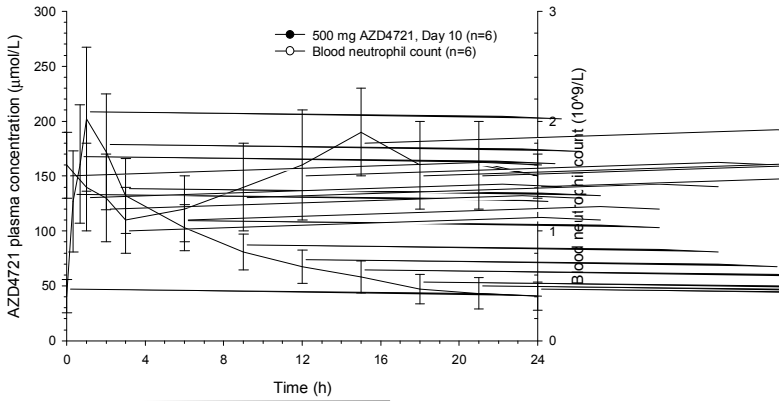
Day 10 – 225 mg AZD4721



Day 1 – 500 mg AZD4721



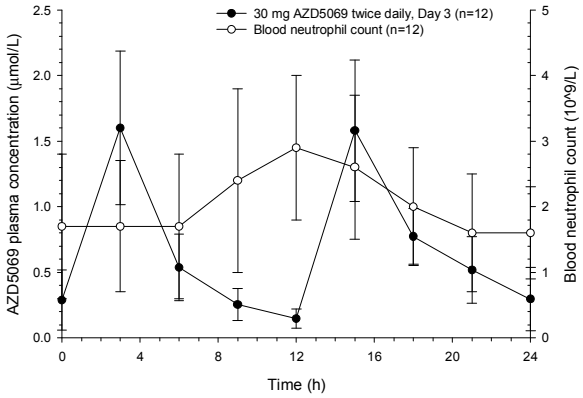
Day 10 – 500 mg AZD4721



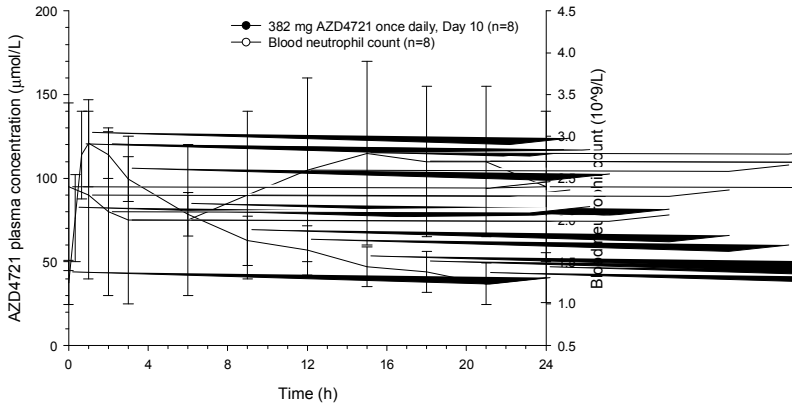
The mean blood neutrophil counts and AZD5069 and AZD4721 plasma concentrations versus time are provided in Figure S10 for Part B.

Figure S10 Arithmetic mean (±SD) blood neutrophil counts and arithmetic mean AZD5069 and AZD4721 plasma concentration (µmol/L) versus time, Day 3 and Day 10 (Safety analysis set), Part B

Day 3 – 30 mg AZD5069 bd daily



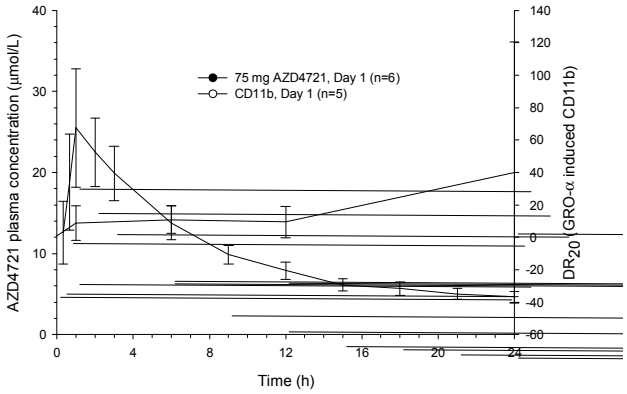
Day 10 – 382 mg AZD4721 od daily



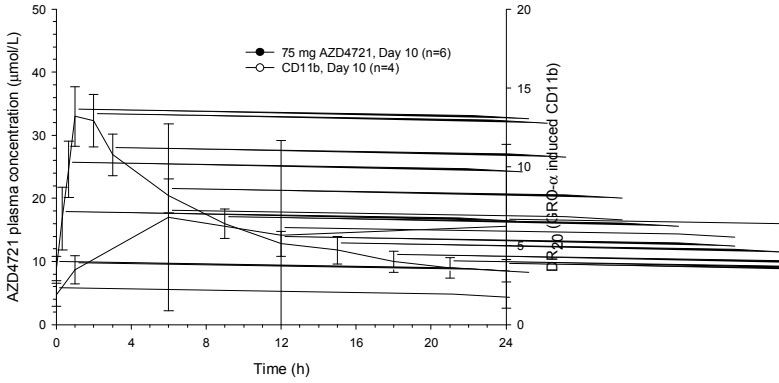
The dose ratio (GRO-α induced CD11b on blood neutrophils) values and AZD4721 plasma concentration values versus time are provided in Figure S11 for Part A.

Figure S11 Arithmetic mean (±SD) dose ratio (GRO-α induced CD11b on blood neutrophils) and arithmetic mean AZD4721 plasma concentration (µmol/L) versus time, Day 1 and Day 10, Part A

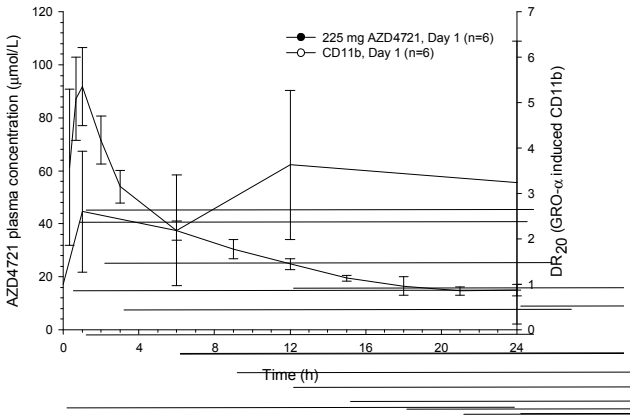
Day 1 – 75 mg AZD4721



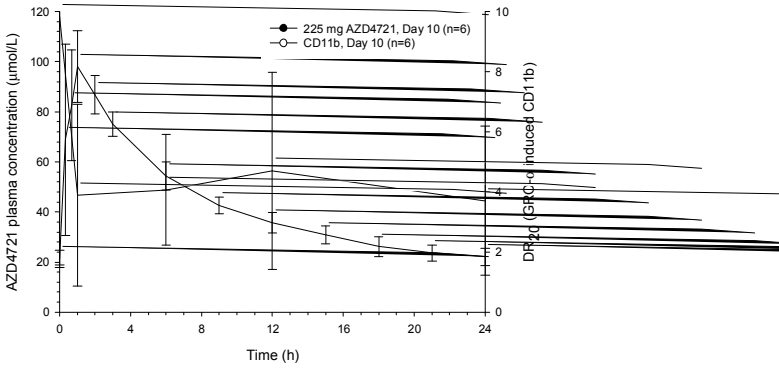
Day 10 – 75 mg AZD4721



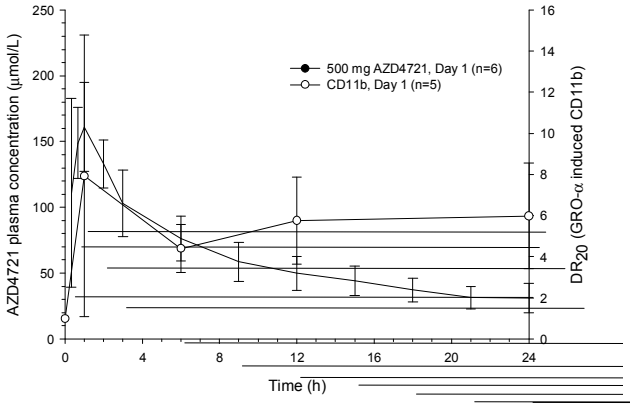
Day 1 – 225 mg AZD4721



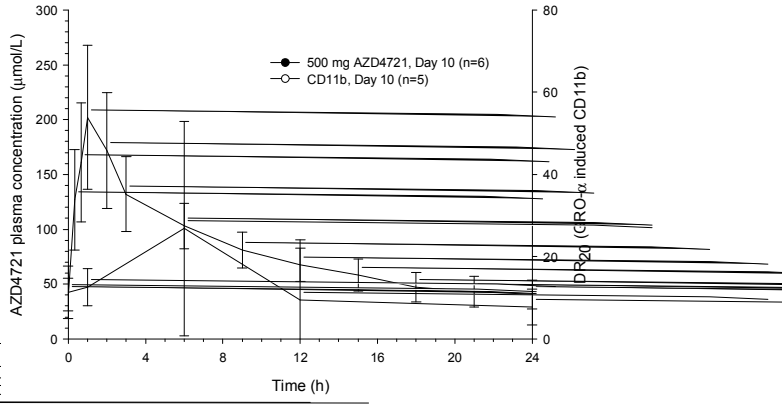
Day 10 – 225 mg AZD4721



Day 1 – 500 mg AZD4721



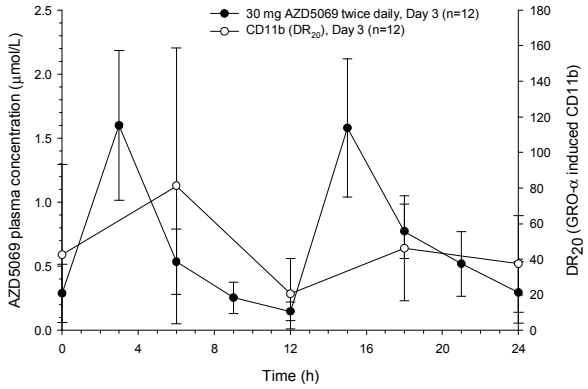
Day 10 – 500 mg AZD4721



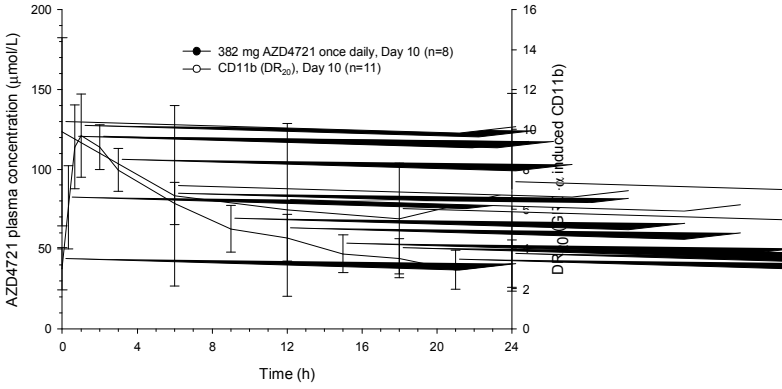
The dose ratio (GRO-α induced CD11b on blood neutrophils) values and AZD5069 or AZD4721 plasma concentration values versus time are provided in Figure S12 for Part B.

Figure S12 Arithmetic mean (±SD) dose ratio (GRO-α induced CD11b on blood neutrophils) and arithmetic mean (±SD) AZD5069, Day 3, and AZD4721, Day 10, plasma concentration (µmol/L) versus time, Part B

Day 3 – 30 mg AZD5069 bd daily



Day 10 – 382 mg AZD4721 od daily



Summary of safety results

Part A

- No deaths, SAEs or DAEs were reported in the study. Overall, at least 1 AE was reported for 13 (48.1%) of the 27 volunteers in Part A with 9 of the 18 volunteers receiving any dose of AZD4721 reporting an AE. The number of volunteers reporting at least 1 AE was higher in the 500 mg dose level when compared to the other 2 dose levels (5/6; 83.3%) and placebo

- Most of the AEs were considered to be of mild intensity by the investigator except for 2 AEs which were considered to be of moderate intensity. Volunteer E0001030 (225 mg) reported moderate AE of headache and Volunteer E0001043 (500 mg) reported a moderate AE of constipation. A total of 15 AEs considered to be causally related to the investigational product was reported by 6 volunteers in both the AZD4721 and placebo groups. In the AZD4721 group (all dose levels), 4 volunteers reported 13 AEs which were considered to be related to the investigational product administration:

  - Volunteer E0001026 (225 mg): myalgia, and headache

  - Volunteer E0001041 (500 mg): abdominal pain, diarrhoea, urine odour abnormal, and constipation

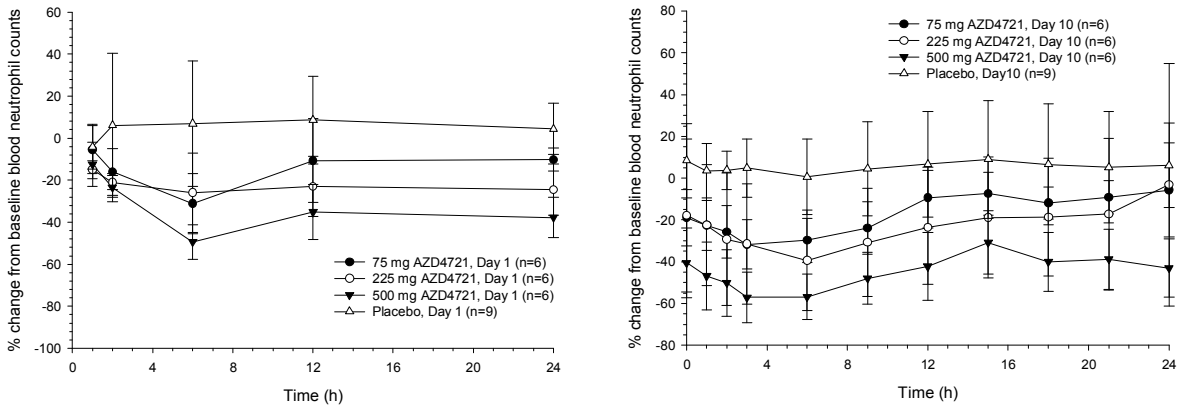
- Volunteer E0001043 (500 mg): urine odour abnormal, abdominal pain, abnormal faeces, and constipation
- Volunteer E001058 (500 mg): oropharyngeal pain, urine odour abnormal and rash

- All the AEs resolved except for 2 AEs of constipation and rash in volunteers E0001041 and E0001058, respectively, which had an unknown outcome
- The number of volunteers reporting at least one AE was higher in the AZD4721 (9 [50.0%] volunteers) group when compared to the placebo (4 [44.4%] volunteers) group. The number of volunteers reporting at least one AE was higher in the 500 mg dose level when compared to the other 2 dose levels (5/6; 83.3% vs 3/6; 50.0% and 1/6; 16.7%). The most commonly reported AE belonged to the System Organ Class (SOC) of gastrointestinal disorders (6/27; 22.7%). In volunteers receiving AZD4721, the most commonly reported AE belonged to the SOC of gastrointestinal disorders and nervous system disorders (4/18; 22.2% each). The most commonly reported AE in volunteers receiving AZD4721 was headache and urine odour abnormal (3/18; 16.7% each)

AZD4721 dosed od for 10 days had an effect on absolute neutrophil counts, with the largest effect observed at the 500 mg dose level. The mean percent change from baseline blood neutrophil counts versus time by treatment are provided in Figure S13 for Part A.

Figure S13 Arithmetic mean (±SD) percent change from baseline blood neutrophil count, Day 1 and Day 10, versus time by treatment (Blood neutrophil analysis set), Part A

Day 1 Day 10



In Part A, on Day 1, 3 volunteers had ANC_{min} values between $1.0x10^9$/L and $1.5x10^9$/L at the 500 mg AZD4721 dose level. On Day 10, 5 volunteers had $ANC_{min,ss}$ values between

$1.0x10^9$/L and $1.5x10^9$/L at the 500 mg AZD4721 dose level. No other volunteers had ANC_{min} or $ANC_{min,ss}$ values below $1.5x10^9$/L on Day 1 or Day 10.

Blood neutrophil parameters calculated from data after AZD4721 and placebo administration on Day 1 and Day 10 are presented in Table S5 and Table S6 for Part A.

Table S5 Summary of blood neutrophil parameters after AZD4721 and placebo dosing (Blood neutrophil analysis set) (Day1), Part A

Variable	Treatment[a]	n	Arithmetic Mean	SD	Median	Min	Max
$ANC_{min,Day\ 1}$	Placebo	9	2.4	0.7	2.1	1.6	3.4
(10^9/L)	75 mg AZD4721	6	2.1	0.5	2.1	1.6	2.8
	225 mg AZD4721	6	2.3	0.5	2.2	1.7	3.0
	500 mg AZD4721	6	1.4	0.4	1.4	0.8	1.7
$ANC_{tmin,Day\ 1}$	Placebo	9	ND	ND	6	1	24
(h)	75 mg AZD4721	6	ND	ND	6	2	12
	225 mg AZD4721	6	ND	ND	6	6	24
	500 mg AZD4721	6	ND	ND	6	6	24
$ANC_{min\ ratio,Day\ 1}$	Placebo	9	0.88	0.09	0.87	0.76	1.06
	75 mg AZD4721	6	0.67	0.11	0.64	0.56	0.82
	225 mg AZD4721	6	0.64	0.08	0.64	0.54	0.74
	500 mg AZD4721	6	0.49	0.07	0.52	0.40	0.57

CV: coefficient of variation; Max: maximum; Min: minimum; ND: not determined; SD: standard deviation
[a] AZD4721 or placebo was administered, orally, od for 10 days

Table S6 Summary of blood neutrophil parameters after AZD4721 and placebo dosing (Blood neutrophil analysis set) (Day 10), Part A

Variable	Treatment[a]	n	Arithmetic Mean	SD	Median	Min	Max
$ANC_{min,ss}$	Placebo	9	2.4	0.8	2.3	1.5	3.8
(10^9/L)	75 mg AZD4721	6	2.1	0.2	2.1	1.6	2.3
	225 mg AZD4721	6	2.0	0.2	2.0	1.7	2.4
	500 mg AZD4721	6	1.1	0.3	1.0	0.9	1.6
$ANC_{tmin,ss}$	Placebo	9	ND	ND	12	1	24
(h)	75 mg AZD4721	6	ND	ND	3	1	6
	225 mg AZD4721	6	ND	ND	6	2	9
	500 mg AZD4721	6	ND	ND	3	2	6
$ANC_{mean,ss}$	Placebo	9	2.9	0.9	2.6	1.9	4.4
(10^9/L)	75 mg AZD4721	6	2.6	0.3	2.7	2.1	2.8
	225 mg AZD4721	6	2.6	0.3	2.5	2.4	3.2
	500 mg AZD4721	6	1.5	0.3	1.3	1.2	2.1
$ANC_{min\ ratio,ss}$	Placebo	9	0.87	0.14	0.88	0.64	1.06
	75 mg AZD4721	6	0.67	0.10	0.64	0.53	0.79
	225 mg AZD4721	6	0.59	0.24	0.54	0.30	1.00
	500 mg AZD4721	6	0.41	0.10	0.45	0.28	0.50
$ANC_{mean\ ratio,ss}$	Placebo	9	1.1	0.2	1.2	0.8	1.2
	75 mg AZD4721	6	0.8	0.1	0.8	0.7	0.9
	225 mg AZD4721	6	0.8	0.3	0.7	0.5	1.3
	500 mg AZD4721	6	0.6	0.1	0.6	0.4	0.7

CV: coefficient of variation; Max: maximum; Min: minimum; ND: not determined; SD: standard deviation
[a] AZD4721 or placebo was administered, orally, od for 10 days

- There were no clinically significant abnormal laboratory results, vital signs, or 12-lead ECG measurements reported

- One abnormal physical examination finding of skin was reported as an AE whose outcome was unknown and related to investigational product by the investigator.

Part B

- No deaths, SAEs or DAE were reported in the study. No deaths, SAEs, and DAEs reported in the study. Overall, at least 1 AE was reported for 7 (58.3%) of the 12 volunteers in Part B of the study. Six (54.5%) of the 11 volunteers and 1 (8.3%) of the 12 volunteers reported at least 1 AE after receiving AZD4721 and AZD5069, respectively.

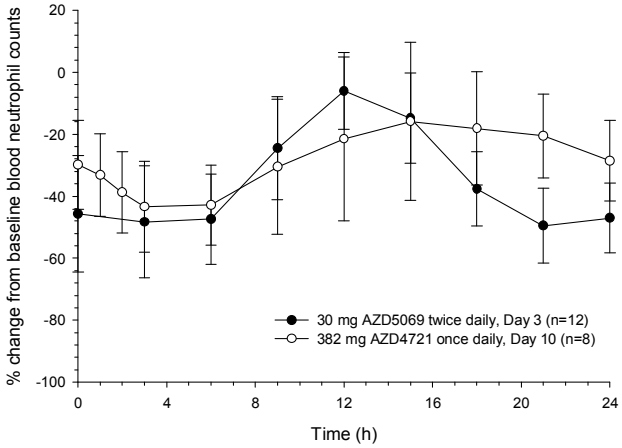
- Most of the AEs were considered to be of mild intensity except for 4 AEs reported by 2 volunteers which were of moderate intensity. Volunteer E001013 (AZD4721) reported moderate headache, pyrexia, and diarrhoea, whilst Volunteer E001018 reported moderate headache. A total of 11 AEs considered to be causally related to the investigational product was reported by 6 volunteers after receiving either AZD4721 or AZ5069:

  - Volunteer E001007 (AZD4721): headache
  - Volunteer E001013 (AZD4721): headache, flatulence, pyrexia, and diarrhoea
  - Volunteer E001014 (AZD5069): abdominal pain, and cough
  - Volunteer E001017 (AZD4721): oropharyngeal pain and nausea
  - Volunteer E001018 (AZD4721): headache
  - Volunteer E001020 (AZD4721): diarrhoea

- All the AEs resolved except for an AE of cough reported by Volunteer E001017 which had an unknown outcome.

- The number of volunteers reporting at least 1 AE was greater after receiving AZD4721 (6/11; 54.5%) when compared to after receiving AZD5069 (1/12; 8.3%). The most commonly reported AEs by SOC in AZD4721 group were gastrointestinal disorders and nervous system disorders in 3 (27.3%) volunteers each. Headache was the most commonly reported AE (3 [27.3%] volunteer). Incidence of AE was higher in AZD4721 group than AZD5069

Figure S14 **Arithmetic mean (±SD) percent change from baseline blood neutrophil count, Day 3 after morning and evening AZD5069 dosing and Day 10 after AZD4721 dosing, versus time (Blood neutrophil analysis set), Part B**



In Part B, on Day 3 of bd 30 mg AZD5069 administration, 9 volunteers had $ANC_{min,ss}$ values between $1.0x10^9$/L and $1.5x10^9$/L. On Day 10 of od 382 mg AZD4721 administration, 2 volunteers had $ANC_{min,ss}$ values between $1.0x10^9$/L and $1.5x10^9$/L. No other volunteers had $ANC_{min,ss}$ values below $1.5x10^9$/L on Day 3 or Day 10.

Blood neutrophil parameters calculated from data after AZD5069 and AZD4721 administration on Day 3 and Day 10 respectively are presented in Table S7 and The statistical comparison of blood neutrophil count parameters after AZD5069 and AZD4721 dosing is presented in Table S8 for Part B.

Table S7 Summary of blood neutrophil parameters after AZD5069 and AZD4721 dosing (Blood neutrophil analysis set) (Day 3 and Day 10), Part B

Variable	Treatment	N	Arithmetic Mean	SD	Median	Min	Max
$ANC_{min,ss}$	AZD5069	12	1.4	0.8	1.3	0.6	3.5
(10^9/L)	AZD4721	8	1.9	1.0	1.7	1.0	4.1
$ANC_{tmin,ss}$	AZD5069	12	ND	ND	3	3	24
(h)	AZD4721	8	ND	ND	6	3	9
$ANC_{mean,ss}$	AZD5069	12	2.1	1.0	1.8	1.3	4.8
(10^9/L)	AZD4721	8	2.4	0.9	2.2	1.5	4.6
$ANC_{min\ ratio,ss}$	AZD5069	12	0.43	0.11	0.44	0.25	0.59
	AZD4721	8	0.54	0.14	0.50	0.38	0.80
$ANC_{mean\ ratio,ss}$	AZD5069	12	0.7	0.1	0.6	0.6	0.8
	AZD4721	8	0.7	0.1	0.7	0.6	0.9

CV: coefficient of variation; Max: maximum; Min: minimum; ND: not determined; SD: standard deviation
AZD5069 was administered, orally, 30 mg bd daily for 3 days in Period 1.
AZD4721 was administered, orally, 382 mg od for 10 days in Period 2

Table S8 Statistical comparison of key blood neutrophil count parameters, after AZD5069 and AZD4721 dosing, Part B

					Comparison of treatment AZD4721 vs AZD5069	
Variable	Treatment	n	Geometric LS mean	Geometric LS mean 95% CI	Ratio (%)	90% CI
$ANC_{min,ss}$	AZD5069	12	1.300	(1.115, 1.516)		
(10^9/L)	AZD4721	8	1.553	(1.290, 1.870)	119.45	(100.19, 142.42)
$ANC_{mean,ss}$	AZD5069	12	1.999	(1.794, 2.228)		
(10^9/L)	AZD4721	8	2.115	(1.849, 2.419)	105.79	(92.56, 120.92)
$ANC_{min\ ratio,ss}$	AZD5069	12	0.4247	(0.3640, 0.4955)		
	AZD4721	8	0.5062	(0.4205, 0.6092)	119.18	(100.16, 141.82)
$ANC_{mean\ ratio,ss}$	AZD5069	12	0.6650	(0.6074, 0.7280)		
	AZD4721	8	0.7097	(0.6326, 0.7961)	106.72	(94.48, 120.54)

CI: confidence interval; LS: least squares
AZD5069 was administered, orally, 30 mg bd for 3 days in Period 1.
AZD4721 was administered, orally, 382 mg od for 10 days in Period 2.

- There were no clinically significant abnormal laboratory results, vital signs, 12-lead ECG measurements, or physical findings reported in this part of the study.

Conclusions