Clinical Study Report Synopsis

Drug Substance	AZD5069
Study Code	D3550C00001
Edition Number	1
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A Phase I, Single Centre, Double-blind, Randomised, Placebo-controlled, Parallel-group Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Oral AZD5069 after Single Ascending Doses in Healthy Male and/or Female Subjects

Study dates: First healthy volunteer enrolled: 17 July 2009
Last healthy volunteer last visit: 4 December 2009

Phase of development: Clinical pharmacology (I)

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

Study centre(s)

One centre in the United Kingdom.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To assess the safety and tolerability of AZD5069 following administration of single ascending doses and to estimate the maximum tolerated dose, if within the predefined exposure limits.	Adverse events, vital signs, electrocardiograms, laboratory variables (including hsCRP and circulating neutrophils), blood pressure, pulse rate, body temperature, QT interval and continuous cardiac monitoring using telemetry	Safety
Secondary	**Secondary**	
To characterise the PK of AZD5069 and provisionally assess the dose proportionality of the PK following administration of single ascending doses of AZD5069.	$AUC_{(0-t)}$, AUC, C_{max}, t_{max}, λ_z, $t_{½}$, CL/F, V_Z/F, MRT, Ae; % dose and CL_R	PK
To measure the effect of AZD5069 on circulating neutrophils.	Numbers of circulating neutrophils	Safety
To investigate the PD activity of AZD5069 by assessment of ex vivo GROα stimulated CD11b expression on neutrophils in whole blood.	Measurement of ex vivo GROα stimulated CD11b expression in whole blood neutrophils	PD
To investigate the relationship between AZD5069 exposure and the effect on circulating neutrophils.	AZD5069 plasma concentration versus numbers of circulating neutrophils	PK/Safety
To investigate the relationship between AZD5069 exposure and the effect on GROα stimulated CD11b expression on neutrophils in whole blood ex vivo.	AZD5069 plasma concentration versus measurement of ex vivo GROα stimulated CD11b expression in whole blood neutrophils	PK/PD

Ae Amount excreted unchanged in urine in milligrams; AUC Area under the plasma concentration-time curve from zero to infinite time; $AUC_{(0-t)}$ Area under the plasma concentration - time curve from zero to the time of the last quantifiable plasma concentration; CD11b Cluster of differentiation molecule 11b; CL/F Apparent oral plasma clearance after an oral dose; CL_R Renal clearance; C_{max} Maximum plasma concentration; GROα Growth related oncogene alpha; hsCRP High sensitivity C-reactive protein; λ_z Terminal elimination rate constant; MRT Mean residence time; PD Pharmacodynamic(s); PK Pharmacokinetic(s); $t_{½}$ Terminal elimination half-life; t_{max} Time to maximum plasma concentration; V_Z/F Apparent oral volume of distribution during the terminal phase.
Note: There were 2 exploratory objectives for this study (pharmacogenetic and metabolite analyses of plasma and urine); these are not presented in the clinical study report.

Study design

This was a Phase I, first time in human, randomised, double-blind, parallel-group, placebo-controlled, single ascending dose study in healthy male or female volunteers conducted at a single centre.

Target subject population and sample size

The study included healthy male and female volunteers aged 18 to 65 years, who provided written informed consent, had suitable veins for cannulation or repeated venepuncture, and had clinically normal physical findings, laboratory values and electrocardiograms. Healthy volunteers with conditions known to interfere with the absorption, distribution, metabolism or excretion of the study drug were not eligible.

Due to the exploratory nature of the study the sample size was not based on formal statistical considerations. The sample size was based on experience from previous similar Phase I studies with other compounds. Up to 81 healthy volunteers were planned to participate in up to 9 cohorts (with up to 9 healthy volunteers in each cohort). Healthy volunteers were randomised to receive either AZD5069 or placebo (6:3).

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

Table S2 Details of investigational product and other study drug

Investigational product	Dosage form, strength, and route of administration	Manufacturer	Batch number
AZD5069	Suspension, 1 mg/g, oral	AstraZeneca	09-004095AZ
AZD5069	Suspension, 50 mg/g, oral	AstraZeneca	09-004102AZ
Placebo	Matching suspension, oral	AstraZeneca	09-003475AZ

Duration of treatment

Study drug (AZD5069 or placebo) was administered as a single oral dose.

Statistical methods

No formal statistical hypothesis testing was performed. Data were summarised descriptively including tables, listings and graphs, as appropriate.

Subject population

The first healthy volunteer entered the study on 17 July 2009 and the last healthy volunteer finished on 4 December 2009. In total, 70 healthy volunteers were randomised into the study at 1 study site, and all but 1 healthy volunteer received 1 administration of study drug (AZD5069 or placebo) during the planned treatment visit. One healthy volunteer in the 200 mg cohort did not receive study drug (AZD5069); this healthy volunteer was not dosed due to the observation of ventricular ectopics on telemetry monitoring.

Of the 69 healthy volunteers dosed, 45 received AZD5069 and 24 received placebo (Table S3).

Table S3 Number of healthy volunteers per cohort

Cohort	AZD5069 dose	Number of healthy volunteers			Ratio active:placebo
		Placebo	AZD5069	Total	
1	0.1 mg	3	6	9	6:3
2	0.5 mg	3	6	9	6:3
3	1.65 mg	3	6	9	6:3
4	5.45 mg	3	6	9	6:3
5	17.99 mg	3	6	9	6:3
6	60 mg	3	4	7	4:3
7	120 mg	3	6	9	6:3
8	200 mg	3	5	8	5:3
Total		24	45	69	5.6:3

No important protocol deviations were recorded during the study. The safety analysis set included all 69 healthy volunteers who received study drug (AZD5069 or placebo), all of whom completed the study. All 45 healthy volunteers who received AZD5069 were included in the pharmacokinetic (PK) analysis set. In total, 61 healthy volunteers were included in the pharmacodynamic (PD) analysis set; 8 healthy volunteers (3 in the placebo cohort and 5 in the AZD5069 0.1 mg cohort) were excluded. Seven healthy volunteers were excluded due to lack of PD data (assay failure) and 1 healthy volunteer (placebo) was excluded due to an adverse event (AE) of campylobacter infection. The healthy volunteer with the AE was excluded from the PK and PD analyses while data were blinded in case the absorption of study drug had been affected; once data were unblinded it became clear this healthy volunteer had received placebo.

The demographic and baseline characteristics of the treatment groups were generally comparable. Medical and surgical history and physical examination findings were as expected for a healthy volunteer population. The healthy volunteers dosed were suitable for the study.

Summary of pharmacokinetic results

The plasma and urine PK parameters for AZD5069 following a single oral administration to healthy male and female healthy volunteers were determined. The geometric mean exposures achieved following the highest dose (200 mg) were maximum plasma concentration (C_{max}) 11900 nmol/L (range 4920 nmol/L to 21800 nmol/L) and area under the plasma concentration-time curve from zero to infinite time (AUC) 69900 nmol.h/L (range 27300 nmol.h/L to 155000 nmol.h/L). At this dose the geometric mean AUC was below the pre-defined exposure limit of 100000 nmol.h/L but 2 healthy volunteers exceeded it: one achieved an AUC of 109000 nmol.h/L and the other 155000 nmol.h/L. No healthy volunteers exceeded the exposure limit for C_{max} of 25700 nmol/L.

The increase in mean C_{max} and AUC was linear and approximately dose proportional from 0.1 mg to 200 mg. Inter-individual variability was typically 2 to 3-fold with the exception of the highest dose group which showed greater inter-individual variability.

The observed time to maximum plasma concentration was between 0.5 hours and 3 hours in all but 1 healthy volunteer (who had a t_{max} of 4.03 hours) and appeared to be independent of dose. A terminal elimination half-life of approximately 11 hours was observed following higher doses, for healthy volunteers where plasma concentrations were measurable to 48 hours or longer. However, this phase was associated with only 10% or less of the AUC. The half-life associated with the phase of elimination apparent at around 8 to 24 hours post-dose was approximately 4 hours. This shorter half-life, which drove the elimination of the majority of the parent compound, is expected to be pharmacologically relevant. The mean apparent oral volume of distribution during the terminal phase associated with the 11-hour terminal half-life ranged between 80.6 L and 151 L. The apparent oral plasma clearance after an oral dose of AZD5069 appeared to be independent of dose and was similar across all dose groups at approximately 9 L/h. Some AZD5069 was excreted unchanged in urine and at least 85% of the total amount excreted was determined in the first 12 hours post-dose in all dose groups. The renal clearance (CL_R) over 48 hours appeared to be independent of dose and CL_R was approximately 0.3 L/h. The mean percentage of dose excreted unchanged in urine was similar in all dose groups and varied between 3.8% and 5.2%. The percentage of dose excreted unchanged in urine varied between 0.71% and 10% in individuals.

Summary of pharmacodynamic results

Proof of mechanism was demonstrated during the study with the cluster of differentiation molecule 11b (CD11b): dose ratio at 20% of the pre-dose response curve (DR20) showing a dose proportional response. A CD11b:DR20 of 2 represents a meaningful change in this assay, and no change to the PD response was seen below AZD5069 5.45 mg. At 4 hours after the 5.45 mg dose the arithmetic mean CD11b:DR20 was 6.077, falling to 1.620 at 24 hours. At AZD5069 60 mg, a large CD11b:DR20 response was observed at both 4 hours and 8 hours (85.95 and 38.10, respectively), which was still meaningful at 24 hours (2.054). Based on the timepoints assessed the assay reached its maximum response at 4 hours at AZD5069 120 mg; thus, for the 200 mg dose, the 4-hour timepoint only was omitted (no sample was taken as the assay had already reached its maximum response). The mean placebo CD11b:DR20 from all post-dose time points in the study was 1.227.

Summary of pharmacokinetic/pharmacodynamic relationships

The PD, as measured by the CD11b assay, showed an increasing effect with increasing dose and PK exposure, with doses of AZD5069 at or above 5.45 mg producing increasing mean DR20 at 4 hours that were above the threshold of 2 (considered to be a meaningful change in the assay response). The doses of AZD5069 5.45 mg, 17.99 mg and 60 mg had mean DR20 values at 4 hours of 6.077, 38.47 and 85.95, respectively, where the upper limit of the CD11b assay was reached. The corresponding mean plasma concentrations at 4 hours were 195, 643 and 2555 nmol/L, respectively.

Based on the limited time points, there was some evidence to suggest that the PD effect was slightly prolonged relative to the PK. For example, at the AZD5069 17.99 mg dose, the mean CD11b:DR20 was 38.47 at 4 hours, reducing to 2.035 at 24 hours. However, the corresponding mean AZD5069 plasma concentration at 4 hours and 24 hours were 643 nmol/L and 10.2 nmol/L, respectively, a 63-fold drop in mean plasma concentration when the DR20 drop over the same period was 19-fold. A similar effect may have been observed with the AZD5069 5.45 mg dose, where the mean plasma concentration dropped 112-fold (from 195 nmol/L at 4 hours to 1.74 nmol/L at 24 hours) compared with a DR20 drop of 3.75-fold (from 6.077 at 4 hours to 1.620 at 24 hours). However, the results for DR20 did show a return to baseline, as the shift dropped below the value of 2 (considered to represent a meaningful change in the assay). At the AZD5069 60 mg dose over the same time period, the mean plasma concentration dropped 50-fold (from 2555 nmol/L at 4 hours to 51 nmol/L at 24 hours) while the DR20 dropped 42-fold (from 85.95 at 4 hours to 2.054 at 24 hours) as the CD11b assay reached a maximum response.

Summary of safety results

There were no deaths, no AEs that were considered serious, and there were no discontinuations due to AEs or any other significant AEs reported during the study. All healthy volunteers who received AZD5069 tolerated the study drug. In total, 22 of the 69 healthy volunteers had an AE; 8 of the 24 healthy volunteers (33%) who received placebo and 14 of the 45 healthy volunteers (31%) who received AZD5069. The total number of AEs reported by these healthy volunteers was 33; 10 AEs were reported in the 8 healthy volunteers who received placebo and 23 AEs were reported in the 14 healthy volunteers who received AZD5069. All AEs were of mild or moderate intensity, except for 1 AE of severe intensity reported in a healthy volunteer who received placebo.

No 2 healthy volunteers who received placebo reported the same treatment emergent AE. In healthy volunteers who received AZD5069, acne (verbatim text: spots on face/chest wall [comedones]; pimples), headache and nausea were each reported for 2 healthy volunteers; all other AEs were reported in no more than 1 healthy volunteer. No treatment emergent AE was reported for more than 1 healthy volunteer who received AZD5069 within any cohort. Two healthy volunteers who received AZD5069 (120 mg cohort and 200 mg cohort) had an event of nausea; the event of nausea in the 120 mg cohort, which was of mild intensity, resolved within 2.5 hours and was considered by the Investigator to be related to study drug.

One healthy volunteer who received placebo had an AE that was severe in intensity (orthostatic hypotension). Five healthy volunteers had a total of 7 AEs that were moderate in intensity; 1 healthy volunteer who received placebo and 4 healthy volunteers who received AZD5069 (1 in each of the 0.5 mg, 1.65 mg, 5.45 mg [in this cohort 1 healthy volunteer had 2 events of moderate headache] and 200 mg [in this cohort 1 healthy volunteer had an AE of moderate abdominal pain and moderate nausea] cohorts). None of these events were considered by the Investigator to be related to study drug.

In total, 4 AEs reported in 3 healthy volunteers were considered by the Investigator to be related to study drug. These were dysuria and headache in the placebo cohort (which were both reported for the same healthy volunteer), dry mouth in the AZD5069 0.5 mg cohort and nausea in the AZD5069 120 mg cohort. All 4 AEs resolved and no concomitant medication was required.

A reduction in circulating neutrophils was expected with AZD5069 based on experience with other CXC chemokine receptor 2 antagonists. Baseline neutrophil counts ranged from 1.80 x 10^9/L to 6.36 x 10^9/L (mean 2.98 x 10^9/L). A dose-dependent reduction in the numbers of circulating neutrophils was observed with AZD5069 at the first timepoint (8 hours post-dose). The mean count at 8 hours post-dose for all healthy volunteers who received placebo was 3.77 x 10^9/L dropping to 2.01 x 10^9/L for healthy volunteers who received AZD5069 17.99 mg, and 0.98 x 10^9/L for healthy volunteers who received AZD5069 200 mg. The number of circulating neutrophils decreased with increasing AZD5069 plasma concentration. The fall in circulating neutrophil numbers was non-progressive and the nadir was observed once the AZD5069 plasma concentration reached approximately 500 nmol/L.

The effect of AZD5069 on circulating neutrophils was reversible. The values for mean circulating neutrophils were in excess of 2.50 x 10^9/L within 48 hours for all AZD5069 doses except for the 200 mg dose (range at 48 hours: 1.83 to 4.05 x 10^9/L); the mean value for circulating neutrophils for healthy volunteers who received AZD5069 200 mg was in excess of 2.50 x 10^9/L at the Day 5 (96-hour) assessment (range: 2.36 to 3.24 x 10^9/L). At AZD5069 doses ≤1.65 mg, values for circulating neutrophils remained within the reference range (1.8 to 7.8 x 10^9/L) at all timepoints. One of 6 healthy volunteers (17%) in the AZD5069 5.45 mg cohort and 2 of 6 healthy volunteers (33%) in the AZD5069 17.99 mg cohort had a value for circulating neutrophils below the reference range at the 8-hour timepoint. Values for all 3 healthy volunteers had returned to within the reference range at the 12-hour timepoint. All 15 healthy volunteers in the AZD5069 60 mg (n=4), 120 mg (n=6) and 200 mg (n=5) cohorts had a value for circulating neutrophils below the reference range at the 8-hour (n=13) or 12-hour (n=2) timepoints. All values were within the reference range at the 48-hour timepoint for healthy volunteers in both the AZD5069 60 mg (2 healthy volunteers at each of the 24-hour and 48-hour timepoints) and AZD5069 120 mg cohort (1 healthy volunteer at each of the 12-hour and 48-hour timepoints, and 4 at the 24-hour timepoint). All values were within the reference range at the 96-hour timepoint for healthy volunteers in the AZD5069 200 mg cohort (2 and 3 healthy volunteers at the 48-hour and 96-hour timepoints, respectively). No AEs were reported as a result of these decreases in circulating neutrophils.

With the exception of circulating neutrophils, there were no clinically relevant changes in haematology, clinical chemistry (including high sensitivity C-reactive protein) or urinalysis parameters in healthy volunteers exposed to AZD5069.

One healthy volunteer who received placebo had an AE of severe orthostatic hypotension; the event resolved and no concomitant medication was required. There were no clinically relevant changes in blood pressure, pulse rate or temperature during the study in healthy volunteers exposed to AZD5069.

No association between AZD5069 and critical electrocardiogram parameters including QT interval corrected for heart rate using Fridericia's formula was observed.