Clinical Study Report Synopsis

Drug Substance	AZD5122
Study Code	D2650C00006
Edition Number	2
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A Phase I, Exploratory Study to Assess the Pharmacokinetics of Single Oral Doses and a Single Intravenous Radiolabelled Microtracer Dose of AZD5122 in Healthy Male Subjects

Study dates:	First healthy volunteer enrolled (Part A): 21 September 2009 Last healthy volunteer last visit (Part A): 6 November 2009 First healthy volunteer enrolled (Part B): 23 October 2009 Last healthy volunteer last visit (Part B): 23 November 2009
Phase of development:	Clinical Pharmacology (1)
International Co-ordinating Investigator:	**Part A:**
	Part B:
Sponsor's Responsible Medical Officer:	

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

Study centre(s)

Two centres in the United Kingdom (1 each for Part A and Part B).

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 investigate the PK in plasma of single oral doses and a single intravenous infusion of a [^{14}C]-radiolabelled microtracer dose of AZD5122 administered to healthy male subjects.	**Oral:** C_{max}, t_{max}, $t_{½}$, $AUC_{(0-24)}$, $AUC_{(0-t)}$, AUC, CL/F, V_z/F and MRT. **Intravenous:** C_{max}, t_{max}, λ_z, $t_{½}$, $AUC_{(0-24)}$, $AUC_{(0-t)}$, AUC, MRT, CL and V_z.	PK
Secondary	**Secondary**	
To investigate the PK in urine of single oral doses of AZD5122 administered to healthy male subjects (Part A only).	Ae (% dose) and CL_R.	PK
To investigate the relationship between AZD5122 exposure and the effect on circulating neutrophils (Part A only).	Numbers of circulating neutrophils versus plasma concentration	PD/Safety
To investigate the PD activity of AZD5122 by assessment of ex vivo GROα stimulated CD11b expression on neutrophils in whole blood, and its relationship to the PK (Part A only).	Analysis of CD11b expression on neutrophils (DR20) versus plasma concentration	PD/PK

Note: There were 2 exploratory objectives for this study (pharmacogenetic and metabolite analyses [of plasma, urine and faeces]); these are not presented in the clinical study report.
Ae: Amount of drug excreted unchanged; AUC: Area under plasma concentration-time curve from zero to infinity; $AUC_{(0-24)}$: Area under plasma concentration-time curve from zero to 24 hrs post-dose; $AUC_{(0-t)}$: Area under plasma concentration-time curve from zero to the time of the last measurable concentration; CD11b: Cluster of Differentiation molecule 11b; CL: Plasma clearance following an IV dose; CL/F: Apparent plasma clearance following an oral dose; CL_R: Renal clearance; C_{max}: Maximum plasma concentration; DR20: Dose ratio at 20% of the pre-dose response curve; GROα: Growth related oncogene alpha; λ_z: Terminal elimination rate constant; MRT: Mean residence time; PD: Pharmacodynamic(s); PK: Pharmacokinetic(s); t_{max}: Time to maximum plasma concentration; $t_{½}$: Terminal elimination half-life; V_z: Apparent volume of distribution during the terminal phase following IV dosing; V_z/F: Apparent volume of distribution during the terminal phase following oral dosing.

Study design

This was a Phase I, 2-part, first time in man study in healthy male volunteers conducted at 2 centres (1 centre for each part). Part A was a randomised, double-blind, placebo-controlled, parallel group, single ascending dose study. Part B was open label and comprised a single cohort who received a single oral dose of AZD5122 (no greater than the maximum dose achieved in Part A) and included a [^{14}C]-radiolabelled intravenous (IV) microtracer dose to assess absolute bioavailability.

Target subject population and sample size

The study included healthy male 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, vital signs and electrocardiograms (ECGs). 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. In Part A, up to 45 healthy volunteers were planned to participate in 5 cohorts (with up to 9 healthy volunteers in each cohort). Healthy volunteers were randomised to receive either AZD5122 or placebo (6:3). Up to 6 healthy volunteers were planned to be dosed in Part B; all healthy volunteers received AZD5122.

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

Table S2 Details of investigational product and other study treatments

Investigational product	Dosage form, strength and route of administration	Manufacturer	Batch number
Part A			
AZD5122	Suspension, 0.2 mg/g, oral	AstraZeneca Research and Development Charnwood	09-005485AZ
AZD5122	Suspension, 1 mg/g, oral	AstraZeneca Research and Development Charnwood	09-005486AZ
Placebo (Avicel)	Suspension, not applicable, oral	AstraZeneca Research and Development Charnwood	09-005465AZ
Part B			
AZD5122	Suspension, 1mg/g, oral	AstraZeneca Research and Development Charnwood	09-005486AZ and 1241/C/03
AZD5122 [^{14}C] radiolabelled	Infusion, microtracer dose containing no more than 10 kBq (270 nCi) [^{14}C], intravenous	Selcia Ltd for the crude preparation RadioChemistry AstraZeneca Research and Development Charnwood for the purification	EN02397-55-1 and 1241/C/04

Duration of treatment

In Part A, study drug (AZD5122 or placebo) was administered as a single oral dose. In Part B, AZD5122 was administered as a single oral dose plus an IV infusion of a radiolabelled microtracer dose ([^{14}C]-AZD5122; 10 µg).

Statistical methods

No formal statistical hypothesis testing was performed. Pharmacokinetic (PK), pharmacodynamic (PD), safety and tolerability data were summarised descriptively including tables, listings and graphs, as appropriate.

Subject population

The first healthy volunteer entered Part A of the study on 21 September 2009 and the last healthy volunteer finished on 6 November 2009. In total, 36 healthy volunteers were randomised into the study at 1 study site; each received 1 administration of study drug (AZD5122 or placebo) during the planned treatment visit.

Of the 36 healthy volunteers dosed, 24 received AZD5122 and 12 received placebo (Table S3).

Table S3 Number of healthy volunteers per cohort (Part A)

Cohort	AZD5122 dose	Number of healthy volunteers			Ratio active:placebo
		Placebo	AZD5122	Total	
1	2 mg	3	6	9	6:3
2	10 mg	3	6	9	6:3
3	20 mg	3	6	9	6:3
4	50 mg	3	6	9	6:3
Total		12	24	36	6:3

The fifth planned cohort was not required because the mean maximum plasma concentration (C_{max}) achieved in healthy volunteers who received AZD5122 50 mg (Cohort 4) ranged from 1040 to 2730 nmol/L, the upper range of which was close to the exposure limit cut-off for C_{max}. As the dose/exposure relationship was linear between 2 and 50 mg no further doses were necessary.

The first healthy volunteer entered Part B of the study on 23 October 2009 and the last healthy volunteer finished on 23 November 2009. In total, 5 healthy volunteers received a single IV infusion of a [^{14}C]-radiolabelled IV microtracer dose of AZD5122 and a single AZD5122 oral dose (35 mg) during the planned treatment visit for Part B at 1 study site. All 5 healthy volunteers completed the study.

No protocol deviations led to exclusion of data from the PK or safety analyses in Part A or Part B of the study. All 24 healthy volunteers who received AZD5122 in Part A of the study and all 5 healthy volunteers who received AZD5122 in Part B of the study were included in the PK analysis sets. The safety analysis sets for Part A and Part B and the PD analysis set for Part A included all randomised healthy volunteers.

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

Summary of pharmacokinetic results

The absorption of AZD5122 following oral administration was rapid: the observed time to maximum plasma concentration was within 30 minutes and 1.5 hours post-dose and appeared to be independent of dose. The plasma concentration versus time profiles, following the oral dose, were similar in Part A and Part B.

The bioavailability was moderate to high with a mean of 53.3%, and a range of 30.2% to 73.5%. The increase in systemic exposure (geometric mean C_{max} and the area under the plasma concentration-time curve from zero to infinity) was approximately dose proportional from 2 mg to 50 mg. The inter-individual variability was moderate, up to approximately 7-fold.

Following IV administration, AZD5122 had moderate clearance (mean 14.4 L/h) and the terminal volume of distribution was low (mean 29.4 L), which indicated minimal tissue distribution. The combination of moderate clearance and low volume of distribution resulted in a short terminal elimination half-life ($t_{½}$) (mean IV $t_{½}$ 1.55 hours). The $t_{½}$ measured following oral administration was slightly longer, measured at approximately 1 hour 45 minutes in Part A for doses 10 mg to 50 mg and 2 hours 15 minutes in Part B.

Approximately 10% of the administered dose of AZD5122 was excreted unchanged in urine (collected in Part A), mostly in the first 12 hours post-dose. Assuming a mean bioavailability of 53.3% (determined in Part B), the 10% excreted unchanged accounts for approximately 19% of the absorbed dose. Mean renal clearance (CL_R) over 48 hours was consistent over the dose range and was typically between 2 and 3 L/h.

Summary of pharmacodynamic results

A meaningful response in the cluster of differentiation molecule 11b (CD11b) ex vivo stimulation assay is represented by a dose ratio at 20% of the pre-dose response curve (DR20) >2, although normal variation may generate a shift of this magnitude: the placebo response was up to 2.840. In this study, a meaningful response was only observed with the highest dose group, 50 mg, at 4 hours post-dose where the mean DR20 was 2.71. This result is consistent with the PK data since plasma concentrations expected to produce a PD response were only reached at around C_{max} following the 50 mg dose.

Summary of safety results

There were no deaths, no adverse events (AEs) that were considered serious, and there were no discontinuations due to AEs or any other significant AEs reported in either part of the study. All healthy volunteers who received AZD5122 tolerated study drug.

In total in Part A, 16 healthy volunteers had an AE; 6 of the 12 healthy volunteers (50%) who received placebo and 10 of the 24 healthy volunteers (42%) who received AZD5122. The total number of AEs reported by these healthy volunteers was 22; 9 were reported in the 6 healthy volunteers who received placebo and 13 were reported in the 10 healthy volunteers who received AZD5122. In healthy volunteers who received placebo, nasopharyngitis was reported for 2 healthy volunteers. In healthy volunteers who received AZD5122, diarrhoea, oropharyngeal pain and rash were each reported for 2 healthy volunteers. All other AEs were reported in no more than 1 healthy volunteer. In Part B, 2 healthy volunteers had a total of 3 AEs (2 AEs of flatulence and 1 AE of headache); there were no local tolerability issues relating to the IV infusion of AZD5122. All AEs reported in both parts of the study were mild or moderate in intensity and none of the AEs reported were considered causally related to study drug by the Investigator.

In Part A, 7 healthy volunteers had a total of 7 AEs that were moderate in intensity; 5 healthy volunteers who received placebo and 2 healthy volunteers who received AZD5122 (1 in each of the 10 mg and 50 mg cohorts). All AEs in Part B were mild in intensity.

There were no clinically relevant changes in haematology, clinical chemistry (including high sensitivity C-reactive protein) or urinalysis parameters in healthy volunteers exposed to AZD5122 in Part A or Part B of the study. No clinically significant change in circulating neutrophil numbers was observed at the timepoints examined, up to and including an AZD5122 dose of 50 mg.

In addition, no relationship was observed between circulating neutrophil numbers and AZD5122 exposure at the timepoints examined. It should be noted that the times at which samples were taken for circulating neutrophils did not correspond to the time at which C_{max} was observed.

There were no clinically relevant changes in blood pressure, pulse rate or temperature during the study in healthy volunteers exposed to AZD5122. No association between AZD5122 and critical ECG parameters including QT interval corrected for heart rate using Fridericia's formula was observed.