Clinical Study Report Synopsis

Drug Substance	AZD5069
Study Code	D3550C00007
Edition Number	Final
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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 Administration of Multiple Ascending Doses for 8 days in Healthy Male or Female Subjects

Study dates: First subject enrolled: 14 December 2009
Last subject last visit: 06 April 2010

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 study centre: London, 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 explore the safety and tolerability of AZD5069 at steady-state, following oral administration of multiple ascending doses to healthy subjects.	Adverse events, laboratory variables (including high sensitivity C-reactive protein (hsCRP) and circulating neutrophils), vital signs (blood pressure, pulse, body temperature), 12-Lead electrocardiogram (ECG), QT interval and continuous cardiac monitoring using telemetry.	Safety
Secondary	**Secondary**	
1. To investigate AZD5069 kinetics following single doses and at steady-state, following twice a day dosing.	Day 1: C_{max}, t_{max}, $AUC_{(0-12)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$ AUC, λ_z, $t_{½}$, V_z/F, CL/F, % AUCextrapolated, $Ae_{(0-24)}$, $CLR_{(0-24)}$. Day 6: C_{max}, t_{max}, $AUC_{(0-12, Day 6)}$, $AUC_{(0-t, Day 6)}$, $AUC_{(0-24, Day 6)}$, CL/F, Rac. Day 8: C_{max}, t_{max}, $AUC_{(0-12, Day 8)}$, $AUC_{(0-t, Day 8)}$, $AUC_{(0 24, Day 8)}$, CL/F. Rac. V_z/F, λ_z, $t_{½}$, $CL_{R(0-12)}$, $Ae_{(0-12, Day 8)}$.	Parmacokinetic (PK)
2. To investigate the pharmacodynamic (PD) activity of AZD5069 by assessment of ex vivo GROα stimulated CD11b expression on neutrophils in whole blood.	DR20	PD
3. To measure the effect of AZD5069 on numbers of circulating neutrophils.	Absolute numbers and % change	PD
4. To investigate the relationship between plasma AZD5069 concentrations and/or systemic exposures and the effect on circulating neutrophils.		PK/PD

$Ae_{(0-12)}$ = Cumulative amount of unchanged drug excreted into urine over a dosing period , $Ae_{(0-24)}$ = Cumulative amount of unchanged drug excreted into urine up to 24 hours post-dose, $AUC_{(0-12)}$ = Area under plasma concentration time curve from zero to 12 hours post-dose, $AUC_{(0-t)}$= Area under plasma concentration time curve from zero to the last quantifiable drug plasma concentration, $AUC_{(0-24)}$ = Area under plasma concentration time curve from zero to 24 hours post-dose , AUC= Area under plasma concentration time curve from zero to infinity, CL/F= Apparent oral clearance following extravascular dosing, $CL_{R(0-12),}$ = Renal clearance over the period zero to 12 hours post-dose, $CL_{R(0-24)}$=Renal clearance over the period zero to 24 hours post-dose C_{max}= Maximum plasma concentration, λ_z = Terminal elimination rate constant , PD=Pharmacodynamics, PK=Pharmacokinetics, $t_{½}$ = Terminal elimination half-life, t_{max}= Time to $C_{max,}$ V_z/F= Apparent volume of distribution during terminal elimination phase, R_{ac}= Accumulation ratio

Study design

A Phase I, single-centre, double-blind, randomised, parallel group, placebo-controlled study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of AZD5069 following multiple ascending dose administration to healthy subjects.

Each subject received a once daily dose of AZD5069 or placebo on Days 1 and 8 and a twice daily dose on Days 2 to 7, administered following a fast of at least 4 hours. After each cohort, a Safety Review Committee evaluated the safety, tolerability and pharmacokinetics of AZD5069 and decided the next dose. Each subject participated in 1 cohort only.

Target subject population and sample size

Up to 36 healthy subjects who smoked were planned to participate in 3 cohorts (with up to 12 subjects in each cohort). In each cohort, subjects were randomised to receive AZD5069 or placebo in a ratio of 9:3.

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

The batch numbers for AZD5069 oral suspension of 1 mg/g were: 09-004095AZ (09-008096AZ and 10-000064AZ), 09-007746AZ (10-000143AZ).

The batch number for AZD5069 oral suspension of 50 mg/g was 09-008098AZ (09-007747AZ).

The batch numbers for placebo oral suspension were: 09-003475AZ (09-008101AZ), 09-003475AZ (10-0020145AZ), 09-006363AZ (10-000989AZ).

Subjects received 10 mg, 40 mg or 100 mg AZD5069 or placebo as an oral suspension.

Duration of treatment

Eight days: subjects received a once daily dose of AZD5069 or placebo on Days 1 and 8 and a twice daily dose on Days 2 to 7.

Statistical methods

The safety analysis set included all subjects who received study treatment and had data collected post dose.

The data were summarised using descriptive statistics.

Subject population

Subjects were aged from 18 to 56 years, with a body mass index from 20 to 29 kg/m^2. Twenty-seven subjects were white, 1 was black or African American, 3 were Asian and 2 were mixed. Subjects all smoked between 5 and 25 cigarettes per day.

Overall, the treatment groups were well balanced with regards to demographic characteristics.

Summary of pharmacokinetic results

Following both a single dose (Day 1) and at steady-state following twice a day dosing (Days 6 and 8), AZD5069 was absorbed relatively fast (median t_{max} 0.78 to 2 hours). Following C_{max}, plasma AZD5069 concentrations declined in a multiexponential manner.

C_{max} and $AUC_{(0-12)}$ data on Day 6 and Day 8 were used to obtain estimates of the observed intra- and inter-subject variabilities. C_{max} displayed moderate inter- and intra subject variability (CV%13 to 35% and 19 to 22%, respectively). $AUC_{(0-12)}$ values appeared to be relatively reproducible within the same subject, (i.e. intra-subject variability as indicated by CVs were 3 to 11%), but were more variable between subjects (i.e. inter-subject variability was moderate to high [CVs ranged between 29 to 62%]). For some unexplained reason, the $AUC_{(0-12)}$ inter-subject variability following the 40 mg dose was approximately half that observed following both the 10 and 100 mg doses, this is clearly seen in the individual dose normalised plots. As the 40 and 100 mg doses were both made from the supplied higher dose strength (50 mg/g), this could not explain the differences in the observed variabilities between these dose groups. The large difference in the inter-subject variability between the 40 mg dose versus the 10 and 100 mg doses was not observed for C_{max}, as seen in the individual dose normalised plots. Thus, caution needs to be exerted upon comparing the geometric mean $AUC_{(0-12)}$ data alone across the different dose groups.

Geometric mean $AUC_{(0-12)}$ appeared to increase in a dose proportional manner from 10 to 40 mg on Day 1, then in a slightly greater than dose proportional manner from 40 to 100 mg (approximately 3.1-fold increase for a 2.5-fold increase in dose). However, when comparing the $AUC_{(0-24)}$ values on Day 1 over the dose range investigated, $AUC_{(0-24)}$ appeared to increase in a slightly less than proportional increase from 10 to 40 mg, (2.6-fold increase for a 4-fold increase in dose), then in a slightly more than dose proportional increase from 40 to 100 mg (3.2-fold increase for a 2.5-fold increase in dose). The discrepancy between the $AUC_{(0-24)}$ and $AUC_{(0-12)}$ data, suggests that different proportions of the terminal phase is seen over the 12 to 24 hour post dose period following the different doses. This is in agreement with the observed terminal half-lives, where a slightly shorter half-life was observed following the 10 mg dose compared to the 40 and 100 mg doses. However, based on the individual dose normalised C_{max} and $AUC_{(0-12)}$ plots, which take the inter-subject variability into account, both C_{max} and $AUC_{(0-12)}$ appear to increase in a dose proportional manner over the 10 to 100 mg dose range, following both a single dose (Day 1) and at steady-state (Day 6 and Day 8).

Based on Days 1, 6 and 8 data along with the trough data, steady-state appears to be attained on Day 3 (after 3-4 doses), thus Day 6 and Day 8 data can be used to obtained steady-state kinetic parameters for AZD5069. Steady-state is theoretically achieved by approximately 3.3 half-lives, thus for a 10.5 hour elimination half-life, (observed following the cessation of steady-state on Day 8), steady-state should be attained by approximately 1.4 days i.e. 3 doses, which is agreement with the observed trough data. The observed accumulation ratio is also similar to that predicted based on single dose kinetics. On the two intensive PK sampling days, the pre-dose and 12 hour samples, were generally similar to each other in magnitude. However, on the remaining days where troughs were taken, (which resemble the pre-dose and 12 hour sample timings on Day 6 and Day 8), there was a consistent pattern in a number of subjects where the morning concentrations appear to be higher than the evening concentrations. The differences were generally larger than those observed on Days 6 and 8 between these two samples. In all cases, the differences between the pre-dose and 12 hour samples were 2-fold or less in magnitude, and did not influence the observed systemic exposures on Days 6 and 8, which were similar to the AUC values on Day 1. The fact that

$AUC_{(Day\ 1)}$ was similar in magnitude to $AUC_{(0-12)}$ on Days 6 and 8, indicated that AZD5069 displayed time independent kinetics.

Summary of pharmacodynamic results

Data from the CD11b assay, in the form of the mean dose ratio DR20 plotted versus time, indicated a dose-dependent response at 4 hours (first sampling time point) after the first AZD5069 dose with a mean DR20 of 7.15, 38.0 and 80.5, respectively for the 10, 40 and 100 mg dose group (placebo mean was 1.06). The levels had returned to baseline at 24 hours post dose. Pre-dose DR20 at Day 6 and Day 8 was above baseline and the increase 4 hours post dose on Day 6 was higher than on Day 1 with mean DR20 values of 7.27, 69.1 and 139, respectively for the 10, 40 and 100 mg dose group (placebo mean was 1.21). Based on previous data, the plasma concentrations at 4 hours post dose in the 100 mg dose group was expected to produce maximum effect based on the conditions of the assay and the samples were therefore not analysed.

DR20 had returned to baseline 24 hours post last dose (Day 9) for the 10 and 40 mg dose group and 48 hours post dose (Day 10) in the 100 mg dose group.

Plots of mean neutrophil count versus time indicated that subjects on AZD5069 treatment generally experienced a dose-related drop in neutrophil count after the first dose on Day 1 (mean change from baseline 12 hours post dose was -0.9, -1.2 and -2.3x 10^9/L, respectively, in the 10, 40 and 100 mg dose group and -0.7x10^9/L in the placebo group). There was a recovery 24 hour post first dose but during the twice daily dosing the neutrophil count (pre-morning dose measurements, 12 hours post-dose) stayed lower for subjects on active treatment. The mean neutrophil count was returning to baseline at the follow-up visit. The decrease in neutrophil count over time was generally less in the 10 mg dose group compared with the higher dose group and the response in the 40 and 100 mg dose group were comparable.

There was a slight increase in mean hs-CRP in the 100 mg dose group on Day 6 (mean change from baseline was 2.8 mg/dL).

Summary of pharmacokinetic/pharmacodynamic relationships

An increase in DR20 in the presence of drug is associated with a reduction in ex-vivo induction of CD11b expression. The DR20 represents the amount of GROα needed to elicit 20% of the maximum CD11b response. These data support the indication of a relationship between AZD5069 concentration and DR20. The DR20 response appeared to be independent of time as at any one concentration, the different sampling times appear to be interspersed. There was an indication of decreasing neutrophils with increasing AZD5069 plasma concentrations.

There is a suggestion that neutrophils decrease with increasing AZD5069 plasma concentrations, with the lowest neutrophil counts being associated with the higher plasma concentrations, but the high inter-subject variability in neutrophil counts makes the data difficult to interpret.

There was no clear relationship between hs-CRP and AZD5069 plasma concentration

Summary of safety results

There were no deaths or other serious adverse events (SAEs) in the study.

There were 2 discontinuations of investigational product due to AEs.

- Subject E0001136 (100 mg AZD5069) was withdrawn on Day 5 due to low neutrophil count (< 1.0 x 10^9 /L for more than 48 hours) which met the individual subject stopping criteria. This was recorded as an AE of neutropenia.

- Subject E0001123 (100 mg AZD5069) was withdrawn on Day 6 due to an AE of C-reactive protein increased which met the stopping criteria as it increased to >3 x ULN.

Both AEs were considered by the investigator to be possibly related to treatment.

There was no apparent dose related trend in AEs. A total of 4/8 (50%) subjects receiving AZD5069 10 mg, 6/9 (67%) subjects receiving AZD5069 40 mg and 4/8 (50%) subjects receiving AZD5069 100 mg reported AEs. In subjects receiving placebo, 2/8 (25%) reported AEs.

The most common AEs were dizziness (2 subjects 40 mg, 1 subject 10 mg), back pain (2 subjects 40 mg) and headache (1 subject 10 mg, 1 subject 40 mg).

There were no AEs of severe intensity. There was 1 AE of moderate intensity (procedural site reaction, placebo). All other AEs were of mild intensity.

Other than the AEs that led to subject withdrawals, there were no clinically significant findings in laboratory values. Circulating neutrophil counts decreased in a plasma concentration related manner but the mean values did not fall outside the extended reference ranges (1.5 x10^{12}/L to 10 x10^{12}/L) during the study. There were no clinically significant abnormalities noted in ECG or vital signs.