AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD5069
Study Code	D3550C00005
Edition Number	1
Date	30 September 2011

A Phase 1, Randomised, Double-Blind, Placebo-Controlled, Parallel Group Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Oral AZD5069 in Healthy Japanese Subjects After Single and Multiple Ascending Doses

Study dates: First subject enrolled: 26 May 2010
Last subject last visit: 22 February 2011

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.

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Study centre(s)

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 single and multiple oral administrations to healthy Japanese subjects.	Adverse events, vital signs (blood pressure, pulse and body temperature), electrocardiograms (ECGs), physical examination, laboratory variables (clinical chemistry, haematology, urinalysis, and high sensitivity C-reactive protein (hsCRP) and circulating neutrophils).	
Secondary	**Secondary**	
To investigate the pharmacokinetics (PK) of AZD5069 in plasma and urine following single and multiple dosing of AZD5069 twice daily in healthy Japanese subjects.	The following PK parameters were determined using plasma AZD5069 concentration-time data from: C_{max}, t_{max}, $AUC_{(0-12)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, AUC, λ_z, $t_{½}$, Vz/F, CL/F, % AUCextrapolated, and from urine data: Ae, CL_R. Vz/F, λ_z, $t_{½}$, and from urine data: CL_R, $Ae_{(0-12)}$. Dose proportionality (AUC, C_{max}, AUC_{ss} and $C_{max,ss}$) and extent of accumulation (R_{ac}) was also assessed.	
To investigate the pharmacodynamics (PD) activity of AZD5069 by assessment of ex vivo GROα stimulated CD11b expression on neutrophils in whole blood, and its relationship to the PK. To measure the effect of AZD5069 on numbers of circulating neutrophils. To investigate the relationship between plasma AZD5069 concentrations and/or systemic exposures and the effect on circulating neutrophils.	Analysis of GRO-α induced CD11b expression on neutrophils.	

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Exploratory	**Exploratory**	
To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (i.e. distribution, safety, tolerability and efficacy) to AZD5069, and associated biomarkers, where appropriate.	DNA samples may be used to explore how genetic variations may affect the response to AZD5069.	
To store remaining plasma samples for further potential metabolism and pharmacokinetic investigations.		

Study design

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

Twenty-seven healthy Japanese subjects were planned to be randomised in 3 cohorts. If deemed necessary by the Safety Review Committee (SRC) up to an additional 3 dose groups could have been added. These additional cohorts, Cohorts 3 to 6, could have been 9 or 12 subjects based on the decision of the preceding SRC meeting. 63 randomised subjects were actually included in the study. Nine healthy subjects were included in Cohorts 1 and 2, and nine or 12 healthy subjects were included in Cohorts 3 to 6. The subjects received either AZD5069 or placebo, randomised 6:3 (cohort of 9) or 8:4 (cohort of 12). Each subject was only dosed in one cohort.

Target subject population and sample size

Sixty three healthy subjects aged 20 to 65 years participated in 6 cohorts. 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.

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

The IP was supplied by AstraZeneca R & D Lund as bulk. AZD5069 and placebo were provided as an oral suspension in 20 mL amber glass bottles containing 20 g each. Placebo consisted of the same ingredients as the active except for the absence of AZD5069. The IP was dispensed by the Pharmacy staff at RPL according to the randomisation scheme and separate instructions.

Table S2 Details of investigational product and other study treatments

Investigational product	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Batch number	Expiry date
AZD5069	1 mg/g, Oral suspension	AstraZeneca	10-000610AZ	28 Feb 11
AZD5069	50 mg/g, Oral suspension	AstraZeneca	09-007747AZ	31 Oct 10
			10-000612AZ	28 Feb 11
Placebo	Oral suspension	AstraZeneca	09-006363AZ	30 Sept 11

Duration of treatment

Single oral dose on Day 1 of AZD5069 suspension (10 mg, 20 mg, 40 mg, 60 mg, 80 mg, 120 mg). From Day 4 subjects received either single (Day 4 to Day 11) or multiple (twice daily doses from Days 4 to 10 and a single morning dose on Day 11) oral doses of AZD5069 (10 mg – 80 mg).

Statistical methods

The safety, tolerability, pharmacokinetic and pharmacodynamic data were summarised descriptively including tables, listings and graphs, as appropriate. Placebo subjects from different dose levels will be pooled for the comparisons.

Subject population

Forty-two (42) healthy male subjects received AZD5069 at doses ranging from 10 to 120 mg, and 21 received placebo. The safety analysis set included all 63 randomised subjects, the PK analysis set included all subjects who received active study drug (42 subjects) and the PD analysis set included 21 subjects (Cohorts 1 [10 mg] and 3 (40 mg] only).

Fourteen (14) subjects were withdrawn from the study. 13 subjects were withdrawn due to adverse events (12 meeting stopping criteria, 1 ventricular tachycardia) and 1 subject due to other events. For these subjects, data was included in the PK/PD analysis up to the point of withdrawal after which recorded values were excluded. In a similar manner, neutrophil data was included in the safety analysis set for these subjects up to the point of withdrawal after which recorded values were excluded.

Summary of safety results

Dose escalation was stopped at 120 mg single dose and 80 mg repeated dose because of withdrawals caused by low levels of circulating neutrophils. Multiple daily doses of AZD5069 up to 80 mg over 7 days given to Japanese healthy male subjects were shown to be well tolerated and demonstrated an acceptable safety profile in terms of AEs, ECG, vital signs and laboratory data other than neutrophils. The systemic exposure (AUC and C_{max}) of escalating single doses of 10-120 mg and repeated doses of 10-80 mg bid was well within the predefined exposure limits.

One SAE was reported (hepatitis) and one subject who was receiving placebo was withdrawn due to an AE (ventricular tachycardia). Expected clinically significant changes were observed in laboratory safety parameters which led to individual stopping criteria being met and subjects withdrawn due to adverse events. Ten (10) subjects were withdrawn from the study due to low neutrophil levels and two subjects were withdrawn from the study due to increased hs-CRP levels. The reason for the raised hs-CRP concentration is not known. With the exception of one subject (hepatitis A), there were no unexpected clinically significant abnormalities observed for laboratory safety parameters or vital signs and ECG assessments. All subjects who met individual stopping criteria were receiving the active compound. At higher plasma concentrations of AZD5069, there were more instances of subjects having low numbers of circulating neutrophils.

Summary of pharmacokinetic results

AZD5069 was rapidly absorbed after oral dosing and plasma concentrations declined with a terminal $t_{1/2}$ of between 8.10-11.9 hours (Day 1) and between 9.51-23.3 hours (Day 11). Following administration of AZD5069 doses (10 mg and above), the time to peak plasma concentrations (t_{max}) occurred between 0.5 hours and 4 hours and appeared to be independent of dose.

Based on trough concentrations, steady-state was reached within two to three days after the start of twice daily dosing. It should be noted that the morning trough concentrations (12 hours post-evening dose) were higher than the evening trough concentrations (12 hours post-morning dose) suggesting diurnal variability in the PK of AZD5069. The reason for this difference in morning and evening trough values is not known.

There was no or minor accumulation after repeated dosing and no major time dependency except for the diurnal variability (described above). The calculation of Rac is affected by higher residual concentrations from the evening dose (morning trough concentrations are not equal to the evening trough concentrations) and the values reported should be interpreted with caution. AZD5069 displayed dose proportional plasma exposure following single and multiple oral dosing over the dose range investigated (10 mg to 120 mg [80 mg multiple dose]). A minor fraction of the AZD5069 dose was excreted unchanged in urine.

Summary of pharmacodynamic results

Data from the CD11b assay presented as mean dose ratio DR20 versus time demonstrated a dose dependent response for the 10 mg and 40 mg doses at 4 hours post-dose on Day 4 (first sampling time point) after the first AZD5069 dose. Overall, increased plasma concentration of AZD5069 resulted in an increase in DR20 confirming the suppression of GRO-α stimulation of CD11b. The 40 mg dose level showed a greater suppressive effect compared with the 10 mg dose level.

Conclusion(s)

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