AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD5069
Study Code	D3550C00010
Edition Number	1
Date	21 January 2011

A Phase I, Two-Part Study to Investigate the Effects of Food on the PK of a Single Oral Dose of AZD5069 in Healthy Adult Volunteers (Part A) and to Compare the PK of AZD5069 in Adult and Elderly Healthy Volunteers (Part B)

Study dates: First subject enrolled: 12 February 2010
Last subject last visit: 21 July 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)

This was a single centre study conducted in London, United Kingdom.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The primary objectives were to compare the pharmacokinetics of AZD5069 following administration of single oral doses when fasting or after a high fat meal (Part A) and to make an initial assessment of any pharmacokinetic differences in the fasted state between adult (18 to 65 years) and elderly adult (>65 years) subjects (Part B).

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To compare the pharmacokinetics of AZD5069 following administration of single oral doses when fasting or after a high fat meal (Part A) To make an initial assessment of any pharmacokinetic differences in the fasted state between adult (18 to 65 years) and elderly adult (>65 years) subjects (Part B)	The following variables were determined for Part A and Part B: C_{max}, t_{max}, $t_{½\lambda z}$, $AUC_{(0-24)}$, $AUC_{(0-t)}$, AUC, CL/F, V_z/F The following variables were determined for diagnostic purposes and are listed but not summarised: λ_z, Rsq for calculation of λ_z and %AUCextrapolated	PK
Secondary	**Secondary**	
To provide further information on the safety and tolerability of AZD5069 following administration of single oral doses to healthy subjects	Adverse events, vital signs, ECGs, laboratory variables (including hsCRP and circulating neutrophils), blood pressure, pulse rate, body temperature	Safety
Exploratory	**Exploratory**	
To collect and store DNA samples for possible retrospective exploratory PGx analysis, investigating the influence of genotype on response, safety, tolerability and PK of AZD5069, and associated biomarkers, where appropriate	Not applicable (any outcomes reported separately from this CSR)	PGx
To store remaining plasma samples for further potential metabolism and PK investigations	Not applicable (any outcomes reported separately from this CSR)	PK

Study design

This was a Phase I, two-part, open label, single centre study. Part A was an assessment of the effect of food (high fat meal) on the PK, safety and tolerability of single oral doses of

AZD5069 (suspension) in healthy adult subjects (18 to 65 years) and Part B was an initial assessment of the PK of AZD5069 in elderly adult (>65 years) versus adult (18 to 65 years) subjects in the fasted state in Part A. The dose of AZD5069 administered was 120 mg, which has previously been administered to healthy subjects and was well tolerated.

Target subject population and sample size

Part A: 16 healthy male subjects and healthy female subjects of non-childbearing potential aged 18 to 65 years (smokers and non-smokers), with body mass index between 18 and 30 kg/m^2 inclusive and weight of at least 50 kg and no more than 100 kg.

Part B: 8 healthy male subjects and healthy female subjects of non-childbearing potential aged >65 years (smokers and non-smokers), with body mass index between 18 and 30 kg/m^2 inclusive and weight of at least 50 kg and no more than 100 kg.

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

Part A: subjects received one single oral dose of 120 mg AZD5069 (suspension of 50 mg/g) following a fast of at least 10 hours and a single oral dose in the fed state (30 minutes from commencing a high fat meal), batch number 09-004102AZ.

Part B: subjects received a single oral dose of 120 mg AZD5069 (suspension of 50 mg/g) after a 10 hour fast, batch numbers 09-004102AZ and 10-000612AZ.

Duration of treatment

Part A: each subject received a single dose of AZD5069 on 2 occasions separated by a minimum 7-day washout period.

Part B: each subject received a single dose.

Statistical methods

The analyses of safety, tolerability and pharmacokinetic data were summarised descriptively including tables, listings and graphs, as appropriate.

Part A: data were presented by treatment regimen (ie, fed or fasted) in Part A. An analysis of variance model for AUC and C_{max} was used for an assessment of the effect of food on the pharmacokinetics of AZD5069. Subjects with AUC or C_{max} in both periods were included in this analysis. Ninety percent confidence intervals for the ratio of fed/fasted will be presented. An analysis of t_{max} using the Wilcoxon Signed Rank Test, and the Lehman median estimator of difference (fed-fasted) and 90% CIs was also presented.

Part B: data were presented by age group and period for subjects in the fasted state only ie, data was summarised for three groups - Elderly adults (>65 years), fasted adults (18 to 65 years) in Treatment Period 1 of Part A, and all fasted adults (18 to 65 years) ie, from Treatment Periods 1 and 2 of Part A. An analysis of variance model for AUC and C_{max} was used to investigate differences in pharmacokinetics between elderly adult (>65 years) and

adult (18 to 65 years) subjects after administration of AZD5069 in the fasted state. For the adult subjects, only the Treatment Period 1, fasted observations were included in the statistical analysis. All elderly subjects were included in the analysis. Ninety percent confidence intervals for the ratio for C_{max} and AUC for the elderly adult (>65 years)/adult (18 to 65 years) were presented. An analysis of t_{max} between age group using the Wilcoxon Signed Rank Test, and the Lehman mediator estimator of difference and 90% CIs were also presented.

Subject population

Part A: 16 healthy adult males (18 to 65 years) were enrolled and randomised. Note that although females of non-childbearing potential were to be screened for Part A of the study no eligible females were recruited. All subjects completed the study and were included in the analysis of safety and pharmacokinetics. Three of the subjects were smokers. Subjects in Part A were well balanced across the 2 treatment arms (fasted-fed and fed-fasted).

Part B: 8 healthy elderly male and female subjects (>65 years) were enrolled on the study. All subjects completed the study and were included in the analysis of safety and pharmacokinetics. The elderly subjects had a lower mean weight and height than the adult males (both those fasted in Treatment Period 1 and pooled data) although mean BMI was similar in all groups. The elderly females were generally shorter than the elderly males; the females had a height range of 154 cm to 163 cm and the elderly males a range of 173 cm to 180 cm. The Part A adult males were generally taller than both the male and female elderly subjects and had a height range of 174 cm to 187 cm (fasted in period 1 only) and 171 cm to 187 cm (fasted in any period). The elderly females had a weight range of 55.8 kg to 78.9 kg and the elderly males had a weight range of 65 kg to 69 kg. The adult males in Part A were generally heavier than both the male and female elderly subjects and had a weight range of 75.9 kg to 93.7 kg (fasted in Treatment Period 1) and 66.5 kg to 93.7 kg (fasted in any period).. There were no smokers amongst the elderly subjects compared with 2 of the adult males fasted in Treatment Period 1 and 3 of the adult males fasted in both periods.

Summary of pharmacokinetic results

While this study was not powered to show bioequivalence statistically, standard bioequivalence limits (80% to 125%) were used to help put the results into clinical context.

Part A: the administration of a high fat meal decreased AZD5069 C_{max} with a geometric LS mean ratio of 49.65% (fed/fasted), with a 90% confidence interval falling completely below the 80% to 125% standard bioequivalence limit. The geometric mean AZD5069 C_{max} after a 10-hour fast was 8440 nmol/L, and 4190 nmol/L when administered 30 minutes after a high fat meal. Food did not appear to influence AZD5069 AUC by a large amount although there was a decrease (90% CI [83.22%, 94.48%]). The geometric mean AZD5069 AUC after a 10-hour fast was 35900 nmol*h/L, and 32400 nmol*h/L when administered 30 minutes after a high fat meal. The high fat meal prolonged AZD5069 t_{max} by a median difference of 3 hours (fasted: 1.23 hours; fed 4.00 hours). The arithmetic mean $t_{½}$ for the fed (10.2 hours) and fasted (9.33 hours) treatment regimens was comparable, with higher variability in estimates for the fed state.

Part B: the primary analysis included a comparison of elderly subjects versus adult subjects fasted during Treatment Period 1. For elderly subjects AUC and C_{max} were higher compared with adult subjects with geometric LS mean ratios of 149% and 123%, respectively, falling above the 80% to 125% standard bioequivalence limit. Geometric mean AZD5069 C_{max} and AUC were 10200 nmol*h/L and 49900 nmol*h/L, respectively. For the primary analysis there was no important difference in t_{max} between the two age groups with a median value of approximately 1.5 hours. The arithmetic mean $t_{½}$ in elderly subjects was 2.3 hours shorter than for adult subjects (Period 1 only), and 1.7 hours shorter than for all fasted adult subjects, however the range of individual $t_{½}$ estimates was similar across age groups.

Even though the C_{max} and AUC data may suggest that the geometric mean may be higher in elderly subjects, the range in values were similar in the two populations. Thus, these limited single dose PK data suggest that no dose alteration is required for an elderly population.

Summary of safety results

Treatment with a single dose of 120 mg (oral suspension) AZD5069 was well tolerated both by healthy adult males in the fed and fasted state and by healthy elderly males and females in the fasted state. Post-treatment AEs were few in number and all were mild in intensity.

There were no clinically relevant post-treatment changes in mean laboratory parameters. Some subjects were observed to have decreases in neutrophil count although the mean neutrophil count of both the adult males in Part A and the elderly males and females in Part B stayed within the limits of the reference range. One adult male subject had a decreased neutrophil count of 1.1 x 10^9 L that fell below the lower extended limit of the reference range (1.5 x 10^9 L) 48 hours after receiving AZD5069 in the fasted state (Treatment Period 1), which returned to baseline by admission to the next period. AZD5069 exposure for this subject fell in the middle of the exposure range with an AZD5069 C_{max} of 7600 nmol/L and AUC of 39000 nmol*h/L. No adverse events or clinically important post-treatment changes were noted for the elderly subject with the highest maximum plasma concentrations, which were 2-fold higher than the average of the elderly population.

A decrease in neutrophil count was expected for this compound as described in Section 3 of the CSR and the Investigator's Brochure. The observed changes in neutrophil count were consistent with previous studies with AZD5069 and were not considered to be clinically relevant in the healthy subjects participating in this study.

There were no clinically relevant findings in vital signs, ECGs or physical examination findings.