AstraZeneca

Clinical Study Report Synopsis

Drug Substance	ZD4054
Study Code	D4320C00028
Edition Number	1
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A Randomised, Open-label, Single-centre, Crossover Study in Healthy Male Volunteers to Assess the Effect of Food on the Pharmacokinetics of a 10 mg Single Oral Dose of ZD4054

Study dates: First healthy volunteer enrolled: 23 June 2008
Last healthy volunteer completed: 20 August 2008

Phase of development: Clinical pharmacology (I)

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

Study period		Phase of development
First healthy volunteer enrolled	23 June 2008	Clinical pharmacology (I)
Last healthy volunteer completed	20 August 2008	

Publications

None at the time of writing this report.

Objectives

The primary objective of this study was to characterise the pharmacokinetic profile of ZD4054 in the presence and absence of food in order to determine whether the pharmacokinetics of ZD4054 were altered by food.

The secondary objective of this study was to assure the safety of the healthy volunteers dosed.

Study design

The clinical study was an open-label, randomised 2-period crossover design to investigate the pharmacokinetic characteristics of ZD4054 in the fed and fasted state.

Target healthy volunteer population and sample size

A total of 30 healthy male volunteers aged between 18 and 65 years (inclusive) with a Body Mass Index (BMI) of 18 to 30 kg/m^2 (inclusive).

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

Investigational product:	ZD4054
Formulation	Tablet
Mode of administration:	oral
Strength:	10 mg
Dose:	10 mg as single dose in each treatment period
Batch number:	51224C07

The investigational product was administered once in fed and once in fasted state.

Duration of treatment

The study comprised of two treatment periods with a single dose of 10 mg each; doses were separated by a wash-out period of a minimum of one week.

Criteria for evaluation - pharmacokinetics (main variables)

Primary endpoints:	C_{max}, AUC_{0-t} and AUC for both treatment regimens; t_{max}, $t_{1/2}$, k_{el}, CL/F, V_{ss}/F and MRT were also to be reported.

Criteria for evaluation - safety (main variables)

Vital signs, ECG recording, clinical chemistry, haematology, urinalysis, adverse events.

Statistical methods

AUC, AUC_{0-t} and C_{max} were logarithmically transformed using natural logarithms (back-transformed results were reported). These parameters were analysed using an analysis of variance (ANOVA) model, fitting effects for sequence, subject within sequence, period and food condition separately for each group.

The results of these analyses were presented in terms of geometric least square means for each food condition, the food effect (the ratio of fed / fasted) and its 90% confidence interval.

If the above resultant 90% confidence interval of the ratio did not lie completely in the acceptance limits [0.8, 1.25], then a statistically significant food-effect could not to be excluded; otherwise, no statistically significant food-effect was to be concluded.

All pharmacokinetic data were listed, and summarised by food condition using standard summary statistics.

Demography and baseline data were summarised and listed using appropriate summary statistics.

All safety data, including adverse events, were summarised by means of descriptive statistics. The safety data addressed the secondary objectives to assure the safety of all subjects by assessment of pulse and BP, ECG, clinical chemistry, haematology and adverse events.

Subject population

In total, 30 healthy male volunteers between the age of 28 and 53 were enrolled into the study and randomised, all of them received treatment and completed the study as per protocol. All volunteers were healthy based on the screening examination, complied with the inclusion criteria and none met any exclusion criteria. The 30 subjects were all included in the safety and in the PK analysis set. No major protocol deviations were recorded.

Summary of pharmacokinetic results

The main PK parameters of ZD4054 derived after single 10 mg dose administration under fasted and fed conditions are shown in Table S1. The results of the statistical analysis of the primary endpoints of the study are summarised in Table S2.

Table S1 Summary of pharmacokinetic parameters of ZD4054 (PK analysis set)

Parameter	Summary statistics	Fasted	Fed
C_{max}	Geometric mean (CV%)	469.6 (22)	356.8 (28.8)
[ng/mL]	n	30	30

Table S1 Summary of pharmacokinetic parameters of ZD4054 (PK analysis set)

Parameter	Summary statistics	Fasted	Fed
AUC	Geometric mean (CV%)	4711 (35.2)	4031 (33.9)
[ng.h/mL]	n	30	30
AUC_{0-t}	Geometric mean (CV%)	4688 (35.4)	4016 (34)
[ng.h/mL]	n	30	30
t_{max}	Median (range)	2.0 (0.75 – 6)	4.0 (1 - 6)
[h]	n	30	30
$t_{1/2}$	Arithmetic mean (SD)	7.652 (2.255)	8.388 (2.452)
[h]	n	30	30
k_{el}	Geometric mean (CV%)	0.09453 (30.7)	0.08617 (30.2)
[1/h]	n	30	30
CL/F	Arithmetic mean (SD)	37.5 (13.4)	43.5 (13.9)
[mL/min]	N	30	30
MRT	Arithmetic mean (SD)	11.09 (2.623)	12.30 (2.556)
[h]	n	30	30
V_{ss}/F	Arithmetic mean (SD)	23.66 (6.4)	30.88 (8.41)
[L]	n	30	30

AUC= area under the plasma concentration-time curve; AUC_{0-t}= area under the plasma concentration-time curve from timepoint 0 to the time of the last quantifiable concentration; CL/F= total apparent clearance; C_{max}= maximum plasma concentration; CV= coefficient of variation; MRT= mean residence time; N= number of subjects; n = number of observation; SD= standard deviation; $t_{1/2}$= terminal half-life; t_{max}= time to reach C_{max}; V_{ss}/F= volume of distribution at steady-state.

Table S2 Summary of GLSMean, geometric mean and 90% CIs for ratio of Fasted to Fed

Pharmacokinetic parameter	Fasted		Fed		Point estimate of GLSmean ratio of fed to fasted	90%CI of GLSmean ratio of fed to fasted
	N	GLSmean	N	GLSmean		
AUC [ng.h/mL]	30	4710.6	30	4031	0.8557	0.8023; 0.9127
AUC_{0-t} [ng.h/mL]	30	4687.9	30	4015.8	0.8566	0.8027; 0.9142
C_{max} [ng/mL]	30	469.6	30	356.8	0.7598	0.7147; 0.8077

AUC= area under the plasma concentration-time curve; AUC_{0-t}= area under the plasma concentration-time curve from timepoint 0 to the time of the last quantifiable concentration; CI= confidence interval; C_{max}= maximum plasma concentration; GLSmean= geometric least square mean; N= number of subjects.

Following administration of ZD4054 with a high-fat breakfast the overall exposure (AUC and AUC_{0-t}) to ZD4054 was significantly decreased by about 14% (AUC treatment ratio: 0.86; 90% CI: 0.80 to 0.91; AUC_{0-t} treatment ratio: 0.86; 90% CI: 0.80 to 0.91). This change in

overall exposure under fed conditions was not considered relevant, the corresponding 90%CIs were contained in the predefined margin of [0.8; 1.25] excluding an effect of food.

The rate of absorption of ZD4054 was slightly delayed after administration under fed (median t_{max} 4.0 hours) compared with fasted conditions (median t_{max} 2.0 hours). This resulted in C_{max} reduced on average by about 24% (treatment ratio 0.86; 90% CI 0.71 to 0.81), thus an effect of food on C_{max} could not be excluded.

The mean terminal half-life remained unchanged under fasted (7.7 hours) compared with fed conditions (8.4 hours). In accordance with the increase in AUC, apparent clearance (CL/F) increased slightly from 37.5 mL/min (range 18 mL/min to 81 mL/min) to 43.5 mL/min (range 13.9 mL/min to 74 mL/min) as well as the volume of distribution at steady-state (V_{ss}/F) from 23.7 L (range 15.4 L to 42.7 L) to 30.9 L (range 20.0 L to 59.7 L) under fasted and fed conditions, respectively.

Summary of safety results

A total of 80 AEs were reported by 28 (93.3%) subjects, ie, 41 and 39 AEs reported by 26 (86.7%) subjects each under fasting and fed conditions, respectively. The most frequent AEs after single dose treatment with ZD4054 under fasting and fed conditions were headache and to a lesser extent nausea, both reported at a similar frequency for both treatment conditions. All AEs were of CTC grade 1 or 2, and no SAE, discontinuations due to AE, or other significant AEs were observed.

There were no clinically relevant changes in safety laboratory variables, vital signs, ECG, and physical examination.