AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1236
Study Code	D4260C00006
Edition Number	1
Date	4 June 2009

A randomised single centre phase I study to investigate the safety, tolerability and pharmacokinetics of oral multiple ascending daily doses of AZD1236 tablet by a single-blind, placebo-controlled, and single dose relative bioavailability of the oral suspension and oral tablet formulations by an open cross-over in healthy Japanese men

Study dates: First healthy volunteer/patient enrolled: September 2008
Last healthy volunteer/patient completed: December 2008

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 study was conducted at Kyushu Clinical Pharmacology Research Clinic in Fukuoka, Japan.

Publications

None at the time of writing this report.

Objectives

Primary objective was:

- To investigate the safety and tolerability of multiple ascending oral doses of AZD1236 given to healthy young subjects for 13 days.

Secondary objectives were:

- To investigate the multiple-dose pharmacokinetics (PK) of AZD1236 in plasma, the degree of accumulation and the time dependency of the pharmacokinetics
- To evaluate the single-dose relative bioavailability of the oral suspension and oral tablet formulations.

Exploratory objective was:

- A blood sample for genotyping was collected for future, possible exploratory genetic research aimed at identifying/exploring genetic variations that may affect pharmacokinetics, safety and tolerability related to AZD1236 treatment. Results from any genetic research performed were reported separately from the clinical study report for the main study.

Study design

The study employed a multiple ascending dose (MAD) part (Groups A and B) and an relative bioavailability (BA) part (Group C).

MAD part was single-blind, placebo-controlled and randomised carried out at a single centre to assess the tolerability, safety and PK of multiple ascending oral daily doses of AZD1236 tablet once daily or twice daily for 13 days in healthy male subjects.

BA part was open, randomized, two-way crossover part consisting of two treatment periods separated by a wash-out of at least 10 days between dosing days to access the relative bioavailability by the PK after single oral administration of AZD1236 suspension or tablet once in the morning on fast condition in healthy male subjects and included 8 healthy subjects.

Target healthy volunteer population and sample size

A sufficient number of subjects were recruited to identify 26 healthy Japanese male volunteers aged between 20 and 45 years inclusive. Subjects had to have a body mass index (BMI) between 19 and 27 kg/m^2, who do not have a clinically relevant medical/surgical history and clinically relevant abnormalities in physical examination, ECG, vital signs (blood pressure, pulse and body temperature) and laboratory values. The subjects were divided into 3 groups (2 groups of 9 subjects each [MAD part] and 1 group of 8 subjects [BA part]).

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

The details of the investigational products are given in Table S-1.

Table S-1 Details of investigational product

Investigational product or test drug	Dosage form and strength	Route of administration	Batch number
AZD1236 tablet	25 mg tablet	Oral	DKC424
Placebo tablet	Placebo tablet matching to the active	Oral	DKC425
AZD1236 oral suspension	Suspension of 20 mg AZD1236/g	Oral	DIE385

Duration of treatment

- MAD part

Each subject received a single oral dose of AZD1236 or placebo on Day 1 and on 13 consecutive days (Days 4 to 16) of the experimental period.

Group A: 75 mg single dose on Day 1 and 75 mg once daily on 13 consecutive days

Group B: 75 mg single dose on Day 1 and 75 mg twice daily on 13 consecutive days

- BA part

Each subject received a single oral dose of 75 mg AZD1236 by suspension or tablet in each treatment period.

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

- Pharmacokinetics

  MAD part:

AZD1236 plasma concentrations and following PK parameters
After single dose: C_{max}, t_{max}, AUC_{0-t}, AUC_{tau}, AUC, $t_{1/2}$, CL/F, V_z/F and MRT
After multiple doses: $C_{ss,max}$, $C_{ss,min}$, $t_{ss,max}$, AUC_{ss}, $t_{ss,1/2}$, CL_{ss}/F and R_{acc}

BA part:

AZD1236 plasma concentrations and following PK parameters: C_{max}, t_{max}, AUC_{0-t}, AUC, $t_{1/2}$, CL/F, V_z/F and MRT

Criteria for evaluation - safety (main variables)

Adverse events, electrocardiogram (ECG), blood pressure, pulse, body temperature, haematology, clinical chemistry and urinalysis and pupillometry (only MAD part).

Statistical methods

PK and safety data were summarised using descriptive statistics. Where appropriate these data were additionally presented graphically. Regarding modes of administration in group C, AUC and C_{max} of two formulations (tablet versus suspension) were compared using descriptive statistics.

Subject population

In total, 48 healthy male Japanese volunteers entered this study, and 26 eligible volunteers were randomised into the study at 1 study site: 18 volunteers were into MAD part and 8 volunteers were into BA part. All subjects randomised to treatment completed the study as scheduled except for 1 subject (Subject E0001012/108 received AZD1236 75 mg once daily, MAD part) who was withdrawn from the study due to adverse event (AE). Of the 22 subjects who were not randomised, 15 subjects voluntarily discontinued the study, 4 subjects did not fulfil the eligibility criteria for the study and 3 subjects were surplus to requirements. The range of age and body mass index (BMI) of all randomised subjects to the study was 20 to 33 years and 19.0 to 26.9 kg/m^2, respectively.

There were no protocol deviations during the study. All randomised subjects (26) and all subjects exposed to AZD1236 (20) were included in safety and PK analysis, respectively. As one subject (E0001012/108) withdrew on Day 6 (2 days after starting multiple doses), PK samples of the subject were not collected on Day 7 and onward. Therefore, PK data for the subject was not included in the summary table and figure for multiple doses.

MAD part

Overall, the demographic and baseline characteristics were similar between treatment groups, and thus the treatment groups were comparable. Eighteen (18) eligible healthy male Japanese volunteers were randomised into MAD part. The range of age and BMI of the randomised subjects was 20 to 33 years and 19.0 to 26.9 kg/m^2, respectively. The demographic and key baseline characteristics of study subjects in MAD part are summarised in Table S-2.

Table S-2 Demographic and baseline characteristics: MAD part (All randomised subjects)

	Treatment	n	Mean	SD	Min	Median	Max
Age (years)	AZD1236 75mg once daily	6	23.2	2.1	21	23.0	26
	AZD1236 75mg twice daily	6	25.2	4.4	20	24.5	33
	Placebo	6	23.2	2.2	21	22.0	26
Height (cm)	AZD1236 75mg once daily	6	171.2	7.0	164	172.0	183
	AZD1236 75mg twice daily	6	170.2	1.7	167	170.5	172
	Placebo	6	170.7	8.4	157	172.0	181
Weight (kg)	AZD1236 75mg once daily	6	65.2	7.4	59	62.0	76
	AZD1236 75mg twice daily	6	66.7	5.2	61	65.5	75
	Placebo	6	60.7	5.6	55	59.0	69
BMI (kg/m^2)	AZD1236 75mg once daily	6	22.20	1.61	19.9	22.30	24.7
	AZD1236 75mg twice daily	6	23.03	2.23	20.6	22.65	26.9
	Placebo	6	20.97	2.96	19	19.85	26.8

BA part

Eight (8) eligible healthy male Japanese volunteers were randomised into BA part. The range of age and BMI of the randomised subjects was 20 to 31 years and 19.0 to 26.1 kg/m^2, respectively

Summary of pharmacokinetic results

MAD part

The absorption of AZD1236 was relatively fast after single and multiple dosing for both 75 mg once daily and twice daily dosing. Mean trough concentrations seemed to be unchanged following 5 days from the start of multiple dosing for both treatments, indicating that steady state appears to have been achieved at that time. The pharmacokinetic parameters of AZD1236 on Day 1 and Day 16 for both treatments are shown in Table S-3.

Table S-3 Summary of pharmacokinetic parameters of AZD1236 on Days 1 and 16 (PK analysis set)

		Day 1			Day 16		
Treatment	**Variable**	**n**	**Geometric Mean**	**Geometric CV (%)**	**n**	**Geometric Mean**	**Geometric CV (%)**
75 mg qd	C_{max} / $C_{ss,max}$ (nM)	6	3500	4.6	5	5830	10.4
	$C_{ss,min}$ (nM)	NA	NA	NA	5	1930	16.2
	t_{max} / $t_{ss,max}$ (h) [a]	6	2.00	2.00-3.00	5	2.00	1.00-3.00
	AUC_{τ} / AUC_{ss} (h*nM)	6	49000	11.7	5	84100	13.0
	AUC (h*nM)	6	77100	16.0	NA	NA	NA
	$t_{1/2}$ / $t_{ss,1/2}$ (h)	6	16.0	11.7	5	16.7	10.3
	CL/F / CL_{ss}/F (L/h)	6	2.34	16.1	5	2.15	13.0
	V_z/F (L)	6	54.0	9.9	NA	NA	NA
	MRT (h)	6	22.8	11.1	NA	NA	NA
75 mg bid	C_{max} / $C_{ss,max}$ (nM)	6	3660	5.4	6	10100	18.8
	$C_{ss,min}$ (nM)	NA	NA	NA	6	6010	21.3
	t_{max} / $t_{ss,max}$ (h) [a]	6	2.00	2.00-4.00	6	2.00	2.00-4.00
	AUC_{τ} / AUC_{ss} (h*nM)	6	32200	5.3	6	96900	19.2
	AUC (h*nM)	6	86900	13.7	NA	NA	NA
	$t_{1/2}$ / $t_{ss,1/2}$ (h)	6	16.8	13.2	6	17.8	17.2
	CL/F / CL_{ss}/F (L/h)	6	2.08	13.7	6	1.86	19.2
	V_z/F (L)	6	50.6	6.8	NA	NA	NA
	MRT (h)	6	24.3	13.5	NA	NA	NA

[a] Data for the t_{max} and $t_{ss,max}$ are shown as median and Min-Max.
$C_{ss,min}$= plasma concentration at 24 hours and 12 hour after last dose for once and twice daily, respectively; AUC_{τ}= AUC_{0-24} and AUC_{0-12} on Day 1 for once and twice daily, respectively; AUC_{ss}= $AUC_{\tau,day16}$

The median t_{max} occurred at 2.0 hours both on Day 1 and Day 16 for both treatments. The elimination half-life was approximately 17 hours and unchanged between Day 1 and Day 16 for both treatments. The geometric mean C_{max} and AUC_{τ} increased 1.7 fold from Day 1 to Day 16 for 75 mg once daily dosing. The increases of C_{max} and AUC_{τ} for 75 mg twice daily dosing were 2.8 and 3.0 fold, respectively. The ratio $AUC_{\tau,day16}/AUC_{day1}$ was 1.1 for both treatments, indicating the accumulation was as expected from single dose data.

BA part

Following administration of AZD1236 as an oral suspension and tablet, similar plasma concentration-time profiles were observed for the two formulations. The ratio (tablet/suspension) of the geometric means for C_{max} and AUC and the associated 90% CIs are shown in Table S-4.

Table S-4 Evaluation of ratios Tablet versus Suspension for pharmacokinetic parameters (PK analysis set)

Variable	Ratio of Tablet / Suspension	90% Confidence interval	
		Lower	Upper
C_{max}	1.125	0.985	1.285
AUC	1.067	0.993	1.147

The C_{max} was slightly higher in tablet formulation (ratio 1.125 and 90%CIs 0.985 to 1.285), but the AUC was similar between the two formulations (ratio 1.067 and 90%CIs 0.993 to 1.147). Whilst the study was not formally powered for bioequivalence, the CI lay within the standard bioequivalence limits of 0.8 to 1.25, the 90% CIs were within the bioequivalence limits except for the upper limit for the C_{max} (1.285). This indicates that there is the potential that the two formulations to be bioequivalent. The other parameters were also similar between the two formulations.

Summary of safety results

In the MAD part of the study AZD1236 tablet was administered orally as single dose of 75 mg, and then once or twice daily doses of 75 mg were administered for 13 consecutive days (Day 4 to 16). No safety and tolerability concerns were identified in this study up to 75 mg twice daily. In the BA part single dose of AZD1236 75 mg of tablet and suspension were administered by open crossover. Administration of AZD1236 tablet or suspension was well tolerated and no new safety issue was identified.

Overall, in the MAD part of the study, 1 (16.7%, AZD1236) and 1 (16.7%, placebo) subject reported a total of 2 and 1 adverse event(s), respectively, during the study; no clinically important difference regarding frequency of adverse events between the AZD1236 and placebo was observed. Comparing 75 mg once daily and 75 mg twice daily of AZD1236, the number of subjects with adverse events and the absolute number of events did not indicate any dose dependence for the ascending doses to 75 mg twice daily. Two adverse events (Pyrexia – 2 occasions) in 1 subject exposed AZD1236 75 mg once daily were moderate in intensity, and both occasions were considered by the investigator to be drug-related; and the other reported adverse event (Back pain, placebo) was mild in intensity and was not considered by the investigator to be drug-related. In the BA part of the study, no adverse event was reported during the study.

There was no death, SAE or other significant adverse event either in MAD part or BA part in this study. One subject who received AZD1236 75 mg once daily (MAD part) was discontinued from study treatment due to adverse event (Pyrexia).

Except for elevated leucocyte cell count, neutrophils, monocytes, platelet count and CRP and decreased in lymphocytes in the subject who was discontinued from study treatment due to

adverse event (Pyrexia), there were no clinically relevant treatment-related changes or trends in any laboratory variables, vital signs, ECG and pupillometry measured in healthy volunteers exposed AZD1236 either in MAD part or BA part of the study. Adverse events reported in MAD part are summarised in Table S-5 and Table S-6.

Table S-5 Number (%) of subjects who had at least 1 AE in any category: MAD part (Safety analysis set)

	AZD1236		Placebo	Total
	75 mg once dily (n=6)	75 mg twice daily (n=6)	(n=6)	(n=18)
	n (%)	n (%)	n (%)	n (%)
Number (%) of subject[a]:				
Any adverse events	1 (16.7)	0	1 (16.7)	2 (11.1)
Any serious adverse events	0	0	0	0
Any serious adverse events leading to death	0	0	0	0
Any serious adverse events not leading to death	0	0	0	0
Any adverse events leading to discontinuation of study	1 (16.7)	0	0	1 (5.6)
Any other significant adverse events	0	0	0	0
Any Maximum Intensity - Mild	0	0	1 (16.7)	1 (5.6)
Any Maximum Intensity - Moderate	1 (16.7)	0	0	1 (5.6)
Any Maximum Intensity - Severe	0	0	0	0
Any drug-related AE[b]	1 (16.7)	0	0	1 (5.6)
Number of events:				
All adverse events	2	0	1	3
All adverse events leading to discontinuation of study	1	0	0	1
All Maximum Intensity - Mild	0	0	1	1
All Maximum Intensity - Moderate	2	0	0	2
All Maximum Intensity - Severe	0	0	0	0
All drug-related AEs[b]	2	0	0	2

a Subjects with multiple events in the same category are counted only once in that category. Subjects with more than 1 category are counted once in each of those categories.
b As assessed by the investigator

Table S-6 Number (%) of subjects who had at least 1 adverse event by System Organ Class and Preferred Term: MAD part (Safety analysis set)

SYSTEM ORGAN CLASS	AZD1236						Placebo			Total		
Preferred term[a]	75 mg once daily (n=6)			75 mg twice daily (n=6)			(n=6)			(n=18)		
	n	(%)	No. of event	n	(%)	No. of event	n	(%)	No. of event	n	(%)	No. of event
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**1**	**(16.7)**	**2**	**0**			**0**			**1**	**(5.6)**	**2**
Pyrexia	1	(16.7)	2	0			0			1	(5.6)	2
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**0**			**0**			**1**	**(16.7)**	**1**	**1**	**(5.6)**	**1**
Back pain	0			0			1	(16.7)	1	1	(5.6)	1

a Medical dictionary for regulatory activities (MedDRA) version 11.1