AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1236
Study Code	D4260C00002
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A Double-blind, Placebo-controlled, Randomised Study to Investigate the Tolerability, Safety and Pharmacokinetics of Oral Multiple Ascending Doses of AZD1236 in Healthy Young Subjects and of an Oral Single Dose of AZD1236 in Healthy Elderly Subjects

Study dates: First healthy subject enrolled: 13 September 2007
Last healthy subject completed: 01 February 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

This study was conducted at PAREXEL International GmbH, Clinical Pharmacology Research Unit, Berlin, Germany.

Publications

None at the time of writing this report.

Objectives

The primary objective was to investigate the safety and tolerability of multiple ascending oral doses of AZD1236 given to healthy young subjects for 13 days.

The secondary objectives were:

- to investigate the single-dose pharmacokinetics (PK) of AZD1236 in plasma and urine, and safety and tolerability of AZD1236 in healthy elderly subjects
- to investigate the multiple-dose pharmacokinetics of AZD1236 in plasma and urine, the degree of accumulation, and the time dependency of the pharmacokinetics in healthy young subjects
- to explore the influence of food on the rate and extent of absorption of AZD1236 during steady state in healthy young subjects

Exploratory objectives were:

- to collect urine and plasma samples for exploratory analysis of metabolites in healthy young and elderly subjects
- to collect blood samples for analysis of matrix metalloproteinases (MMP) activity and MMP9 protein after multiple dosing of AZD1236 in healthy young subjects
- to collect pharmacogenetic samples (blood) for possible future pooled analysis.

Study design

This study was double-blind, placebo-controlled and randomised clinical study carried out at a single centre to assess the tolerability, safety, PK and pharmacodynamics (PD) of multiple ascending oral doses (15, 75 and 500 mg) of AZD1236 in healthy male subjects aged 18-45 years and the tolerability, safety and PK of a single oral dose (75 mg) of AZD1236 in healthy male subjects aged ≥65 years. The investigational product is intended for the treatment of chronic obstructive pulmonary disease (COPD).

Target healthy volunteer population and sample size

The study was conducted in a total of 27 healthy, young, non-smoking males aged between 18 to 45 years, who were divided into three dose groups of nine subjects each, and in 10 healthy,

elderly, non-smoking males aged ≥65 years. Subjects had to have a body mass index (BMI) between 19 and 30 kg/m^2, had a clinically non-significant medical history, electrocardiogram (ECG) and physical examination and negative serology results. Twenty-six of the young subjects and all of the elderly subjects completed the clinical study. One subject on placebo discontinued treatment due to an adverse event (AE).

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

- AZD1236 (batch no. 07-011426AZ-DIE 385), oral suspension, with strength 20 mg/g. The starting dose (Group A) in young subjects was 15 mg. The following doses were 75 (Group B) and 500 mg (Group C).

- Placebo (batch no. 07-011425AZ/DIE 384), oral suspension, matching the AZD1236 suspension. Placebo was administered in the same way as AZD1236.

Duration of treatment

Each subject in Groups A, B and C 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. Each elderly subject in Group D received a single oral dose of AZD1236 or placebo on Day 1.

Criteria for evaluation - safety and tolerability (main variables)

Adverse events, ECG including heart rhythm monitoring for young healthy subjects, vital signs (blood pressure, pulse, and body temperature), laboratory parameters (haematology, clinical chemistry and urinalysis [including serum cortisol and plasma adrenocorticotropic hormone (ACTH) concentrations only in young subjects]), pupillometry.

Criteria for evaluation - pharmacokinetic (main variables)

AZD1236 plasma and urine concentrations and calculated pharmacokinetic parameters (for Groups A, B and C): C_{max}, t_{max}, AUC_{0-t}, AUC_{0-24}, AUC, $t_{1/2}$, λ_z, CL/F, V_z/F, MRT, $C_{ss,max}$, $C_{ss,min}$, $t_{ss,max}$, AUC_τ, $t_{ss,1/2}$, $\lambda_{z,ss}$, CL_{ss}/F, R_{ac}, A_e, $A_{e,ss}$, CL_R, $CL_{R,ss}$

AZD1236 plasma and urine concentrations and calculated pharmacokinetic parameters (for Group D): AUC_{0-t}, AUC, t_{max}, C_{max}, $t_{1/2}$, MRT, CL/F, λ_z, V_z/F, A_e, CL_R

Criteria for evaluation – pharmacodynamic (main variables), young subjects only

Ex vivo zymosan-stimulated MMP activity in plasma (normalised to MMP9 protein and/or neutrophil count).

Criteria for evaluation – Genetics

Pharmacogenetic samples (blood) for possible future pooled analysis.

Statistical methods

No formal hypotheses were tested considering that the primary objective of this study was to evaluate the safety of AZD1236.

The pharmacokinetic parameters based on plasma concentrations constitute outcome variables for the secondary objective. The PK parameters were used to describe the pharmacokinetic profile of AZD1236, particularly to investigate the degree of accumulation, the time dependency and the preliminarily influence of food.

For dose proportionality analysis, a linear regression analysis ("power model") was applied to logarithmically transformed C_{max}, $C_{ss,max}$, AUC and AUC_{τ} as dependent variable and the logarithmically transformed dose as independent variable. All results were interpreted in a descriptive way only. Considering the exploratory nature of this investigation no adjustment of α-level was done. No formal confirmatory statistics were planned or performed.

Time-dependency was evaluated by comparing AUC_{τ} of Day 16 with AUC of Day 1. The ratio between log-transformed AUC_{τ} (Day 16) and AUC (Day 1) was calculated by back-transforming the difference between the geometric means. 90% confidence intervals for this ratio were calculated by back-transformation of the univariate 90% confidence intervals for the arithmetic mean based on the t-distribution for the differences between log-transformed parameters.

The food effect was exploratively examined by calculating confidence intervals for the ratio between AUC_{τ} and $C_{ss,max}$ of AZD1236 (Day 10, fed) vs. AUC_{τ} and $C_{ss,max}$ of AZD1236 (Day 16). These intervals were calculated using similar approach as for the time-dependent analysis. For t_{max} differences between fed and fasted were summarised and tested for significance by means of the non-parametric Wilcoxon signed rank test.

Data were presented by standard summary statistics and additional descriptive methods including individual data listings and plots of individual and group data.

Subject population

In the young subjects, all subjects planned per dose level (6 active, 3 placebo) were randomised and received the correct dose of investigational product as planned in the clinical study protocol. However, one of the placebo-treated subjects discontinued treatment due to an AE, while all other young subjects completed the study. All young subjects on active treatment were included in the PK analysis set. In the elderly, all subjects planned (8 active, 2 placebo) were randomised, received the correct dose, completed the study and were analysed.

All subjects were healthy based on the screening examination and complied with the inclusion criteria while none met any exclusion criterion. No major protocol deviations were recorded.

Overall, the treatment groups were well balanced with regards to demographic characteristics. The subject population characteristics are presented in Table S1.

Table S1 Demographic characteristics of the young and elderly subjects

		Young subjects (Groups A to C)					Elderly subjects (Group D)		
Demography	**Statistics**	**Placebo n=9**	**15 mg n=6**	**75 mg n=6**	**500 mg n=6**	**Total n=27**	**Placebo n=2**	**75 mg n=8**	**Total n=10**
Age (years)	Mean	38.4	35.7	34.0	38.0	36.7	68.5	70.1	69.8
	SD	4.4	4.3	9.6	6.1	6.2	3.5	4.5	4.2
	Median	38.0	35.5	35.0	38.0	37.0	68.5	69.0	69.0
	Min–Max	33–45	29–42	23–43	29–45	23–45	66–71	65–76	65–76
BMI (kg/m^2)	Mean	25.88	24.68	25.87	24.53	25.31	25.70	26.55	26.38
	SD	2.32	3.04	2.04	1.90	2.31	2.26	1.91	1.88
	Median	25.50	24.80	26.75	24.85	25.60	25.70	26.40	26.40
	Min–Max	22.9–29.1	20.1–29.1	22.8–28.0	21.5–26.3	20.1–29.1	24.1–27.3	23.7–29.7	23.7–29.7
Weight (kg)	Mean	80.98	82.07	83.85	78.58	81.33	83.35	81.71	82.04
	SD	7.82	9.52	9.41	11.28	9.00	9.97	5.11	5.64
	Median	80.30	82.45	84.55	81.80	81.00	83.35	81.35	81.35
	Min–Max	72.8–98.5	70.2–97.5	73.2–98.0	64.3–88.6	64.3–98.5	76.3–90.4	74.4–89.0	74.4–90.4
Height (cm)	Mean	177.0	182.5	179.8	178.5	179.2	180.0	175.6	176.5
	SD	6.2	2.9	4.7	6.6	5.5	2.8	6.0	5.7
	Median	177.0	182.5	179.5	180.0	180.0	180.0	173.5	174.0
	Min–Max	168–185	179–187	175–187	169–186	168–187	178–182	171–187	171–187

Summary of pharmacokinetic results

The pharmacokinetic parameters derived from the AZD1236 plasma concentrations are shown in Tables S2 for young and elderly subjects.

Table S2 Summary of pharmacokinetic parameters of AZD1236 on Days 1 and 16 – young and elderly subjects

			Young subjects (Groups A to C)						Elderly subjects (Group D)
			Day 1			Day 16			Day 1
Parameter	**Statistics**	**n**	**15 (mg)**	**75 (mg)**	**500 (mg)**	**15 (mg)**	**75 (mg)**	**500 (mg)**	**75 (mg)**
AUC (h*nM)	GMean	6	12809	58400	179612	NA	NA	NA	76717
	CV (%)	6	12.4	13.4	37.8	NA	NA	NA	11.6
AUC_{0-24} / AUC_{τ} (h*nM)	GMean	6	7890	30864	66209	12916	54258	144359	40413
	CV (%)	6	8.6	9.0	36.9	10.8	13.6	24.0	8.0
C_{max} / $C_{ss,max}$ (nM)	GMean	6	512	1725	3514	809	2875	7625	2241
	CV (%)	6	9.9	9.7	38.6	12.1	14.2	23.5	10.4
$C_{ss,min}$ (nM)	GMean	6	NA	NA	NA	322	1427	4691	NA
	CV (%)	6	NA	NA	NA	19.5	22.1	24.2	NA
t_{max} / $t_{ss,max}$ (h)	Median	6	3.05	4.06	4.01	2.04	3.03	3.52	4.14
	Min–Max	6	1.03–4.05	2.05–8.02	3.02–12.00	0.70–4.05	2.03–4.10	1.05–4.03	3.00–6.00
$T_{1/2}$ / $t_{ss,1/2}$ (h)	GMean	6	16.60	19.96	31.60	18.53	19.33	20.20	20.71
	CV (%)	6	8.4	18.7	52.4	10.8	15.6	23.1	15.6
CL/F / CL_{ss}/F (L/h)	GMean	6	2.819	3.090	6.699	2.795	3.328	8.334	2.354
	CV (%)	6	12.4	14.0	44.1	10.6	14.9	20.6	11.2
V_Z/F (L)	GMean	6	67.54	89.00	305.41	NA	NA	NA	70.26
	CV (%)	6	8.0	12.4	28.4	NA	NA	NA	6.7
CL_R / $CL_{R,ss}$ (L/h)	GMean	6	0.7769	1.3451	0.8845	1.5531	1.1309	0.9493	0.8723
	CV (%)	6	18.8	27.4	39.9	16.1	33.5	34.6	23.2

CV=Coefficient of variation; GMean= Geometric mean; Max=Maximum; Min=Minimum; n=number of subjects; NA=not applicable
For elderly subjects: n=8.

The absorption of AZD1236 given in a suspension was relatively fast after single and multiple dosing at all dose levels. Peak plasma concentrations occurred at 3.0 to 4.1 hours (Day 1) and 2.0 to 3.5 hours (Day 16) in the young subjects and at 4.1 hours in the elderly. The elimination half-life was approximately 20 hours in the young and elderly subjects.

The pharmacokinetic properties of AZD1236 seemed to be time-independent. AZD1236 showed an accumulation of approximately 1.6 to 2.2-fold for both C_{max} and AUC_{τ}, as expected from single dose data. Steady state was achieved after approximately 5 days. Exposure to AZD1236 in the young subjects increased less than proportional to dose over the dose range investigated (15, 75 and 500 mg). Exposure to AZD1236 in the elderly subjects

was approximately 1.3-fold higher for C_{max} and AUC compared with the young subjects following a single dose of 75 mg AZD1236.

Eating a high-fat breakfast between 0.5 and 1 hour before dosing influenced the exposure to AZD1236 following doses of 75 and 500 mg at steady state showing an increase of C_{max} and AUC by approximately 1.2-fold (75 mg) and approximately 2.4-fold (500 mg). The absorption rate of AZD1236 was slower in the fed state compared to fasting conditions.

Summary of pharmacodynamic results

No pharmacodynamic results are reported herein.

Summary of pharmacogenetic results

Pharmacogenetic samples will be reported separately.

Summary of safety results

Overall, 82% of the 27 young subjects and 60% of the 10 elderly subjects exposed either to AZD1236 or placebo reported a total of 87 and 6 adverse events, respectively, of mild to moderate intensity during this clinical study. The highest number of adverse events in the young subjects was observed in the placebo-pooled group (44 events in 89% of the 9 subjects) accounting for half of all AEs in this population. In the elderly, a similar percentage of subjects (50% placebo vs. 63% AZD1236) reported any AE, however the low number of placebo treated subjects (n=2) does not allow firm conclusions.

In the young subjects, the most frequent adverse event was headache (18 events being reported by 44% of the subjects), followed by ocular hyperaemia (13 events in 22% of the subjects), flatulence (10 events in 33% of the subjects), fatigue (10 events in 19% of the subjects) and arthralgia (6 events in 11% of the subjects). These were typical AEs observed in a clinical study with healthy volunteers and similar to the AE spectrum found in SAD study DC4260C00001. The ocular hyperaemia was almost limited to the first dose group (15 mg and placebo) and was considered to be related to refurbishment of the unit ward. The number of subjects with AEs and the absolute number of events did not indicate any clear dose-response relationship for the ascending doses of AZD1236 in this study part. Despite an apparent increase in headache with AZD1236 dose, the details of this AE (onset time, duration, number of AEs per subject) do not indicate any systematic dose-response relationship. In the elderly subjects, the only AEs reported were injection site phlebitis (2 events after AZD1236 75 mg) and headache (3 events after AZD1236 75 mg and 1 event after placebo). Overall, there was no death, serious adverse event (SAE) or other significant adverse event in this clinical study. One young subject having received placebo was discontinued from study treatment due to adverse events (elevated liver function tests).

There were no clinically significant changes in vital signs (blood pressure, pulse and body temperature), laboratory values (haematology, clinical chemistry and urinalysis), physical examination, telemetry and pupillometry data during the course of this clinical study. Regarding electrocardiograms, the measured variables RR, PR (PQ) and QRS intervals as well

as heart rate did not show any dose- or treatment-related change over time. All individual QTc intervals were well below a critical margin of 500 ms and there appeared to be no difference in the mean profiles between any dose level and placebo over time. The maximum change from baseline in individual QTcX values was <30 ms at any time. None of the individual QTc values raised any clinical concern by the Investigator.