AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD4818
Study Code	D3540C00010
Edition Number	1
Date	30 September 2008

A randomised, placebo-controlled single-blind, single-centre Phase I study to assess the safety, tolerability and pharmacokinetics of single and multiple ascending inhaled doses of AZD4818 in healthy Japanese male volunteers

Study dates: First healthy volunteer/patient enrolled: 18 January 2008
Last healthy volunteer/patient completed: 29 May 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 Osaka Pharmacology Clinical Research Hospital, Osaka, Japan.

Publications

None at the time of writing this report.

Objectives

The primary objective of this study was to investigate safety and tolerability of single and multiple ascending inhaled doses of AZD4818 in healthy Japanese male volunteers by assessment of:

- Adverse event (AE), safety laboratory tests (haematology, clinical chemistry, urinalysis), 12-lead electrocardiogram (ECG), body pressure (BP), pulse rate, body temperature, spirometry.

The secondary objective of this study was to investigate pharmacokinetic (PK) profile of AZD4818 following single and multiple ascending inhaled doses in healthy Japanese male volunteers by assessment of:

- PK parameters
- Plasma concentrations of AZD4818.

Study design

The study was a single-blind, randomised, placebo-controlled Phase I study with single and multiple ascending dose levels of inhaled AZD4818 carried out at a single centre to investigate the safety, tolerability and PK of AZD4818 in healthy Japanese male volunteers. The investigational product is intended for the treatment of chronic obstructive pulmonary disease (COPD).

Target healthy volunteer population and sample size

In total 30 healthy male Japanese aged between 20 to 45 years and having body mass index (BMI) between 18.0 to 27.0 kg/m^2 were to be randomised into the study. The randomised subjects were divided into three dose groups (9 subjects each in 200 µg/day group and 600 µg/day group, 12 subjects in 1200 µg/day group). All of the randomised subjects completed the study except 1 subject on placebo discontinued after single dose and before starting multiple doses due to a protocol deviation.

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

The details of the investigational products are given in Table S1.

Table S1 Details of investigational products

Investigational products	Dosage form, strength	Route of administration	Batch number
AZD4818 Turbuhaler®	Dry powder inhaler, AZD4818 50 µg/dose [a], 60 doses/Turbuhaler	Inhalation	07-012046AZ
AZD4818 Turbuhaler	Dry powder inhaler, AZD4818 150 µg/dose [a], 60 doses/Turbuhaler	Inhalation	07-012048AZ
Placebo Turbuhaler	Dry powder inhaler, Matching placebo to AZD4818 Turbuhaler, 60 doses/Turbuhaler	Inhalation	07-012008AZ

a 1 g of AZD4818 is equivalent to 1.264 g of AZD4818 benzoate.

Duration of treatment

Each subject received a single inhaled dose of AZD4818 or placebo followed by a 72-hour washout and then multiple doses twice daily for 10 and a half consecutive days (200 µg/day and 600 µg/day groups) or for 20 and a half consecutive days (1200 µg/day group).

Criteria for evaluation - pharmacokinetics (main variables)

1. Plasma concentrations of AZD4818

2. PK parameters

   - Day 1 (single dose): AUC_{0-t}, $AUC_{0-\infty}$, $AUC_{(0-12)}$, C_{max}, t_{max}, $t_{½}$, CL/F, V_z/F, MRT

   - Day 14/Day 24 (last day of multiple doses): AUC_{0-t}, $AUC_{(0-12)ss}$, C_{max}, $C_{min,ss}$, t_{max}, $t_{½}$, CL/F, V_z/F, MRT, R_{acc} (calculated as $AUC_{(0-12)ss}/AUC_{(0-12)}$)

Criteria for evaluation - safety (main variables)

Adverse events, safety laboratory tests (haematology, clinical chemistry and urinalysis), 12-lead ECG, BP, pulse rate, body temperature, spirometry.

Criteria for evaluation – Genetics

CC-chemokine receptor 1 (CCR1) gene

Statistical methods

Safety data were listed for each subject and were compared between active treatment and placebo. Safety data except for AEs and PK data were presented by descriptive statistics for

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each treatment group. Where appropriate these data were additionally presented graphically. AEs were summarised by the System Organ Class (SOC) and Preferred Terms (PT) using Medical Dictionary for Regulatory Activities (MedDRA) for each dose level.

Subject population

A total of 42 volunteers from a single centre entered this study; and 30 eligible healthy male Japanese subjects were randomised as planned and received at least one administration of investigational product. Six (6) and 3 subjects received active and placebo, respectively, in 200 µg/day and 600 µg/day groups. In 1200 µg/day group, 8 and 4 subjects received active and placebo, respectively. A single subject (Subject 206 [placebo]) discontinued the treatment after receiving the single dose and before starting multiple doses; all the other randomised subjects (29) completed the study. All randomised subjects (30) and all subjects exposed to AZD4818 (20) were included in safety and PK analysis, respectively.

Overall, the demographic and baseline characteristics were similar between treatment groups, and thus the treatment groups were comparable. The range of age and BMI of randomised subjects was 20 to 36 years and 18.4 to 26.7 kg/m^2, respectively. The demographic and key baseline characteristics of study healthy volunteers are summarised in Table S2.

Table S2 Demographic and baseline characteristics (All randomised subjects)

	AZD4818			Placebo
	200 µg/day n=6	600 µg/day n=6	1200 µg/day n=8	n=10
Age (years)				
n	6	6	8	10
Mean	22.5	22.0	26.5	25.7
SD	3.5	2.5	3.7	5.5
Min	20	20	22	21
Median	21.0	21.0	26.5	23.0
Max	29	27	33	36
Height (cm)				
n	6	6	8	10
Mean	174.27	174.95	173.44	173.18
SD	7.83	2.53	6.53	3.38
Min	160.2	170.0	163.2	167.8
Median	174.90	175.70	173.25	173.10
Max	181.8	177.0	184.0	179.0
Weight (kg)				
n	6	6	8	10
Mean	68.97	65.17	65.96	64.11
SD	12.51	3.20	9.84	5.77
Min	51.0	59.8	52.4	54.2
Median	73.15	65.00	66.20	64.95
Max	83.2	68.9	82.0	71.6
BMI (kg/m^2)				
n	6	6	8	10
Mean	22.58	21.30	21.89	21.36
SD	2.80	1.50	2.69	1.79
Min	18.4	19.2	18.9	18.6
Median	23.50	21.15	21.00	21.45
Max	25.3	23.8	26.7	24.7

Summary of pharmacokinetic results

After single dose of AZD4818, the plasma concentrations decreased rapidly below lower limit of quantification (LLOQ). Hence the pharmacokinetic parameters could not be evaluated except for C_{max} and t_{max}. The t_{max} occurred within 10 minutes independent of dose and the C_{max} seemed to increase proportionally with dose increments.

A summary of PK parameters after twice daily doses is given in Table S3. For 100 µg bid (*bis in die* [twice a day]) the plasma concentrations after the last dose were below LLOQ for later time points, hence some PK parameters could not be determined in some subjects. All subjects showed the C_{max} within 10 minutes after the last dose in all doses. The C_{max} and $AUC_{(0-12)}$ seemed to increase proportionally with dose increments. The terminal $t_{½}$ was estimated to on average 83.7, 76.5 and 107 hours after the last dose of 100, 300 and 600 µg, respectively. The increase of C_{max} by multiple doses was 1.3 to 1.6 fold. The R_{acc} for $AUC_{(0-12)}$ could be evaluated only for 600 µg bid and the mean R_{acc} was 2.77.

Table S3 Summary of PK parameters of AZD4818 following twice daily inhalations via Turbuhaler on Day 14 or Day 24 - PK analysis set

Dose	Parameter	N	Geometric mean	CV(%)	Min	Median	Max
100 µg bid	$AUC_{(0-12)}$ (pM.h)	5	866	20.6	644	848	1100
Day 14	C_{max} (pM)	6	875	32.9	507	916	1190
	C_{min} (pM)	5	43.9	23.7	35.8	39.3	56.6
	t_{max} (h)	6	NA	NA	0.0833	0.0833	0.167
	$t_{½}$ (h)	1	83.7	NC	83.7	83.7	83.7
300 µg bid	$AUC_{(0-12)}$ (pM.h)	6	2350	8.75	2100	2360	2640
Day 14	C_{max} (pM)	6	2390	11.6	2150	2280	2850
	C_{min} (pM)	6	116	10.9	99.0	115	130
	t_{max} (h)	6	NA	NA	0.0833	0.0833	0.167
	$t_{½}$ (h)	6	76.5	43.7	54.7	67.8	171
600 µg bid	$AUC_{(0-12)}$ (pM.h)	8	5680	15.5	4520	5570	6880
Day 24	C_{max} (pM)	8	4850	20.4	3750	4820	6990
	C_{min} (pM)	8	326	13.0	270	314	393
	t_{max} (h)	8	NA	NA	0.0833	0.167	0.167
	$t_{½}$ (h)	8	107	34.6	79.7	97.1	226
	R_{acc}	3	2.77	14.6	2.37	2.83	3.16

NA: Not applicable, NC: Not calculable

Summary of pharmacogenetic results

Pharmacogenetic samples will be reported separately.

Summary of safety results

In this study, AZD4818 demonstrated a good safety profile and was shown to be well tolerated at inhaled dose up to the highest dose of AZD4818 given (600 µg single dose followed by 600 µg twice daily doses for 20 and a half consecutive days). There were no deaths, serious adverse events, adverse events leading to discontinuation or any other significant adverse event.

In total 22 adverse events were reported during the study by a total of 14 (46.7%) subjects out of 30 subjects exposed either to AZD4818 or placebo. All adverse events were mild in intensity except for 1 moderate (placebo). There were no clinically important differences in the incidence and intensity of adverse events in the active group and placebo group, and also the number of subjects with adverse events and the absolute number of events did not indicate any dose dependence for the ascending doses of AZD4818.

There were no clinically significant changes or trends in any laboratory parameter, vital signs (BP, pulse rate and body temperature), ECG and spirometry measured in healthy volunteers exposed to AZD4818 during the study.

Adverse events are summarised in Table S4 and Table S5.

Table S4 Summary of adverse events (Safety analysis set)

AE category	AZD4818				Placebo
	200 µg/day n=6	600 µg/day n=6	1200 µg/day n=8	Total[d] n=20	n=10
Number (%) of subjects[a]:					
Any AE	2 (33.3)	4 (66.7)	4 (50.0)	10 (50.0)	4 (40.0)
Any AE with mild intensity	2 (33.3)	4 (66.7)	4 (50.0)	10 (50.0)	4 (40.0)
Any AE with moderate intensity	0	0	0	0	1 (10.0)
Any AE with severe intensity	0	0	0	0	0
Any drug-related AE[b]	2 (33.3)	4 (66.7)	1 (12.5)	7 (35.0)	2 (20.0)
Total number of AEs[c]:					
All AEs	3	6	4	13	9
All AEs with mild intensity	3	6	4	13	8
All AEs with moderate intensity	0	0	0	0	1
All AEs with severe intensity	0	0	0	0	0
All drug-related AEs[b]	3	5	1	9	2

a Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than one category are counted once in each of those categories.
b As assessed by the investigator
c Multiple events in the same category are counted multiple times in that category. Multiple events belonging to more than one category are counted multiple times in each of those categories.
d Total number of subjects on AZD4818

Table S5 Number (%) of subjects[a] who had at least 1 adverse event by preferred term, arranged by system organ class (Safety analysis set)

SYSTEM ORGAN CLASS	AZD4818				Placebo
Preferred term[b]	200 µg/day	600 µg/day	1200 µg/day	Total[c]	
	n=6	n=6	n=8	n=20	n=10
INVESTIGATIONS	**2 (33.3)**	**3 (50.0)**	**3 (37.5)**	**8 (40.0)**	**3 (30.0)**
Blood thyroid stimulating hormone increased	2 (33.3)	2 (33.3)	1 (12.5)	5 (25.0)	0
White blood cell count decreased	0	1 (16.7)	1 (12.5)	2 (10.0)	1 (10.0)
Electrocardiogram QT prolonged	0	0	1 (12.5)	1 (5.0)	0
Blood bilirubin increased	0	0	0	0	1 (10.0)
Forced expiratory volume decreased	0	0	0	0	1 (10.0)
Blood alkaline phosphatase increased	0	0	0	0	1 (10.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**0**	**2 (33.3)**	**0**	**2 (10.0)**	**1 (10.0)**
Upper respiratory tract inflammation	0	2 (33.3)	0	2 (10.0)	1 (10.0)
GASTROINTESTINAL DISORDERS	**0**	**0**	**1 (12.5)**	**1 (5.0)**	**0**
Diarrhoea	0	0	1 (12.5)	1 (5.0)	0
CARDIAC DISORDERS	**0**	**0**	**0**	**0**	**1 (10.0)**
Ventricular extrasystoles	0	0	0	0	1 (10.0)

a Number of subjects with adverse events, sorted by SOC followed by PT in decreasing order of total frequency. A subject can have one or more PT reported under a given SOC.
b Medical dictionary for regulatory activities (MedDRA) version 11.0
c Total number of subjects on AZD4818

Date of the report

30 September 2008